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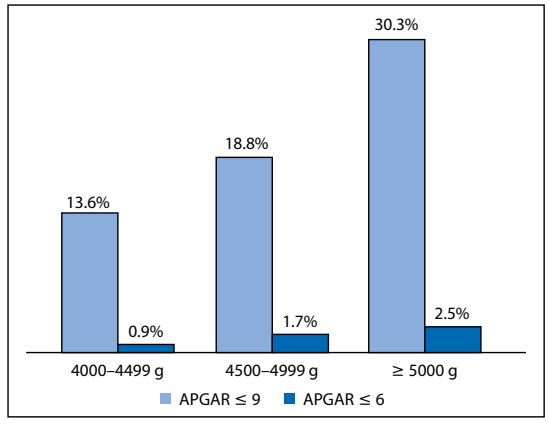

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The relevance of blood gases levels in newborns: the sampling matters

Joanna M. Jassem-Bobowicz[1], Katarzyna Stefanska[2]

[1]*Division of Neonatology, Medical University of Gdansk, Poland*
[2]*Department of Obstetrics, Medical University of Gdansk, Poland*

Dear Editor,

we have read with interest the article entitled "Relationship between Apgar score and umbilical cord blood acid-base balance in full-term and late preterm newborns born in medium and severe conditions" by Marta Mlodawska et al. [1]. The authors should be commended for addressing this important question, but the article requires some comments.

The authors question the correlation between clinical assessment with Apgar score and umbilical cord blood gases levels. This is a substantial question for informing the care of neonates, particularly on the use of therapeutic hypothermia, and communicating prognosis to newborn's parents. However, umbilical vein sampling, used in the above-mentioned study even in most severe cases, is inferior to arterial blood sampling. Puncture of the umbilical vein is less complicated due to its size, thinner wall, and easier identification, and is practiced in many hospitals. On the other hand, this technique provides insufficient information on the fetus health status and prognosis [2]. Cord vein compression may constrict blood flow from the placenta, while the arteries still carry blood rich in carbon dioxide from the fetus back to the placenta. In consequence, higher production of carbon dioxide by the fetus will only be detectable in the umbilical arteries and not in the umbilical vein. Ideally, both umbilical and arterial cord blood samples should be used for the evaluation of the placental and fetal status [3]. Another important aspect is the timing of umbilical cord sampling, which should be captured due to ongoing metabolic changes in the placenta even after birth. To avoid bias caused by further metabolic changes after birth, arterial and venous samples should preferably be taken from a double-end clamped piece of the umbilical cord [3, 4]. Nevertheless, the method of umbilical cord sampling for other purposes, including stem cells acquisition or blood group phenotyping for the neonatal risk assessment, requires further investigation [5, 6].

The topic addressed in this study is clinically relevant and warrants a prospective study with a well-designed blood sampling technique.

Conflict of interest

The authors declare no conflict of interest.

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Corresponding author:
Joanna M. Jassem-Bobowicz
Division of Neonatology, Medical University of Gdansk, Poland
e-mail: jmjassem@gmail.com

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Congenital adrenal hyperplasia in adolescence — a gynecological perspective

Joana Correia Oliveira[*1, 2], Filipa Costa Sousa[*1], Sara Teixeira Campos[1], Fernanda Bento Geraldes[1], Joana Lopes Belo[1], Maria Helena Leite[1], Maria Alice Mirante[3], Maria Fernanda Aguas[1]

[1]Gynecology Department, University Hospital Center of Coimbra (CHUC), Coimbra, Portugal
[2]Faculty of Medicine of Coimbra University, Coimbra, Portugal
[3]Pediatric Endocrinology Department, University Hospital Center of Coimbra (CHUC), Coimbra, Portugal
**these authors contributed equally to this work*

ABSTRACT

Objectives: Analysis of congenital adrenal hyperplasia (CAH) cases, gynaecological implications, referral reasons to gynaecologist and treatment.

Material and methods: Retrospective, longitudinal, single-centre study with female CAH paediatric patients ≥ 10 years-old, followed between 1998–2018 in gynaecology and endocrinology departments at a public university tertiary hospital.

Results: 47 patients, 34.0% (n = 16) with classic, 66.0% (n = 31) with non-classic forms (NCAH), CYP21 deficit and 46,XX karyotype. We found a normal median menarche age [11.5 IQR 2 (6–15) years-old], but significantly earlier in NCAH (p = 0.003). Precocious puberty occurred in 48.9%, n = 23. Primary amenorrhea occurred in salt-wasting form (21.4%, n = 3). Oligomenorrhea and hirsutism were significantly more prevalent in NCAH (p = 0.018, p = 0.014 respectively) and acanthosis nigricans and virilization signs in classic forms (p = 0.05, p = 0.000 respectively). Sixteen patients (34.0%) were referred to gynaecology, mostly due to menstrual irregularities (50.0%, n = 8). Medical treatment with isolated or combined corticoids, oestrogen and progestogen were chosen in all but one case. Gonadotropin-releasing hormone analogues were used in 19.0% (n = 9). Surgery was performed in 34.0% (n = 16) patients, median age 2.0 IQR 2.5 (0.6–90) years-old.

Conclusions: This paper highlights the importance of a multidisciplinary approach. Early treatment contributes to a phenotypical feminine differentiation and normalization of the hypothalamus-pituitary-ovarian axis, which is essential given the gynaecologic and obstetric consequences of untreated cases.

Key words: congenital adrenal hyperplasia; hyperandrogenism; steroid 21-hydroxylase; menstruation disorders; amenorrhea

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INTRODUCTION

Congenital adrenal hyperplasia (CAH) is one of the most frequent genetic disorders of sexual development.

According to the enzymatic activity, the most severe, or classic, form of CAH is characterized by neonatal adrenal insufficiency with salt-wasting (SW), or it may only be only in early childhood due to virilization signs (simple virilizing form — SV). In girls, the androgen excess can cause virilization of the external genitalia, and therefore sexual ambiguity typical of the classic form includes clitoromegaly, labioscrotal fold fusion, and a common urogenital sinus [1].

The non-classic form (NCAH) is less severe, the clinical features being hyperandrogenism with no neonatal sexual ambiguity. Most females with NCAH are asymptomatic during prepubertal years and premature pubarche can be the primordial sign. Different degrees of clinical hyperandrogenism usually follow (acne, hirsutism, male-pattern balding) together with precocious puberty, menstrual cycle disorders, and infertility. Some cases of NCAH remain asymptomatic [2].

Objectives

In this study our aim was to retrospectively analyze the gynaecologic healthcare management of female patients with CAH in a tertiary paediatric hospital of a Southern European country.

Corresponding author:
Joana Correia Oliveira
Gynecology Department, University Hospital Center of Coimbra (CHUC), Coimbra, Portugal
e-mail: joana.correia.oliveira@hotmail.com

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MATERIAL AND METHODS

We undertook a retrospective, longitudinal, single-center study between 1998 and 2018, with a group of females with CAH who were ≥ 10 years old. The girls in our study group had been born between 1989 and 2008 and at diagnosis, each girl was entered on an electronic CAH database by the assistant endocrinologist. Forty-seven subjects were included in our study: 16 girls (34.0%) with classic CAH, and 31 girls (66.0%) with NCAH, and all with CYP21 deficiency genetically proven and 46,XX karyotype. We performed a descriptive analysis of the general sample and within each, specified the CAH form for each, and compared data for the classic and non-classic forms. Parameters evaluated include gynaecological implications and the main reasons recorded for the original referral to the childhood and adolescence gynaecologist. Statistical analysis was performed using IBM SPSS Statistics Version 24.0. Descriptive statistics were analyzed as mean and standard deviations for variables with normal distribution, and as median and interquartile ranges for variables without normal distribution. Variables were described in percentages (%) and absolute numbers (n). Nominal variables were compared using Pearson's chi-squared test or Fisher's exact test according to Cochran's rule. The comparison of continuous variables was performed with either Student's T-tests (parametric test, applied after verifying the homogeneity of variances using Levene's test) or the Mann-Whitney test (non-parametric test). The significance level is 0.05, with a corresponding confidence level of 95%.

Our study was conducted in accordance with the ethical principles of the Declaration of Helsinki of the World Medical Association.

RESULTS

The neonatal adrenal insufficiency with salt-wasting (SW) form of CAH was present in 29.8% (n = 14) of subjects, the simple virilizing (SV) form in 4.3% (n = 2), and the remainder (66.0%, n = 31) of the cases were NCAH. The diagnosis of SW was made prior to 1 year of age (plus, there was one case of prenatal diagnosis); for SV, the median age of diagnosis was 3 (2.0–4.0) years old; and for NCAH, the mean age of diagnosis was 10.6 ± 4.1 (1.0–17.0) years old. Only 8.5% (n = 4) of cases had a family history of CAH, and all of these were NCAH. Among concomitant comorbidities (Fig. 1), adrenal insufficiency was the most frequent (n = 20), corresponding to 42.6% of the patients (16 in classic form and at least one episode of adrenal insufficiency in each of four patients with NCAH forms).

Precocious puberty occurred in 48.9% (n = 23) subjects. The mean age of pubarche was 6.9 ± 2.6 (3–13 years old);

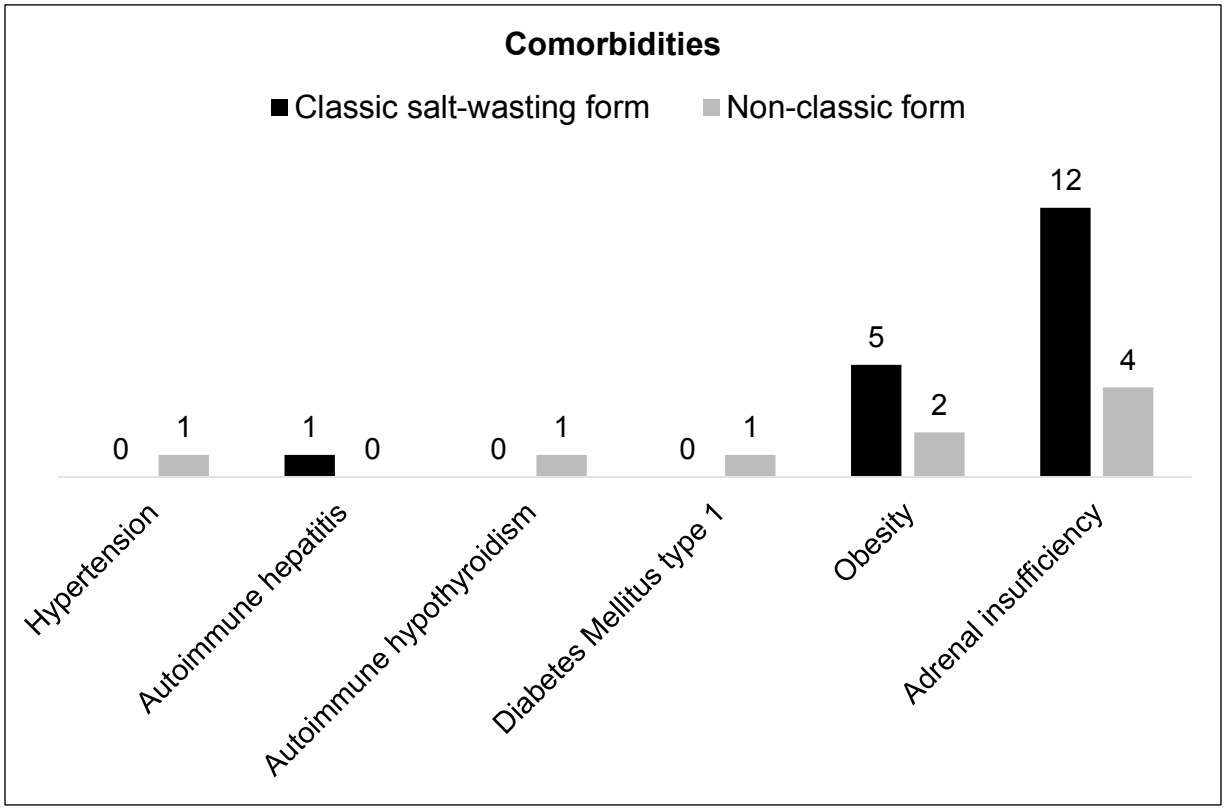

Figure 1. Patients' comorbidities

Table 1. Characterization of gynecological and therapeutic data

	All n = 47	Classic salt-wasting n = 14 (29.8%)	Classic simple virilizing n = 2 (4.3%)	Non-classic n = 31 (66.0%)	Classic vs non-classic forms (p value)
Demographic data					
Age at diagnosis, yr ($\bar{x}$,σ) or M, [range]	7.7 IQR 13 [0–17]	N/A < 1	3 [2.0–4.0]	10.6 ± 4.1 [1.0-17.0]	—
Sexual development					
Pubarche, yr ($\bar{x}$,σ) or M, IQR [range]	6.9 ± 2.6 [3.0–13.0]	9.0 IQR 7.0 [4.0–13.0]	4.0 [3.0–5.0]	6.5 ± 1.8 [4.0–11.0]	> 0.05 Mann-Whitney U
Thelarche,yr ($\bar{x}$,σ) or M, IQR [range]	8.9 ± 2.3 [4–13]	10.6 ± 2.1 [7–13]	6 [4–8]	8.4 ± 1.9 [5–11]	> 0.05 Independent samples t-test
Menarche,yr ($\bar{x}$,σ) or M, IQR [range]	11.5 IQR 2 [6–15]	13.1 ± 1.3 [11–15]	12 [11–13]	11 IQR 2 [6–14]	0.003 Mann-Whitney U
Menstrual disturbances					
Primary amenorrhea (%, n)	6.4 (3)	21.4 (3)	—	—	**0.035** Fisher's exact test
Secondary amenorrhea (%, n)	8.5 (4)	7.1 (1)	—	9.7 (3)	> 0.05 Fisher's exact test
Oligoamenorrhea (%, n)	48.9 (23)	28.6 (4)	—	61.3 (19)	**0.018** Chi-squared test
Polimenorrhea (%, n)	4.3 (2)	—	—	6.5 (2)	> 0.05 Fisher's exact test
Signs of hyperandrogenism					
Clinical hirsutism (%, n)	61.7 (29)	42.9 (6)	—	74.2 (23)	**0.014** Chi-squared test
Acne (%, n)	53.2 (25)	42.9 (6)	50.0 (1)	58.1 (18)	> 0.05 Chi-squared test
Acanthosis nigricans (%, n)	19.1 (9)	42.9 (6)	—	9.7 (3)	**0.05** Fisher's exact test
Stretch marks (%, n)	31.9 (15)	50.0 (7)	—	25.8 (8)	> 0.05 Chi-squared test
Virilization signs (%, n)	38.8 (18)	78.6 (11)	100.0 (2)	16.1 (5)	**0.000** Chi-squared test
Medical therapy					
C (%, n)	40.4 (19)	42.9 (6)	100.0 (2)	35.5 (11)	—
C + E + antiandrogenic P (%, n)	40.4 (19)	57.1 (8)	—	35.5 (11)	—
C + E + antiandrogenic P + metformin (%, n)	10.6 (5)	—	—	16.1 (5)	—
E + antiandrogenic P (%, n)	6.4 (3)	—	—	9.7 (3)	—
GnRHa (%, n)	56.3 (9)	14.3 (2)	50.0 (1)	19.4 (6)	—
Surgical intervention					
Age at first surgery (M, IQR), [range]	2.0 IQR 2.5 [0.6–9]	2 IQR 2.8 [0.6–9]	3.5 [3–4]	—	—
Surgical re-intervention (%, n)	8.5 (4)	8.5 (4)	—	—	—

C — corticoid; E — estrogen; GnRHa — gonadrotropin releasing hormone analogs; IQR — interquartile range; M— median; N/A — not applicable; P — progestogen; $\bar{x}$ — mean; σ — standard deviation

the mean age of the larche was 8.9 ± 2.3 (4–13 years old); and the median age of menarche was 11.5 IQR 2 (6–15 years old). These data are presented for each CAH form in Table 1. Regular menstrual cycles were referred to by 31.9% (n = 15) of subjects; and of the others, 6.4% (n = 3) had primary amenorrhea, 8.5% (n = 4) secondary amenorrhea, and 53.2% (n = 25) irregular cycles (48.9%, n = 23 oligomenorrhea, and 4.3%, n = 2 polymenorrhea).

Clinical hirsutism was present in 61.7% (n = 29) subjects, acne in 53.2% (n = 25), acanthosis nigricans in 19.1% (n = 9), stretch marks in 31.9% (n = 15), and virilization signs in 38.8% (n = 18). Sexual ambiguity was observed in 16 (34.0%),

and all of these were of the classic form. Signs of virilization were classified using the Prader scale as n = 4 (25.0%) at grade 1, n = 4 (25.0%) at grade 2, n = 7 (43.8%) at grade 3, and n = 1 (6.3%) at grade 4.

Sixteen patients (34.0%) were referred to a gynecologist: six with classic CAH form with a mean age 15.8 ± 2.9 (13–21 years old), and 10 with NCAH with a mean age of 15.5 ± 1.8 (13––19 years old). The main reason for the referrals was menstrual irregularities (50.0%, n = 8); and other reasons were secondary amenorrhea (18.8%, n = 3), sexual ambiguity (6.2%, n = 1), hirsutism (12.5%, n = 2), and primary amenorrhea (12.5%, n = 2). Of the 37 supra-pubic/transvaginal ultrasounds performed, 16.7% (n = 6) of subjects had polycystic ovaries, and all were NCAH patients.

Medical treatment with isolated corticotherapy was chosen for 40.4% (n = 19) of patients. Estrogen combined with an antiandrogenic progestogen was chosen for 6.4% (n = 3) patients. In a further 40.4% of patients (n = 19), corticotherapy in combination with oestrogen with an antiandrogenic progestogen were administered. Corticoid plus oestrogen plus antiandrogenic progestogen plus metformin was chosen in 10.6% (n = 5) of cases. One patient with NCAH remained under clinical follow-up. Concomitantly, in order to prevent advanced bone age, gonadotropin-releasing hormone analogs (GnRHa) were used in 19.0% subjects (n = 9) with a mean age of 6.8 ± 1.7 (3–9) years old at the start, and of 11.1 ± 1.2 (10–13) years old at the end of treatment.

Surgical treatment was performed in 34.0% of subjects (n = 16), always during childhood [median age at first surgery 2.0 IQR 2.5 (0.6–9)]. The surgical methods performed were clitoral hoodoplasty in 25.0% (n = 4), genitoplasty (vulvar and vaginal) in 6.3% (n = 1), clitoroplasty plus genitoplasty in 31.3% (n = 5), clitoroplasty plus genitoplasty with additional closure of urethrovaginal fistula in 6.3% (n = 1), and clitoroplasty plus genitoplasty with surgical repair of ureters and urethra in 31.3% (n = 5) cases. Re-intervention was needed in 25.0% of these patients (n = 4) who were at Prader 3 (n = 3) and Prader 4 stages (n = 1). The re--intervention surgeries were clitoroplasty (n = 2 patients) and vaginoplasty (n = 2 patients).

The gynaecological and therapeutic data for each CAH form are specified in Table 1.

Simultaneous assistance was provided to patients by other specialties: urology (urologic surgery) in 29.8% (n = 14), paedopsychiatry in 17.0% (n = 8), paediatrics (neurodevelopment) in 10.6% (n = 5), genetics (genetic counselling) in 59.6% (n = 28), and psychology in 4.3% (n = 2) of cases. During the follow-up of these girls, there was 1 case of evolving pregnancy.

DISCUSSION

To the best of our knowledge, patients with classic forms are usually diagnosed early in life as clinics undertake prompt investigations. However, patients with NCAH may only be diagnosed later in life, mainly due to precocious puberty, abnormally accelerated growth velocity (crossing percentiles), or menstrual cycle disorders [3].

In Portugal there is no national neonatal screening for CAH, and newborns are only investigated if there are clinical signs of this disorder or there is a family background suggesting a heightened risk. Nevertheless, neonatal screening tests can produce false-negative results, so newborns with atypical genitalia should be investigated further, regardless [4].

Our patients all had genetically confirmed CAH at the time of data analysis, so this paper will not focus on the diagnoses, except for our prenatally diagnosed case, which was detected in a mid-trimester ultrasound due to clitoris hypertrophy with the absence of testicles. A female karyotype 46,XX and high amniotic fluid 17-hydroxyprogesterone were confirmed by amniocentesis.

In terms of comorbidities, three patients had autoimmune disorders. Falhammar H. et al. [5], investigated a possible correlation between the CYP21A2 gene and these disorders, as its location is known to be highly immunologically active. In 714 patients with 21-hydroxylase deficiency, they discovered an increased prevalence of autoimmune disorders.

Although gonadotropin-dependent precocious puberty is a possible consequence of CAH, our patients had a normal median menarche age. However, the age of menarche in NCAH was statistically significantly earlier than in the classic forms. Our findings are similar to a study by Lien Trinh et al. [6], in which girls with CAH with earlier puberty showed a mean age of menarche identical to the general population, but in contrast to our findings, they found no significant differences between different CAH forms. In this and other parameters, that study's different racial and ethnic origins and treatment protocols may account for the difference between our two studies.

Premature pubarche is diagnosed when pubic or axillary hair or apocrine odor start when females are younger than eight years old [7]. In a series of 220 cases including 25 children < 10 years old with NCAH, Moran C. et al., found a premature pubarche rate of 10.5% in this sub-group [3, 8]. That rate was markedly lower than the rate of 54.8% (17 out of 31) in the same sub-population in our study. We found no significant differences in the timing of pubarche between classic and NCAH cases. The earlier onset of pubarche in classic CAH cases compared with that in the general population is also described in literature. We agree with Völkl T. et al. [9], who speculate that this might be due to an incomplete adrenal androgen suppression when attempting to avoid steroid overtreatment.

Oligomenorrhea and chronic anovulation are frequent in NCAH patients but can also arise in classic forms even with appropriate treatment [3]. In inadequately cases, the onset of menarche might be delayed [6]. During the development of puberty, evaluation of potential lower genital tract obstructions to menstrual flow should be investigated in those girls with classic CAH who have not undergone surgery previously, as these obstructions can be responsible for primary amenorrhea. Two of our three cases of primary amenorrhea (all of them classic forms) had previously undergone vulvovaginoplasty, but had not undergone any subsequent surgical intervention, so we concluded that menstrual flow obstruction was not the cause of amenorrhea [10]. Moran C. et al. [8], reported a 54% prevalence of oligomenorrhea in NCAH, which was a slightly lower result than our 61.3%. We found a higher significant prevalence of oligomenorrhea in NCAH, and we postulate that as classic form patients were diagnosed and treated earlier, the rate of these menstrual irregularities was less frequent.

Because of menstrual disorders, female adolescents might assume that they have no need for contraception. The gynaecologist has a critical role in managing family planning issues in order to avoid undesired pregnancies. Combined hormonal contraception is a first-line option.

Hirsutism and acne are common in NCAH, with hirsutism being the most commonly presenting feature [3]. Hirsutism was the most common sign of hyperandrogenism in our sample, and as expected, there was a significant difference between classic and NCAH cases, with it being more prevalent in the latter. There are reports in the literature of a 60% prevalence of hirsutism in NCAH forms, compared with our even higher prevalence of 74.2%. The prevalence of acne in NCAH forms is described in the literature as 33%, which is a lower value than our finding of 58.1% [8].

The first-line treatment for both CAH forms are glucocorticoids, and for the classic form, together with mineralocorticoids and salt supplementation. Ensuring the suppression of adrenal androgens is sometimes difficult, and one of the major risks of overtreatment is growth retardation and other features of Cushing syndrome [10]. Indeed, besides acne, hyperandrogenism can lead to other dermatologic manifestations, such as acanthosis nigricans and stretch marks [9]. We found a statistically significantly higher incidence of acanthosis nigricans in classic forms, probably due to the subjects undergoing a longer period of steroid therapy.

Virilization signs, as expected, were significantly more prevalent in classic forms and only in these cases were virilized external genitalia present at birth. Nevertheless, NCAH can also present later in life with clitoromegaly, androgenic alopecia, perianal hair, adult apocrine odor and hoarseness of voice [11]. *In utero* androgen exposure only occurs in classic forms, justifying the expected differences in virilization signs [12].

The endogenous hyperandrogenic environment of CAH can interfere with ovarian function, thus causing a polycystic ovarian morphology, which is consistent with our finding that 19.4% of our NCAH patients had these features [3]. Carmina et al. [13], reported polycystic ovarian morphology in 80% of a group of adult women with NCAH, but Pall et al. [14], found a prevalence of only 24%.

The goals of medical therapy are to prevent adrenal crisis and growth retardation, to improve sexual maturation and reproductive function, to determine the optimal timing for spontaneous puberty, regularize menstrual cycles and fertility, improve the symptoms of hyperandrogenism, and promote self-esteem [15]. These can be achieved by replacing deficient steroids and concomitantly trying to decrease adrenal sex hormones and prevent iatrogenic glucocorticoid excess [16].

Without corticoid treatment, classic forms are markedly at risk of adrenal insufficiency [17]. Nonetheless, glucocorticoids can also be part of NCAH treatment in pre- and peripubertal phases if there is an advanced bone age or early onset of pubarche [2]. Additionally, about one third of NCAH patients have partial cortisol insufficiency and may benefit from glucocorticoid supplementation. Steroid treatment can, paradoxically, lead to a secondary cortisol insufficiency, and thus in severe, stressful situations possible adrenal insufficiency must be cautiously predicted and prevented through an increase in glucocorticoid doses [18]. Steroid treatment accounted for the episodes of adrenal insufficiency in our cases of NCAH. Indeed, all our patients with classic forms and 87.1% (n = 27) NCAH patients were prescribed glucocorticoids. Towards adult age, NCAH patients should only receive this treatment if there is significant hyperandrogenism [2].

In patients with central precocious puberty, with whom there is the possibility of advanced bone age, therapy with GnRH analogs can bring benefits by preventing the small but present risk of short adult stature in NCAH patients [19]. However, GnRH analogs are not recommended as a routine treatment [2]. Nine of our patients were prescribed GnRH analogs, until they reached their normal pubertal age, because they exhibited growth velocity > 6 centimeters/year and/or bone age > 1 year than their chronological age.

In our sample, hydrocortisone and fludrocortisone were the glucocorticoid and mineralocorticoid of choice, respectively. Dexamethasone was used during pregnancy to prevent female fetus virilization in the single prenatal diagnosis case and hydrocortisone was started in the newborn after birth. In our case, a female baby was born with normal external genitalia.

Oral contraceptives combining estrogen and progestogen with antiandrogenic effects (EP) are the first-line treatment to improve hyperandrogenism and oligomenorrhea, as they suppress adrenocorticotropic hormones, and ovarian and adrenal androgens [20]. If EP are not sufficient, antiandrogens can be added, but their potential teratogenicity should be borne in mind. In our patients, antiandrogenic progestogens were the first choice among the EPs and there was no need to administer additional antiandrogens. EPs can be used over a long period, have fewer side effects than glucocorticoids, and are more effective regarding hirsutism [21]. Many of our patients with NCAH were concurrently receiving low doses of corticotherapy. Indeed, we tried to conjugate the antiandrogenic effects of glucocorticoids and EP. Long-term glucocorticoids are useful in managing hirsutism and regularizing ovulatory cycles in classic forms, but EP can, in addition, provide effective contraception. Eleven of our NCAH patients were only under corticotherapy because they did not tolerate EP, had some relative contraindication, or did not wish to take them. Glucocorticoids, as previously stated, can also be used to control menstrual cycles and signs of hirsutism.

Metformin was used in five of our patients, all with NCAH. The medication has been extensively studied in the context of hyperandrogenism caused by polycystic ovary syndrome. As NCAH is associated with insulin resistance, patients may benefit from metformin therapy as an insulin-sensitizer.

Only subjects with the classic form may be born with external genitalia malformation, including clitoral enlargement, partial or complete labial fusion or the presence of a common orifice for urethra and vagina (urogenital sinus), due to the effects of androgen excess during embryonic development [1]. Collaborating with our hospital's urology department was essential for our surgical approach.

If Prader stage ≥ 3 is identified, there is a formal indication for reconstructive clitoral and perineal surgery, performed between two and six months after birth [1]. Contrary to this, our eight patients with Prader stage 3 or 4 were submitted to surgery later than this reference period (minimum 7-months-old). Even so, there is still no consensus among experts on what is the correct surgical timing. Most authors concur that performing clitoris hypertrophy correction in early infancy is best, but patient advocacy groups disagree with this early procedure if it not essential for the patient's physical well-being [22]. Moreover, patients who have undergone earlier genital surgery are at higher risk of developing long-term complications, such as esthetic defects, urinary incontinence, vaginal stenosis, sexual dysfunction, and diminished clitoral sensation [1]. Half of our Prader ≥ 3 patients (4 of 8) underwent surgical re-interventions, reinforcing this idea. The uterus and the ovaries are unaffected in this endocrinological disorder, except for the six cases in our study with polycystic ovarian morphology on ultrasound, which were induced by the hyperandrogenic environment.

Few women with the classic form will be able to conceive. This is due to glucocorticoid undertreatment, remaining hyperandrogenism, and subsequent anovulatory cycles; or because of genital malformations that prevent fertilization [23]. One of our patients had a successful spontaneous pregnancy and another is still trying to conceive with the help of medically assisted reproduction techniques.

CONCLUSIONS

This case series study highlights the importance of undertaking a multidisciplinary approach involving endocrinology and gynaecology experts, as well as other medical and surgical specialties. Early and appropriate treatment is decisive as it contributes to a phenotypical feminine differentiation and normalization of the hypothalamus-pituitary-ovarian axis, which is essential given the gynaecological and obstetric consequences of untreated cases.

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Conflict of interest

The authors declare no conflict of interest.

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The impact of cystocele repair on urge symptoms in women with pelvic organ prolapse

Pawel Szymanowski, Paulina Banach, Andrzej Wisniewski, Wioletta K. Szepieniec

Andrzej Frycz Modrzewski Cracow University, Cracow, Poland

ABSTRACT

Objectives: The purpose of this study was to evaluate the impact of cystocele repair on urinary urge symptoms and to determine the likelihood that urge symptoms are caused by cystocele and therefore cured by cystocele repair. The secondary aim was to assess the impact of baseline cystocele stage POP on the improvement of urge symptoms following surgical treatment of POP.

Material and methods: A total of 321 female patients with cystocele stages II, III or IV (POP), who underwent repair surgery for pelvic organ prolapse, were included. A retrospective analysis was performed to determine the presence of urge symptoms in patients with cystocele and to evaluate how many patients were cured from urge symptoms by the cystocele repair. Postoperative data were obtained by interview during a follow-up examination six weeks after surgery.

Results: Preoperatively, 52.02% of all patients diagnosed with cystocele stages II, III or IV POP experienced urge symptoms. Urge symptoms were cured in 88.62% of patients with cystocele stages II after POP repair ($p < 0.005$). 88.60% of patients with cystocele stage II POP and 88.68% of patients with cystocele stages III to IV POP reported improvement in urge symptoms ($p < 0.005$). Despite cystocele repair, 11.4% of patients with preoperative cystocele stage II POP and 11.32% with preoperative cystocele stages III and IV POP reported persistent urge symptoms. 5.84% of the study group who showed no urge symptoms preoperatively, experienced *de novo* urge symptoms after following surgery ($p < 0.005$).

Conclusions: Cystocele repair cured urge symptoms in the majority of patients. Therefore, repair of bladder prolapse may help to differentiate urge symptoms from other urinary tract dysfunctions and assist in determining a proper diagnosis and treatment.

However, the severity of POP had no significant influence on the improvement in urge symptoms following cystocele repair. Risk of de novo urge symptoms after anatomical repair still needs to be explored.

Key words: cystocele; urge symptoms; urinary incontinence; urinary urgency; overactive bladder; pelvic organ prolapse

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INTRODUCTION

Urinary urge symptoms, defined as a complaint of sudden difficult to defer desire to pass urine, is a lower urinary tract dysfunction (LUTD) that affects millions of women of all ages [1–3]. The disorder has a substantial influence on quality of life, as it not only affects patients' physical comfort, but also their psychological and social well-being. Those with the condition are thus at an increased risk of depression and limited social and sexual function [2, 4]. As the prevalence of urge symptoms and urinary incontinence (UI) is increasing globally [5], finding adequate treatment strategies for the condition becomes one of the most important present-day aims for physicians.

Urinary urge symptoms should be understood as either urge dry (urinary urgency), that is, without leakage of urine, or urge wet, also known as urgency urinary incontinence (UUI). UUI is a urinary leakage accompanied by or immediately preceded by a sensation of an urgent need to urinate. After UI diagnosis, its type (urge, overactive bladder, stress, mixed or overflow) should be identified, as this allows the proper treatment strategy to be determined [2]. Urgency constitutes one of several mixed urinary incontinence (MUI) symptoms. MUI is defined as the involuntary leakage of urine associated with urgency but also with exertion, effort, sneezing, or coughing [6]. It is desirable to differentiate urge symptoms (dry and/or wet) from overactive bladder

Corresponding author:
Paulina Banach
Andrzej Frycz Modrzewski Cracow University, Cracow, Poland
e-mail: paulinabanach.kaafm@gmail.com

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(OAB). While OAB is a diagnosis characterized by daytime increased urinary frequency and nocturia, urgency is also one of its symptoms. OAB is then divided into OAB wet, with urgency urinary incontinence, and OAB dry when no UI coexists [3, 7]. Distinguishing between urinary urgency or urgency UI and OAB nomenclature might contribute to improving of the treatment results.

It should be emphasized that OAB may only be diagnosed after first excluding urinary tract infections and other obvious pathologies [1, 8]. Considering the definition of OAB, pelvic organ prolapse (POP) repair may help to differentiate urge symptoms from OAB, and therefore, assist in determining a proper diagnosis and treatment. POP, which is a prolapse or drooping of any of the pelvic floor organs, including bladder, uterus, vagina, small bowel, and rectum, should be considered as an 'other pathology' in the OAB definition, and thus be repaired before any other treatment indication. Only the persistence of urge symptoms following POP surgery with no urinary tract infections will confirm diagnosis of OAB.

POP often coexists with urinary urgency or UUI [3, 9]. Whereas some authors have reported that POP affects 50% of parous women, 20% of whom are symptomatic, OAB symptoms are believed to coexist with POP in 88% of patients [10]. Evaluating the influence of POP on the urge symptoms is therefore fundamental. One hypothesis suggests that POP may have an impact on the female urethra and additionally play a role in mechanical bladder outlet obstruction (BOO). As a result, a prolapse within the pelvic cavity may cause OAB symptoms [11].

More than 50 years ago it was reported that prolapse-related bladder and bowel function disorders can only be resolved by surgical repair that restores the right anatomy [12, 13].

Since then, the influence of POP on OAB symptoms has been discussed in numerous studies, most of them identifying a discernable improvement in OAB symptoms after POP restoration [10, 14–18]. While some authors demonstrated the effectiveness of pessary use in urinary urgency and UI [15], others highlighted improvement in OAB symptoms after surgical correction of anterior vaginal wall prolapse [16, 17]. In some studies, attention has been drawn to preoperative factors associated with persistent OAB symptoms, but no significant correlation between preoperative cystocele severity and improvement in OAB symptoms after surgical correction have been established [18]. On the other hand, Miranne et al. [10], described a higher risk of persisting OAB symptoms in women with more severe apical and/or anterior POP.

Therefore, the relationship between cystocele repair and urge symptoms remains inconsistent, and the effect of POP repair still needs to be explored. Our hypothesis is that urge symptoms constituting OAB may result from an anatomical obstruction, namely cystocele. Our approach to cystocele treatment, resulting in the resolution of urge symptoms, was from a practical clinical perspective based on collective experience with effective reconstructions of anatomical defects. The objective of our study was to evaluate the impact of cystocele repair surgery on urge symptoms. A secondary aim was to evaluate the impact of baseline cystocele stage POP on improvements in urge symptoms shortly after surgical treatment of POP.

MATERIAL AND METHODS

Patient characteristics

Data were collected from 371 women with cystocele stages II to IV (POP), who underwent anatomical repair between April 2016 and February 2020. POP severity evaluation was based on the Pelvic Organ Prolapse Quantification system (POP-Q) [19]. Following surgery for cystocele repair, all the women were retrospectively examined to determine the presence of urge symptoms and to identify how many of them were cured and in how many the problem appeared *de novo*. A comprehensive urogynecologic examination, including a vaginal examination and taking the subject's urogynecologic history, was performed prior to surgery and six weeks after surgery. A Pelvic Floor Distress Inventory (PFDI-20) short form was completed for each patient to determine the presence of urinary urge symptoms both pre- and postoperatively [20]. Preoperative urge symptoms were defined as a positive response to items numbered 15 and/or 16 of the PFDI-20: 'Do you usually experience frequent urination?', 'Do you usually experience urine leakage associated with a feeling of urgency, that is a strong sensation of needing to go to the bathroom?'. The absence of urge symptoms after surgical repair was considered evidence that the condition was cured. Women with cystocele stage I POP only, patients with active urinary tract infections, and those who underwent previous anti-incontinence surgery were excluded from the study. The reduction of urinary urge symptoms after cystocele repair was considered as a cure in cases of the complete disappearance of symptoms, and in cases where urge symptoms persisted, regardless of the severity, as no recovery.

Three hundred twenty-one patients diagnosed with cystocele met the inclusion criteria. Table 1 lists the baseline characteristics of the study population. Two hundred ninety-six patients enrolled in the study were non-smokers, and 25 admitted to smoking. One hundred forty-four women had a BMI within the norm (18.5–24.99), 172 above the norm (< 25), and 5 had a BMI below the norm (< 18.5). One hundred of the patients were of premenopausal and 221 of postmenopausal age, with a median age of 56.64. Two hundred eighty-five of the women had given birth vaginally

Table 1. Baseline characteristics of the study population

	POP 2, 3, 4 (n = 321)	POP = 2 (n = 232)	POP = 3, 4 (n = 90)	p value
Age [yr]	56.64 ± 14.84	54.42 ± 15.03	62.33 ± 12.75	< 0.001
Premenopausal patients	100 (31.15%)	87 (37.66%)	13 (14.44%)	< 0.001
Postmenopausal patients	221 (68.85%)	144 (62.34%)	77 (85.56%)	< 0.001
BMI [kg/m^2]	25.74 ± 4.32	25.38 ± 4.14	26.61 ± 4.64	0.019
Parity	2.10 ± 1.03	2.00 ± 0.82	2.35 ± 1.41	0.113
Urge	167 (52.02%)	114 (46.35%)	53 (58.89%)	0.124

POP — pelvic organ prolapse; BMI — body mass index

Table 2. Baseline characteristics of patients with pelvic organ prolapse (POP) and coexisting urinary urge symptoms

	POP = 2 + urge (n = 114)	POP = 3, 4 + urge (n = 54)	p value
Age [yr]	56.18 ± 15.23	65.62 ± 11.25	< 0.001
Premenopausal patients	40 (35.09%)	4 (7.55%)	< 0.001
Postmenopausal patients	74 (64.91%)	49 (92.45%)	< 0.001
BMI [kg/m^2]	25.93 ± 4.18	27.66 ± 4.88	0.045
Parity	2.13 ± 0.87	2.46 ± 1.57	0.499

BMI — body mass index

at least once. The study group comprised 167 subjects with, and 154 subjects without, preoperative urinary urge symptoms. Within the study group with preoperative urge symptoms there were 80 (47.9%) women with dry, 71 (42.5%) with wet, and 16 (9.6%) with mixed urinary incontinence. We evaluated the influence of preoperative cystocele of stages II to IV (POP) on urinary urge symptoms. The study group was then divided into two subgroups depending on the preoperative cystocele severity, namely the anatomically less severe group (cystocele stage II) and the anatomically more severe group (cystocele stage III and IV). Table 2 lists the baseline characteristics of the study subgroups with POP coexisting with urinary urge symptoms.

All methods were carried out in accordance with relevant guidelines and regulations. The study was conducted in accordance with the Declaration of Helsinki and the protocol was approved by the Ethical Review Board of Andrzej Frycz Modrzewski Cracow University, Poland (Decision No. KBKA/25/)/2017). A written informed consent for inclusion was obtained from all participants.

Data analysis

Statistical analysis was performed using Statistica software (ver. 13.3, StatSoft, Poland). Data expressed on a qualitative scale were presented as the number and percentage of the sample. Either the Chi-squared test ($\chi 2$) or the Fisher exact probability test were used to compare the relationships between variables expressed in the qualitative scale. Data expressed on a quantitative scale were presented as means with standard deviations (SD). As the data were not normally distributed (Shapiro-Wilk test), the Mann-Whitney test was used. Results were considered statistically significant when p value ≤ 0.05.

RESULTS

Three hundred twenty-one women met the inclusion criteria. The study group comprised 167 (52.02 %) of the total number of patients with preoperative urinary urge symptoms and 154 (47.98%) without preoperative urge symptoms. Of the preoperative urge symptoms group, there were 80 (47.9%) with dry, 71 (42.5%) with wet, and 16 (19.6%) with mixed urinary incontinence. There were no significant differences between the groups of patients with urinary urge symptoms, in terms of mean body mass index and parity (p > 0.005) (Tab. 2).

Urge symptoms were significantly improved after surgical repair. One hundred forty-eight (88.62%) of the 167 patients with cystocele stage II POP reported improvement in urge symptoms (p < 0.005). One hundred fourteen women (68.26%) with preoperative urge symptoms had cystocele stage II POP (less severe anatomical group) and 53 (31.74%) had stage III to IV POP (more severe anatomical group). One hundred and one (88.60%) of the 114 patients in the less severe anatomical group and 47 (88.68%) of the 53 patients in the more severe anatomical group reported improvement in their urge symptoms (p < 0.005). There was no significant difference in improvement of urge symptoms comparing the cystocele stage II POP group and the cystocele stage III to IV POP group (88.60% versus 88.68%, respectively, p > 0.005; Tab. 3)

72 (90%) of the 80 patients with dry urge symptoms reported improvement after cystocele repair, for stages II POP,

Table 3. Changes in urge symptoms depending on pelvic organ prolapse (POP) severity

	CYSTOCELE			
Urge symptoms	POP 2, 3, 4 (n = 167)	POP 2 (n = 114)	POP 3, 4 (n = 53)	p value
Cure	148 (88.62%)	101 (88.60%)	47 (88.68%)	0.806
Persistence	19 (11.38%)	13 (11.40%)	6 (11.32%)	0.806

and 5 (6.25%) of them noticed no changes in urge symptoms after cystocele repair. In the remaining 3 (3.75%) patients, their dry urge symptoms changed into wet. 61 (85.92%) of the 71 patients with wet urge symptoms reported improvement after a cystocele correction, 5 (7.04%) had no changes in urge symptoms, and 5 patients (7.04%) wet urge symptoms changed into dry. Fifteen (93.75%) of the 16 patients with mixed urinary incontinence reported improvement after cystocele repair at stage II POP and in one patient (6.25%) mixed urge symptoms changed into wet (Tab. 4, 5). Both no changes and transition in urge symptoms were considered persistence.

Despite cystocele repair, 13 (11.4%) of the 114 patients with cystocele stage II POP and 6 (11.32%) of the 53 women with cystocele stages III and IV POP reported persistent urge symptoms, which were considered OAB (Tab. 3). Nine (5.84%) of the 154 women without preoperative urge symptoms reported *de novo* urge symptoms. Three (33.33%) of the 9 patients with urge symptoms diagnosed *de novo*, reported dry and 6 (66.66%) of the patients reported wet urge symptoms (Tab. 6).

Table 4. Changes in urge symptoms depending on its type

	Dry	Wet	Mixed
Cure rate	72/80	61/71	15/16
%	(90)	(86)	(94)
Persistence	8//80	10//71	1/16
%	(10)	(14)	(6)

Table 5. Transition in urge symptoms

	Dry — > Wet	Wet — > Dry	Mix — > Dry/Wet
Transition	3	5	1

Table 6. Urge symptoms *de novo*

	All (154)	Dry	Wet
Urge *de novo*	9	3	6
	(5.84)	(1.96)	(3.90)

DISCUSSION

The results of the present study revealed the existence of urge symptoms among patients with cystocele stages II, III and IV POP. At baseline, 52.02% of the study group with preoperative cystocele experienced urinary urgency. Prior projects mostly focused on urge symptoms and OAB symptoms concomitant with POP, with their occurrence rates varying between 53% and 69% [21, 22]. In contrast to these findings, OAB occurrence rates in patients without POP have been reported in only 4–9% of cases [12, 23], which could confirm a correlation between both disorders and thus underline the importance of our study.

In the group of patients with POP experiencing urinary urgency or UUI, pharmacotherapy and other non-surgical treatments seem to be less effective. The adequate treatment strategy in patients with POP is the defect's resolution resulting in the removal of the bladder obstruction. In the present study, 148 patients (88.62%) with cystocele stage II POP reported improvement in urge symptoms ($p < 0.005$) after cystocele repair. One hundred and one (88.60%) of 114 patients in the less severe anatomical group, and 47 (88.68%) of the 53 patients in the more severe anatomical group, reported an improvement in postoperative urge symptoms ($p < 0.005$). Our findings are similar to results from previous studies reporting an improvement in OAB symptoms after anatomical repair of the prolapse in patients with coexisting POP [12, 24–26]. These comparable results are shown in Table 7. The reported cure rates range from 70.2% in the Liedl B et al. [12], research to 87.6% in the study by Papa Petros PE [26]. These findings support the hypothesis that urinary urgency recedes after removing of the bladder obstruction and therefore, that OAB symptoms should also improve after POP surgical repair.

Interestingly, the cure rate of urge symptoms in patients with cystocele stage II POP revealed no significant differences compared with that in the more severe anatomical group (88.60% of 88.68%, $p > 0.005$). Our findings are consistent with previously published results [9, 12] and lead us to conclude that patients with more severe prolapse respond to treatment equally well as those with less advanced stages. On the other hand, Miranne et al., described a higher risk of persisting OAB symptoms in women with more severe apical and / or anterior POP [10]. This indicates that there is good reason for clinicians to perform further research in the field of pelvic floor surgery.

Table 7. Comparison of results from previous studies

	Goeschen et al., 2015 [21]	Caliskan et al., 2015 [22]	Liedl et al., 2016 [11]	Petros, 1997 [23]
Urge				
Cured cases/observed cases	102/127	70/95	92/131	85/97
Cure rate, %	80.3	73.7	70.2	87.6
95% CI	73–87	65–83	62–76	83–92
Urge incontinence				
Cured cases/observed cases	44/55	49/70	72/106	74/86
Cure rate, %	80.0	70.0	67.9	86.0
95% CI	69–91	59–81	59–77	81–91

In our study, *de novo* urinary urgency or UUI occurred in 9 (5.84%, $p < 0.005$) of 154 patients after cystocele repair, including three women with dry and six with wet urgency symptoms. Therefore, urinary urgency or UUI should be included in the surgical risk of cystocele repair. Our results are in line with those of other studies. DI BIASE M et al., assessed that the risk of *de novo* UI after cystocele repair was 4.1% [27]. Table 5 shows the transformation in urinary urge symptoms. Determining which factors predict the persistence of urinary urgency after POP surgical treatment and whether preoperative POP severity has an impact on the improvement of OAB symptoms are yet to be examined [9]. More research is needed to explain the change from urinary urgency to UUI and *vice versa*. In our research, five patients with wet urge symptoms switched to dry urge symptoms, and three patients with dry, urge symptoms switched to wet urge symptoms after the surgery. However, these results proved statistically insignificant and require further investigation. Dry urgency symptoms are less inconvenient for patients and affects the quality of life to a lesser extent than wet urgency symptoms. It stands to reason that the transition from wet to dry urgency can be perceived as an improvement. In contrast, the change from dry urge symptoms to urge incontinence should be considered a deterioration of the patient's condition.

Many public health studies have highlighted that OAB symptoms negatively affect people's everyday life [28, 29]. Of the entire spectrum of OAB symptoms, urinary urgency and UUI have the greatest impact on patients' comfort and quality of life. Patients who experience OAB with UI were found to have a lower quality of life in the social and functional domains than patients with diabetes [28]. Therefore, OAB should be analyzed from both the medical and the economic points of view. American women with OAB symptoms generate an economic burden comparable to the costs of treating breast cancer or diabetes [12]. The proper surgical treatment depends on identifying the cause of urge symptoms which should be a priority for pelvic floor surgery. What may be required, is a re-definition of OAB diagnosis, stating that diagnosis can only be made after POP is excluded. We support previous hypotheses that qualification for surgery ought to be individualized and performed precisely. An adequate treatment strategy linked to the cause of the disorder should be recommended, as that will provide long-lasting improvement of the symptoms. The surgical treatment should be chosen depending on the defect causing the cystocele. Currently the surgeons have a wide range of surgical techniques to choose from, contingent on the defect's level and its type. The anterior colporrhaphy is recommended if cystocele is caused by a central defect. In case of cystocele caused by a lateral defect, lateral repair should by indicated. New laparoscopic techniques are required, when the apical influences the formation of a cystocele 30–33. Anatomical correction may also help to improve both cystocele and urinary urgency.

The strengths of our study include participation of a large group of respondents and an objective assessment with a precise physical examination of anatomical correlations before and after the surgery. The follow-up examination shortly after the surgery (6 weeks) enabled the exclusion of other factors in patients (weight, age, hormonal changes, longer period of work) that had the potential to impact on the surgical outcome. The limitation of our study is the lack of a long-term efficacy evaluation. However, our study revealed that urge symptoms may be caused by bladder prolapse, thus POP repair might indicate a proper treatment. Further studies are required to evaluate the recurrences of urge symptoms after a longer period.

CONCLUSIONS

A short-term efficacy evaluation indicates that just the anatomical correction may help to improve urinary urgency. Cystocele repair resulted in a cure of urge symptoms in most patients and thus should be repaired before any other treatment indication. However, the severity of preoperative POP had no significant influence on the improvement of those symptoms. Postoperative persistent urinary urgency or UUI considered OAB, were not related to baseline POP. The risk of *de novo* urge symptoms after anatomical repair still needs to be explored.

Conflict of interest

The authors declare no conflict of interest.

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Effect of mucinous differentiation in endometrioid type endometrial cancers on prognosis

Bahadir Saatli[1], Orkun Ilgen[1], Selim Kandemir[1], Seda Eryigit[2], Meral Koyuncuoglu[2], Cagnur Ulukus[2], Erkan Cagliyan[1]

[1]Dokuz Eylul University School of Medicine Department of Obstetrics and Gynecology, Izmir, Turkey
[2]Dokuz Eylul University School of Medicine Department of Pathology, Izmir, Turkey

ABSTRACT

Objectives: To evaluate the influence of mucinous differentiation in endometrioid endometrial cancer regarding spread and prognosis.

Material and methods: Endometrioid endometrial cancer cases between 2015 and 2020 were collected retrospectively and divided into two groups according to the cytoplasmic mucin including. Prognostic factors and cancer spread related parameters were evaluated.

Results: A total of 219 patients were enrolled in this study. One hundred twenty-two (55.7%) were endometrioid and 97 (44.3%) were in the mucinous differentiated endometrioid catagory. Age was similar between the groups (59.3 vs 58.7, $p = 0.62$), however, grade 3 lesions were more frequent in endometrioid type endometrial cancer (8.7% vs 1.4%, $p < 0.01$). Poor prognostic factors including myometrial invasion, lymphovascular space invasion (LVSI), lymph node metastases, peritoneal cytology, endocervical involvement, and stage were not significantly different between groups ($p = 0.23$, $p = 0.49$, $p = 0.40$, $p = 0.15$, $p = 0.17$, $p = 0.55$). The median overall survival time of endometrioid and mucinous differentiated endometrioid type endometrial cancer patients was determined 88.5 and 96.8 months, respectively ($p = 0.46$).

Conclusions: Mucinous differentiation in the endometrioid type of endometrial cancer does not seem to affect the prognosis in endometrioid endometrial cancer patients.

Key words: mucinous differantiation; endometrioid endometrial cancer; endometrial cancer prognosis

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INTRODUCTION

Endometrial cancer (EC) is the most frequently seen gynecologic malignancy worldwide [1]. Thirty percent of the newly diagnosed endometrial cancers are grade 1 —endometrioid subtype according to the studies [2]. The disease is mostly limited to the uterus and does not spread extrauterine space except 15% of cases [3]. Risks for extra-uterine metastasis, recurrence, and death were a myometrial invasion, lymphovascular space invasion (LVSI), and lymph node invasion [4, 5]. On the other hand, serous and clear cell types of EC are associated with poor prognostic factors including higher tumor grade, later stage, and decreased overall survival compared with endometrioid and mucinous types [6]. In addition, deep myometrial invasion, LVSI, and lymph node involvement are more frequent in serous papillary type EC than endometrioid type EC [7].

Mucinous EC is a rare histopathologic subtype defined as including intracytoplasmic mucin of more than 50% of the cancer cells [8, 9]. However, sometimes endometrioid EC cells may have mucinous differentiation less than 50% of the cells [10]. This entity may be called endometrioid cancer with mucinous differentiation. Advanced stages and pelvic lymph node metastasis were detected more frequently in pure mucinous EC rather than mucinous, squamous, or tubal differentiation variant of endometrioid EC [10, 11]. This study aims to evaluate the influence of mucinous differentiation of the endometrioid EC on myometrial invasion, LVSI, endocervical involvement, lymph node involvement, peritoneal washing cytology, stage, and overall survival (OS).

Corresponding author:
Orkun Ilgen
Department of Obstetrics and Gynecology, Dokuz Eylul University Hospital, Izmir, Turkey
phone: 90 506 2884461, e-mail: mdorkunilgen@gmail.com

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MATERIAL AND METHODS

Study population

Clinicopathological data of the patients with the diagnosis of endometrial cancer (EC) who applied to the Dokuz Eylul University Hospital from January 2015 to January 2020 were collected from the hospital database retrospectively. Ethical approval from the local ethics committee was obtained for this study. Patients with the diagnosis of primary EC who were performed hysterectomy with bilateral salpingo-oophorectomy were included in the conducted study. Performing pelvic and/or para-aortic lymphadenectomy decision was made with being grade 3 carcinoma or more than 50% cancer invasion of the myometrium or endocervical involvement in frozen section evaluation. Eligible patients had been undergone detailed physical and gynecological examinations. Patients with insufficient clinicopathological data, or those that were treated with chemotherapy or radiotherapy before the surgery were excluded.

Data collection

The Hospital's electronic medical record database was used to obtain patients' clinicopathological data. (i) Basic information including age, menopause status, years in menopause, reproductive history, history of cancer in the family, comorbidities, and overall survival. (ii) Histopathological data including tumor grade, histopathological subtype, clinical-stage, depth of myometrial invasion, lymphovascular space invasion (LVSI), lymph node invasion, and peritoneal cytology. The International Federation of Gynecology and Obstetrics (FIGO) — 2009 staging and histologic typing system of World Health Organization (WHO) were used to determine tumor grade and clinical stage. Adjuvant therapies [radiation therapy (RT) or chemotherapy (CT)] were decided according to the pathological findings. Adjuvant therapies were given to the patients with extrauterine spread or high-risk early-stage disease.

Patients were divided into two groups as mucinous differentiated endometrioid (cytoplasmic mucin including cells lower than 50% among cancer cells) or pure endometrioid ECs. Endpoints of the present study were clinical-stage, depth of myometrial invasion, LVSI, lymph node invasion, endocervical involvement, and peritoneal cytology.

Statistical analysis

Mann-Whitney U and T-test were used to analyze the association between categorical and continuous variables. Associations between continuous variables were evaluated by using Pearson and Spearman correlation test. Kaplan-Meyer and the log-rank test was used to determine the median survival time. The comparison of proportions was calculated by the chi-square test. P value < 0.05 was considered statistically significant. All analyses were performed by using IBM SPSS Statistics Version 25.

RESULTS

A total of 219 patients were included in the analysis. One hundred twenty-two were endometrioid and 97 were mucinous differentiated endometrioid subtype of EC. The clinicopathologic data of the patients were shown in Table 1. Mean ages of the enrolled patients were similar in two groups; mean ages in the endometrioid type EC group and mucinous differentiated endometrioid type EC group were 59 ± 9 and 58 ± 9 years, respectively. Age, menopausal status, history of cancer in the family were similar between the groups. Grade 3 tumor was determined more frequent in the endometrioid type EC group (8.7% vs 1.4%, $p < 0.01$).

Association between endometrial cancer spread related parameters and histopathologic subtype was summarized in Table 2. A total of 79 patients were diagnosed with more than 50% myometrial invasion (36.1%), while the remaining 140 patients were determined with less than 50% myometrial invasion (63.9%). Thirty-eight (17.4%) of the patients whose myometrial invasion more than 50% were in mucinous differentiated EC group. However, this difference was not found statistically significant ($p = 0.23$). No significant difference was found between the histopathologic subtype of EC and LVSI, lymph node invasion, peritoneal cytology, endocervical involvement, stage (p values were 0.49, 0.40, 0.15, 0.17, 0.55, respectively).

Median survival times of endometrioid and mucinous differentiated EC groups were determined 88.5 ± 1.6 and 96.8 ± 2.5 months, respectively. On the other hand, the 5-year overall survival rate was 95% in the endometrioid EC group and 93% in the mucinous differentiated EC group (Tab. 3, Fig. 1).

DISCUSSION

This study represents the effect of mucinous differentiation on endometrioid histologic type of EC. Our hypothesis while performing this study was that mucinous differentiation has a negative effect on the prognosis of endometrioid EC such as deeper myometrial invasion, LVSI, more lymph node metastasis, and advanced stage. These presumes were considered due to the results of certain previous studies [10, 11].

A previous study conducted by Musa et al. [11] represented that, mucinous histology of EC was more likely to invade lymph nodes rather than endometrioid histology subtype of EC (17% vs 3%, $p = 0.01$). However, there was no detected significant difference regarding the myometrial

Table 1. Clinicopathologic data of the patients

		Endometrioid n = 122	Mucinous differentiated endometrioid n = 97	p value
Age [years] (mean ± SD)		59.3 ± 9.9	58.7 ± 9.4	0.62
Menopause [years] (mean ± SD)		11.4 ± 8	9.2 ± 8.9	0.06
Menopause status [n (%)]	No	19 (8.6)	24 (10.9)	0.08
	Yes	103 (47)	73 (33.3)	
History of cancer in family [n (%)]	No	108 (49.3)	91 (41.5)	0.13
	Yes	14 (6.3)	6 (2.7)	
Diabetes status [n (%)]	No	83 (37.8)	67 (30.5)	0.46
	Yes	39 (17.8)	30 (13.6)	
Tumor grade [n (%)]	1	72 (32.9)	66 (30.1)	< 0.01*
	2	31 (14.2)	28 (12.8)	
	3	19 (8.7)	3 (1.4)	

Table 2. Association between endometrial cancer spread and histopathologic subtype

		Endometrioid n (%)	Mucinous differentiated endometrioid n (%)	p value
Myometrial invasion	< 50%	81 (37.0)	59 (26.9)	0.23
	> 50%	41 (18.7)	38 (17.4)	
Lymphovascular space invasion	Negative	78 (35.6)	61 (27.9)	0.49
	Positive	44 (20.1)	36 (16.4)	
Lymph node invasion	Negative	107 (48.9)	87 (39.7)	0.40
	Positive	15 (6.8)	10 (4.6)	
Peritoneal cytology	Negative	110 (50.2)	92 (42.0)	0.15
	Positive	12 (5.5)	5 (2.3)	
Endocervical involvement	Negative	84 (38.4)	60 (27.4)	0.17
	Positive	38 (17.4)	37 (16.9)	
Stage	IA	63 (28.8)	41 (18.7)	0.55
	IB	17 (7.8)	18 (8.2)	
	II	30 (13.7)	27 (12.3)	
	III	11 (5.0)	11 (5.0)	
	IV	1 (0.5)	1 (0)	

Table 3. Survival outcomes between histopathologic subtypes

	Endometrioid n = 122	Mucinous differentiated endometrioid n = 97	p value
Survival time [months] (mean ± SD)	88.5 ± 1.6	96.8 ± 2.5	0.46
Five year overall survival rate [%]	95	93	

SD — standard deviation

invasion and LVSI. Besides, there was another similar study conducted by Galic et al. [10] by obtaining data from the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) database. Advanced stages (FIGO stage III/IV) were more likely seen in mucinous histology of EC compared to endometrioid histology (12.9% vs 10.7%, p = 0.001). Although lymph node metastasis and advanced stages were determined in mucinous histology according

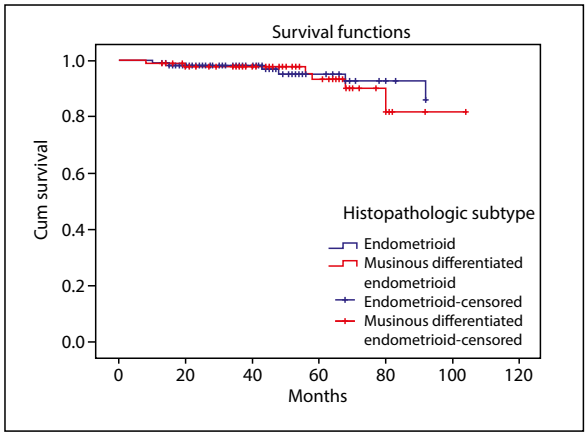

Figure 1. Survival curve of histopathologic subtypes

to both studies, survival rates were not affected by the histopathologic subtypes [10, 11]. In another study conducted by Duzguner et al. [8], eleven mucinous type of EC patients were investigated regarding prognostic factors and it was found that mucinous histology is associated with a better prognosis. In their study, only one patient had pelvic lymph node metastasis. Besides, 10 patients were in FIGO stage I, and only one patient was in stage IIIC1 disease. By contrast, another previous study claims that lymph node metastasis was higher in the mucinous type of EC compared with endometrioid type EC. The same study was not found any significant difference between two histopathologic types of EC regarding LVSI, deep myometrial invasion, and cervical involvement [12]**.** In the present study, lymph node metastasis, and the advanced stage had not a statistically significant difference between the two groups (6.8% vs 4.6%, p = 0.4; 5.5% vs 5%, p = 0.55; respectively). These results are similar to the results of a study conducted by Worley et al. [13]. Furthermore, Parameters that have a negative impact on the prognosis of EC including LVSI, endocervical involvement, and peritoneal washing cytology was similar between the mucinous differentiated EC and endometrioid EC similar to the results of the previous study conducted by Worley et al. [12] and Gungorduk et al [13].

The mean age of the patients was not significantly different in the current study. The mean age of the endometrioid histology without mucinous differentiation group was slightly older (59.3 vs 58.7 p = 0.62). However, Galic et al. [10] found that women older than 60 years were more likely to have mucinous differentiation compared to those younger than 60 (62.6% vs 56%, p = 0.0001). The myometrial invasion was not detected significantly different between groups (18.7% vs 17.4%, p = 0.23) as same as the study conducted by Musa et al. [11] and Gungorduk et al. [12] (17.1% vs 22%, p = 0.336). Recent studies showed that the survival rates of EC patients with mucinous differentiation were not significantly different from those without mucinous differentiation [10–13]. In the present study, the median survival time of the mucinous differentiated endometrioid EC and pure endometrioid EC were found similar (88.5 months vs 96.8 months, p = 0.46, respectively).

Besides, in a study conducted by Abdulfatah et al. [14], no difference was found between the mucinous differentiated endometrioid ECs and ECs without mucinous differentiation in terms of tumor stage, tumor grade, myometrial invasion, LVSI, lymph node involvement, cervical involvement, and overall survival. By contrast with, grade 3 tumors were found significantly higher in the endometrioid type EC in the present study (8.7% vs 1.4%, p < 0.01). The other results of the present study are similar to the results of the study of Abdulfatah et al. [14].

There are several limitations of this study. First of all, the present study was designed retrospectively. However, in our center clinical and pathological data of almost all patients were recorded to the hospital database at the first evaluation immediately with minimal data loss. Second, re-evaluation of the pathologic specimens for the present study was not performed. All the pathologic results belong to the first evaluation of the specimens by two pathologists who are especially focused on gynecology.

CONCLUSIONS

Pure mucinous differentiation was found associated with certain poor prognostic factors according to the previous studies [10, 11, 13]. However, poor prognostic factors including myometrial invasion, LVSI, lymph node metastases, endocervical involvement, peritoneal cytology, and the stage was not found associated with mucinous differentiation in the present study that investigates the influence of mucinous differentiation on endometrioid type EC. As a result of these, it can be said that prognosis does not seem to be affected by mucinous differentiation in endometrioid type EC patients.

Contributions

OI: manuscript writing, data management, data analysis. BS: project development and administration. SK: data collection and analysis. SE: data management and collection. MK: supervision, review of the manuscript. CU: data management, review of the manuscript.

Ethical approval

This study was carried out in consensus with our university´s ethics guidelines. The ethics committee approval was obtained for this study.

IRB approval

This study was carried out in consensus with our university´s ethics guidelines.

Conflict of interest

The authors declare no conflict of interest.

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Prenatal diagnosis and molecular cytogenetic characterization of Xp22.32p22.31 microduplication in a Chinese family

Weixin Cui[1*], Xi Li[2*], Yan Jin[3], Juan Zhang[4]

[1]*Department of Obstetrics, Maternal and Child Health Hospital of Hubei Province, Wuhan, Hubei, PR China*
[2]*Department of Gastroenterology, Peking University Shenzhen Hospital, Shenzhen, Guangdong, PR China*
[3]*Department of of child Health Care, Maternal and Child Health Hospital of Hubei Province, Wuhan, Hubei, PR China*
[4]*Department of Stomatology, Maternal and Child Health Hospital of Hubei Province, Wuhan, Hubei, PR China*
[*]these authors contributed equally to this work

ABSTRACT

Objectives: To explore the relationship between Xp22.32p22.31 microduplication and mental retardation identifiable by chromosomal G-banding and chromosomal microarray analysis (CMA).

Material and methods: Chromosomal G-banding, CMA, and physical and mental examinations were performed on four members of a Chinese family.

Results: The mother and one baby had the same microduplication (arr[GRCh37] Xp22.32p22.31(5970505-6075215)x2), and the baby had mental retardation.

Conclusions: Xp22.32p22.31 microduplication in males could cause mental retardation. Combination of NIPT, prenatal ultrasound, chromosomal G-banding and CMA has high accuracy in risk assessment for prenatal diagnosis.

Key words: prenatal diagnosis; Xp22.32p22.31 microduplication; chromosomal microarray analysis; mental retardation

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INTRODUCTION

Neuroligin 4 X-linked (NLGN4X) represents a critical X-linked postsynaptic scaffolding protein affecting excitatory synapsis development and maintenance, which is involved in multiple neuropsychiatric pathologies, including cognitive impairment, autism spectrum disorders (ASD), anxiety, attention deficit hyperactivity disorder (ADHD) and Tourette's syndrome. The NLGN4X gene is located on the X chromosome (Xp22.3). Chromosomal rearrangements, including duplications and deletions, could cause diverse genetic diseases [1].

Xp22.32p22.31 microduplication represents a common finding in clinical cytogenetics [2, 3]. The clinical significance of Xp22.32p22.31 microduplication remains unclear. We report a prenatal diagnosis case with a family in which the mother and one child had Xp22.32p22.31 microduplication, and this child further developed mental retardation. The mother was a carrier of the microduplication with normal phenotype. The above findings may help delineate the phenotypic features of Xp22.32p22.31 microduplication, suggesting a pathogenetic cause for mental retardation.

MATERIAL AND METHODS

Case report

This study had approval from the Ethics Committee of Maternal and Child Health Hospital of Hubei Province. The guardians of the children provided signed informed consent.

Corresponding author:
Juan Zhang
Department of Stomatology, Maternal and Child Health Hospital of Hubei Province, Wuhan, Hubei, PR China
e-mail: zhangjinhuahk@126.com

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In 2017, a 36-year-old, gravida 1, para 0 woman with diamniotic twin pregnancy was submitted to amniocentesis for cytogenetics and chromosomal microarray analysis (CMA) at gestation week 18 since noninvasive prenatal testing (NIPT) suggested high odds of sex chromosome aneuploidy. The parents had no family history of chromosomal aberrations or congenital anomalies. No sign of spontaneous abortion was found in early pregnancy. The totality of prenatal laboratory indexes were within respective normal ranges, and the patients had normal karyotypes.

Cytogenetic assessment of G-band metaphases obtained from amniotic fluid cells after culture was performed. Chromosome samples were prepared by the G-banding method (resolution, 300–400 bands). In total, 20 metaphases were examined for both fetuses, and karyotyping followed the ISCN 2016 nomenclature [4].

Chromosomal Microarray Analysis (CMA) of uncultured amniotic fluid cells was carried out with the Affymetrix CytoScan 750 K chip, which encompasses 550 k nonpolymorphic and 200 k SNP markers, with a probe spacing averaging 4.1 kb.

RESULTS

The karyotypes of both fetuses were 46, XY. The CMA result of fetus A was normal, but that of fetus B revealed a 105-kb chromosomal duplication, arr[GRCh37] Xp22.32p22.31 (5970505-6075215)x2 (Fig. 1). Then, CMA examination of the parents was performed. Parental CMA showed the father was normal, while the mother had a duplication of the same region as fetus B.

Ultrasound revealed no dysmorphisms or intrauterine growth restriction (IUGR). At 24 weeks of gestation, fetus A had an estimated fetal weight of 660 g, an abdominal circumference of 19.5 cm, a head circumference of 21.9 cm, a femur length of 4.2 cm and a fetal heart rate of 150 bpm; fetus B had an estimated fetal weight of 630 g, an abdominal circumference of 19.1 cm, a head circumference of 21.2 cm, a femur length of 4.0 cm and a fetal heart rate of 145 bpm [5]. The parents were comprehensively examined, and no overt anomalies were identified.

The parents were told that Xp22.32p22.31 microduplication in males could be associated with mental retardation in genetic counseling. However, they decided to continue the pregnancy. At pregnancy week 36, two male babies were delivered vaginally. After childbirth, both babies underwent comprehensive physical exams, which were unremarkable. At the age of two years, both babies underwent Gessell examination: baby A was normal (Development Quotient, DQ = 91), while baby B had mental retardation (DQ = 69). The IQs (Intelligence Quotients) of babies A and B were 105 and 73, respectively.

DISCUSSION

Xp22.32p22.31 microduplication could be tightly associated with both specific epilepsy genes and brain maturation events. However, discordant findings have been reported for the pathogenicity of Xp22.32p22.31 microduplication, which is considered in some instances to have unspecified function or to be benign [6], and in others to induce developmental abnormalities such as autism, cognitive impairment,

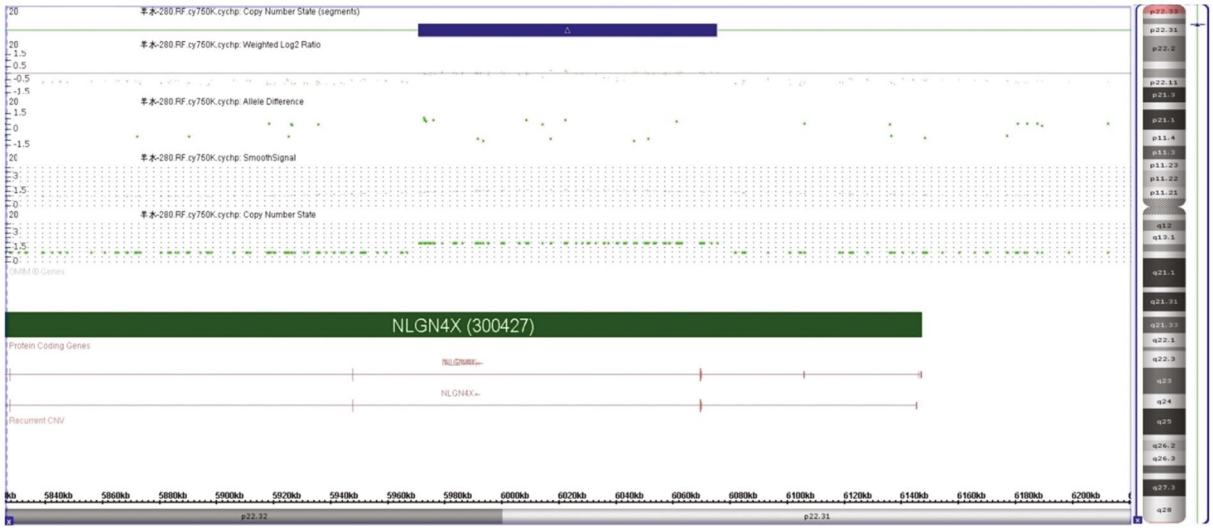

Figure 1. CMA revealed the Xp22.32p22.31 microduplication (arr[GRCh37] Xp22.32p22.31(5970505-6075215)x2)

hypotonia and eating disorders [7, 8]. Cognitive impairment and learning troubles in baby B suggest a probable pathogenic role for Xp22.32p22.31 microduplication.

Even if the clinical importance of this rearrangement remains debatable, its possible pathogenetic role has been recently suggested, although it may require further genetic factors [7]. The phenotype varies and is common in neurobehavioral diseases, with seizures found in 3–44% of cases [9, 10]. Cognitive impairment ranges between mild and severe mental retardation, with associations with autism spectrum disorder, speech and reading troubles, dyslexia, and attention deficit hyperactivity disorder in some affected individuals.

In addition, these phenotypic differences might be associated with further genetic modifiers, including decreased penetrance, distinct genes in the duplication region and position effect [11]. Additionally, X chromosome inactivation may also significantly affect the occurrence of this duplication [12].

As shown above four members of a family were examined, and one child had maternally inherited Xp22.32p22.31 microduplication associated with cognitive disability and mental retardation while his mother was asymptomatic. Xp22.32p22.31 microduplication in males could cause mental retardation and must be taken seriously.

Combination of NIPT, prenatal ultrasound, chromosomal G-banding and CMA has high accuracy in risk assessment for prenatal diagnosis [13].

Ethics approval and consent to participate

This study had approval from the Ethics Committee of Maternal and Child Health Hospital of Hubei Province. The guardians of the children provided signed informed consent.

Conflict of interest

The authors declare no conflict of interest.

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Transabdominal and transvaginal ultrasound assessment of cervical length — can transvaginal approach be avoided?

Andrzej Korniluk[1], Przemyslaw Kosinski[2], Piotr Dobrowolski[3], Miroslaw Wielgos[4]

[1]*Department of Obstetrics and Gynecology, Mazovian Voivodeship Hospital in Siedlce, Poland*
[2]*Department of Obstetrics, Perinatology and Gynecology, Medical University of Warsaw, Poland*
[3]*Department of Hypertension, Institute of Cardiology, Warsaw, Poland*
[4]*Department of Obstetrics and Gynecology, Medical University of Warsaw, Poland*

ABSTRACT

Objectives: This study aimed to compare transabdominal (TA) and transvaginal (TV) ultrasound assessment of cervical length during pregnancy and to establish cervical length above which transvaginal measurement is not necessary.

Material and methods: Cervical length was measured using TA and TV method in the first (11 + 0–13 + 6 weeks), the second (20 + 0–21 + 6 weeks) and the third trimester (28 + 0–31 + 6 weeks) in 250 women with singleton pregnancy and low risk for preterm birth.

Results: If the cervical length measured in the second trimester of pregnancy with transabdominal approach is ≥ 28.5 mm and ≥ 30.5 mm in the third trimester, it can be assumed with 100% sensitivity the cervical length measured with transvaginal method will be > 25 mm. Transabdominal cervical length measurement in the second and third trimester allows 89% and 65% of patients, respectively, to avoid transvaginal scan.

Conclusions: Second and third trimester screening by transabdominal cervical length measurements in a group of pregnant women with low risk for preterm birth is useful to determine which patients require transvaginal measurement.

Key words: cervical length measurement; transabdominal ultrasonography; transvaginal ultrasonography; preterm delivery

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INTRODUCTION

Preterm delivery invariably remains the biggest, unsolved problem of perinatal medicine [1]. It is estimated that the problem of preterm delivery affects 9.6% of births worldwide. Despite the huge progress that has been made in recent decades, the incidence of preterm births has not been significantly reduced [1]. However, a number of actions are undertaken to not only implement medical procedures or drugs that reduce the number of preterm births [2], but also to identify a group of patients at high risk of this complication. An important step towards achieving this goal was the introduction of ultrasound cervical length assessment and new biochemical methods [3]. Studies have confirmed that the shorter the cervix, the greater the risk of preterm birth [4] and this relationship is further compounded if there were preterm births in the past and the mother is at an advanced age [5].

Transvaginal cervical length measurement at 18–24 weeks of singleton pregnancy is currently considered the best way to assess the risk of preterm delivery. This method has been well described in published studies and has the recommendations of most scientific societies in the world [6, 7]. Nevertheless, the transabdominal ultrasound assessment of cervical length also seems to correlate well with transvaginal measurements. In the United States in 2015, a national survey on the frequency of using cervical length screening in the general population showed that 32% of pregnant women did not have a cervical length measurement. Transvaginal cervical length measurement was performed in 32% of pregnant women and was used

Corresponding author:
Przemyslaw Kosinski
Department of Obstetrics, Perinatology and Gynecology, Medical University of Warsaw, Poland
e-mail: pkosinski@wum.edu.pl

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mostly in clinical sites. However, transabdominal cervical screening was performed most often (36%) [8]. Therefore, it seems advisable to develop an effective population screening model for preterm delivery - using both transvaginal and transabdominal measurements. Widespread cervical length screening in a low-risk population is an important element in preventing preterm delivery, as confirmed by randomized clinical trials that showed a 45% reduction in the risk of preterm delivery in women with the short cervix after vaginal progesterone administration [2, 9]

The objective of this study was to compare methods of transabdominal and transvaginal cervical length measurement during routine ultrasound scans in the first trimester (11 + 0–13 + 6 weeks), in the second trimester (20 + 0–21 + 6 weeks) and in the third trimester (28 + 0–31 + 6 weeks) of pregnancy in a population at low risk of premature delivery. An attempt was made to correlate the cervical length by transabdominal scan which can predict a transvaginal cervical length of 25 mm and less.

Objectives

This study aimed to compare transabdominal (TA) and transvaginal (TV) ultrasound assessment of cervical length during pregnancy and to establish cervical length above which transvaginal measurement is not necessary.

MATERIAL AND METHODS

From April 2016 to August 2018, the study covered two hundred and fifty (n = 250) women with singleton pregnancy. Each patient underwent three ultrasound scans: in the first trimester (11 + 0–13 + 6 weeks), in the second trimester (20 + 0–21 + 6 weeks) and in the third trimester (28 + 0–31 + 6 weeks). In addition, during each scan, transabdominal and transvaginal cervical length measurements were made after emptying the bladder. The study population was a group of pregnant Caucasian women without a positive history of premature delivery. The study inclusion criteria were live singleton pregnancy and no symptoms of threatening preterm delivery. Patients qualified for the study received a questionnaire to fill with questions regarding demographic data and obstetric history. The results regarding delivery and the newborn are derived from post-delivery medical records. All ultrasound scans were performed using a Voluson S6 apparatus (GE Healthcare, Kretztechnik, Austria), convex C1–5RS head, 2-5 MHz, and E8C–RS vaginal head, 4-10 MHz by one operator certified by the Fetal Medicine Foundation (FMF) (*Certificate of Competence in Cervical Assessment*). Transvaginal cervical length measurement was performed in accordance with the FMF guidelines [10], while transabdominal cervical length measurement was performed after modification of the FMF guidelines according to Lisa Saul [11]. The scoring of cervical visualization was based on the visualization of the landmarks described (no visualization, moderate visualization or excellent visualization). The image was considered sufficient for evaluation if at least three landmarks were revealed. The optimal image is one in which four or more landmarks were successfully visualized. (Fig. 1).

Patients were asked to empty their bladders before the study. In order to obtain precise results of transabdominal cervical length measurement, in addition to visualizing at least three landmarks, it was necessary to visualize the internal orifice of the cervix.

Statistical analysis

For normal distribution, the values of variables between the groups were compared by Student's t-test and one-way ANOVA with Duncan's post-hoc test, and for non-normalized variables, by non-parametric analysis of variance tests: Mann-Whitney-Wilcoxon or Kruskal-Wallis. The correlation

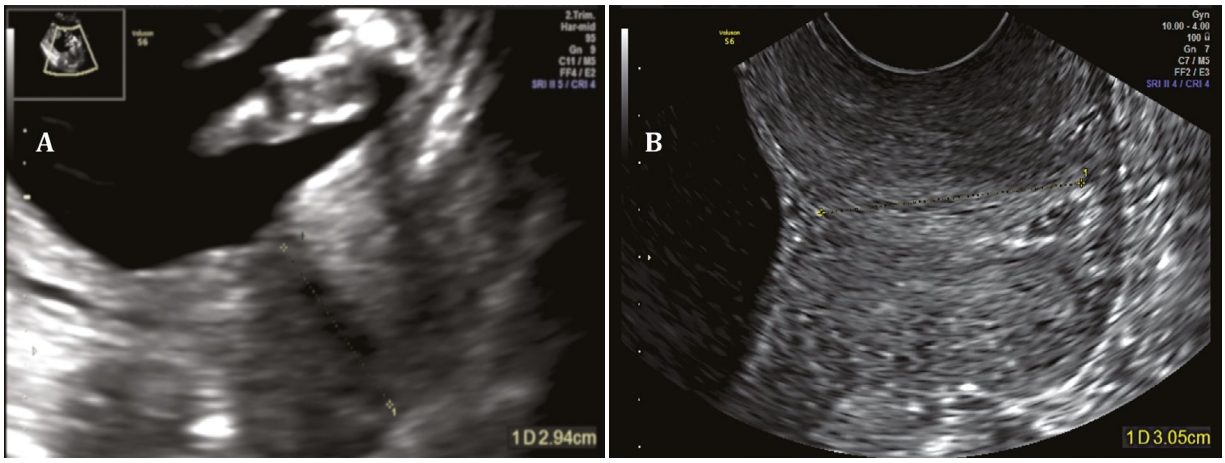

Figure 1. Cervical length measurement in the same patient taken with two different methods at 20 weeks of gestation; **A.** Transabdominal measurement (cervical length: 29.4 mm); **B.** Transvaginal measurement (cervical length: 30.5 mm)

study was conducted using Pearson or Spearman correlation analysis. The receiver operating characteristic (ROC) logistics curve was used to evaluate the usefulness of transabdominal cervical length measurement in recognizing a cervical length shorter than 25 mm by transvaginal scan. The area under the area under curve (AUC) with the confidence interval and coordinates of the ROC curve points was calculated.

Sensitivity, specificity as well as positive and negative predictive values for excluding a cervical length less than 25 mm were calculated for selected cut-off points of cervical length measured by transabdominal scan. The p value < 0.05 was adopted as statistically significant. The SPSS 15.0 statistical package was used for the calculations.

RESULTS

The study included 250 patients qualified in the first trimester of pregnancy. Two patients were excluded from the study due to fetal anatomical defects at the later stages of pregnancy. Three patients had a miscarriage after the 12th week of pregnancy (study group in the second trimester n = 245). Moreover, between the second and third trimester, measurement data were not collected in five patients (study group in the third trimester n = 240). The median age at study enrolment was 30 years. The median of body mass index (BMI)in the study group was 23.57. The demographic characteristic of the study population is described in Table 1.

Cervical length in transabdominal (TA) and transvaginal (TV) measurements in three trimesters of pregnancy is presented in Table 2.

Analysis of the area under the ROC curve showed that the values of cut-off point of the cervical length measured by transabdominal scan in the second trimester of pregnancy (28.5 mm) are characterized by high sensitivity in excluding a cervical length < 25 mm measured by transvaginal scan (area under the ROC graph 0.995) (Fig. 2). The optimal balance was found between high sensitivity (100%) and specificity for the cut-off point of 28.5 mm in transabdominal measurement.

Sensitivity and specificity as well as the positive and negative predictive value of the cut-off point of cervical length measured by transabdominal scan in the second trimester of pregnancy (> 28.5 mm) in predicting a cervical length < 25 mm measured by transvaginal scan (Tab. 3).

Analysis of the area under the ROC curve showed that the values of cut-off point of the cervical length measured by transabdominal scan in the third trimester of pregnancy (> 30.5 mm) are characterized by high sensitivity in excluding a cervical length < 25 mm measured by transvaginal scan (area under the ROC graph 0.995) (Fig. 3). The optimal balance was found between high sensitivity (100%) and specificity for the cut-off point of 30.5 mm in transabdominal measurement. Based on the analysis of individual points of the ROC curve, the cut-off point of cervical length meas-

Table 1. Demographic characteristic of the study population

	Mean ± SD	Median	IQR	Range
Body weight [kg]	68.3 ± 14.0	65	53.2–76	41.6–119.8
Height [cm]	166.7 ± 6.2	166	163–171	154–182
Age [years]	30.9 ± 4.1	30	27–33	21–41
BMI	24.6 ± 4.7	23.5	21.2–27.3	17.1–41.1

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

Table 2. Cervical length measurements made by transabdominal (TA) and transvaginal (TV) scan

Number of patients	n = 248		n = 245		n = 240	
CL [mm]	1st trimester		2nd trimester		3rd trimester	
TA/TV	TA	TV	TA	TV	TA	TV
Min	**28.0**	25.4	18.0	15.0	12.0	6.3
5 centile	30.2	31.0	28.0	28.3	25.9	24.0
25 centile	35.0	36.0	33.0	34.0	30.0	32.0
50 centile	38.3	38.8	36.0	38.3	34.0	35.0
75 centile	40.0	42.0	39.0	40.5	37.4	39.0
95 centile	43.0	46.0	42.0	44.0	41.0	42.0
Max	49.0	53.0	48.0	50.0	54.0	46.4
Mean (SD)	37.7 (3.8) *	38.8 (4.6) *	35.8 (4.4) **	37.2 (5.2) **	33.7 (4.9) ***	34.4 (5.6) ***

TA — transabdominal cervical length measurement; TV — transvaginal cervical length measurement; CL — cervical length (mm); SD —s tandard deviation; *TA vs TV in the first trimester — p < 0.0001; **TA vs TV in the second trimester — p < 0.0001; ***TA vs TV in the third trimester — p = 0.09

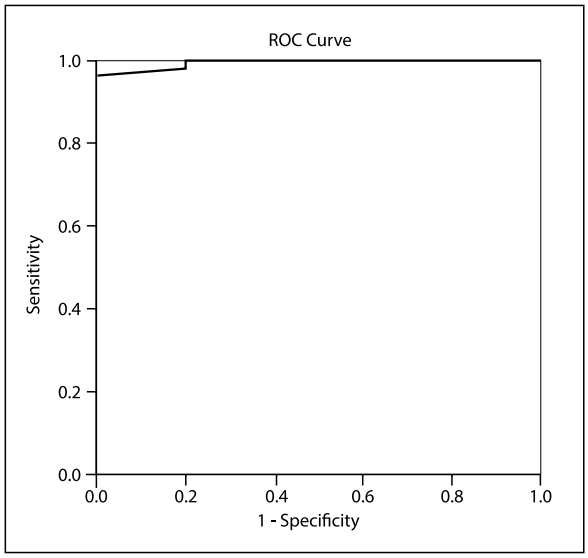

Figure 2. The receiver operating characteristic (ROC) curve graph for transabdominal cervical length measurement in excluding a cervical length less than 25 mm measured by transvaginal scan in the second trimester of pregnancy (AUC = 0.995)

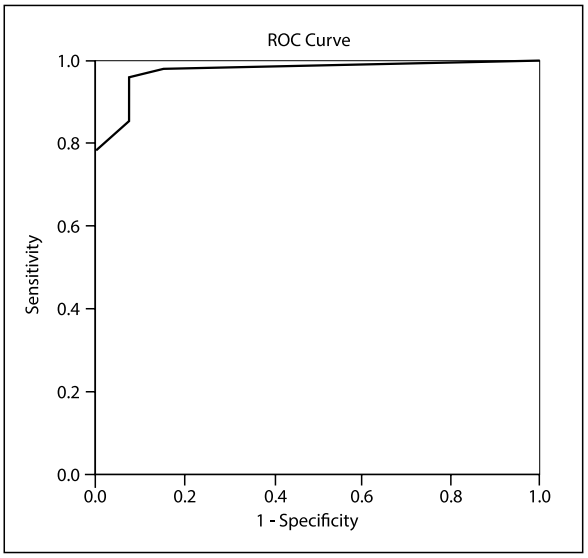

Figure 3. The receiver operating characteristic (ROC) curve graph for transabdominal cervical length measurement in excluding a cervical length less than 25 mm measured by transvaginal scan in the third trimester of pregnancy (AUC = 0.978)

Table 3. Sensitivity and specificity as well as the positive and negative predictive value of the cut-off point of cervical length measured by transabdominal scan in excluding a cervical length less than 25 mm measured by transvaginal scan in the second trimester of pregnancy

	Cervical length (TA) < 28.5 mm
Sensitivity [%]	100
Specificity [%]	96.5
PPV [%]	38.5
NPV [%]	100

PPV — positive predictive value; NPV — negative predictive value

Table 4. Sensitivity and specificity as well as the positive and negative predictive value of the cut-off point of cervical length measured by transabdominal scan in excluding a cervical length less than 25 mm measured by transvaginal scan in the third trimester

	Cervical length (TA) < 30.5 mm
Sensitivity [%]	100
Specificity [%]	78
PPV [%]	22.4
NPV [%]	100

PPV — positive predictive value; NPV — negative predictive value

ured by transabdominal scan in the third trimester of pregnancy (30.5 mm) was chosen, characterized by high sensitivity in predicting a cervical length less than 25 mm in transvaginal measurement.

Sensitivity and specificity as well as positive and negative predictive value of the cut-off point of cervical length measured with transabdominal method in predicting a cervical length < 25 mm measured with transvaginal scan (Tab. 4).

DISCUSSION

Only effective population screening, which will not be limited to pregnant women at high-risk of premature delivery, but will also include pregnant women at low-risk of premature delivery, can have a significant impact on reduction in the percentage of preterm births, because as much as 93% of all preterm births occur in this group [12]. Transvaginal scan is uncomfortable, and many patients decline this scan. In this study we aimed to measure cervix transabdominally and tried to find out a value which would predict a cervical length of 25 mm by transvaginal scan, as a cervical length of 25 mm is predictive of preterm birth.

Based on the results obtained, it can be assumed that if transabdominal cervical length measurement in the second trimester of pregnancy is above 28.5 mm, then with 100% sensitivity a cervix shorter than 25 mm can be excluded in transvaginal scan. This allows 89% of patients to avoid transvaginal ultrasound. Nevertheless, to ensure high sensitivity of transabdominal screening measurement, in 11% of patients it will be necessary to perform transvaginal ultrasound scan.

If transabdominal cervical length measurement in the third trimester of pregnancy is above 30.5 mm, then with 100% sensitivity a cervix shorter than 25 mm can be excluded in transvaginal scan. Transabdominal cervical length measurement in the third trimester allows 65% of patients to avoid transvaginal ultrasound to exclude a cervix shorter than 25 mm. To ensure a high sensitivity of transabdominal

Table 5. A summary of data comparing transabdominal (TA) and transvaginal (TV) cervical length measurement in studies by various authors

Study author	GA [week]	Size of the study group [CL TV < 25 mm]	Bladder condition in screening CL–TA	Assessment TA/TV blinded	Cut-off value for TA method	Mean CL TA [mm]	Mean CL TV [mm]	CL TA longer/ shorter than TV	TA–TV difference [mm]
Andersen et al. 1990 [19]	< 30	125	full	no	–	46.8	40.9	longer	5.9
Andersen et al. 1991 [20]	6–40	186	empty	no	–	43.7	41.6	longer	2.1
To et al. 2000 [21]	22–24	149	full	–	–	34	37	shorter	–3
Saul et al. 2008 [11]	14–34	191 (14)	empty	yes	< 30	35.7	36.1	similar	–0.4
Stone et al. 2010 [22]	18–20	203	empty	no	–	36.6	39.1	shorter	–2.5
Hernandez-Andrade et al. 2012 [23]	6–39	220 (20)	full	yes	< 25 < 30	34.6	34.8	similar longer	–0.2
Fridman et al. 2013 [13]	18–24	1217 (76)	full empty	no no	≤ 26 ≤ 36	33.5	36.1	shorter	–2.6
Roh et al. 2013 [24]	20–30	475	empty	no	< 27	38.8	39.3	similar	–0.5
Marren et al. 2014 [18]	18–20	198 (13)	full empty	no no	< 30 < 25	33.3 33.7	39.2 33.1	longer similar	6.0 0.6
Pandipati S et al. 2015 [14]	18–23	1580	empty full	no	≤ 35 ≤ 36	39.8 39.0	41.8 41.2	shorter shorter	–2.0 –2.2
Peng C R et al. 2015 [17]	20–24	174	empty	no	< 29	36.0	37.6	shorter	–1.6
Westerway et al. 2015 [15]	16–41 16–23 24–35 > 36	491 335 139 17	full	no	< 25	33 33.6 32.1 27.9	35 36.2 33.1 25.6	shorter shorter shorter longer	–2.0 –2.7 –1.0 2.3
Rhodes et al. 2016 [16]	17–23	404	empty	no	≤ 35	38.5	42.3	shorter	–3.8
Cho et al. 2016 [25]	20–29	771	empty/full	no	–	37.8	38.2	similar	–0.4
Puttanavijarn et al. 2017 [26]	16–23	160	empty	no	< 30	36.4	41.2	shorter	–4.8
Korniluk 2020	11–14 20–22 28–32	250 247 (4) 242 (10)	empty	no	< 25	37.7 35.8 33.7	38.8 37.2 34.4	shorter shorter shorter	–1.1 –1.4 –0.7

GA — gestational age (weeks); CL — cervical length (mm); TV — transvaginal scan TA — transabdominal scan

screening, in 35% of patients it will be necessary to perform a transvaginal ultrasound scan in the third trimester.

The values of the calculated cut-off points are similar to those presented in other publications, where the described range of values is between 29 mm and 36 mm [13–17]. Only in the study by Marren et al. [18], due to the inability to achieve optimal sensitivity (15.4%) and specificity (93.2%), the authors were unable to determine the cut-off point of cervical length measured by transabdominal scan for predicting a cervical length below 25 mm measured by transvaginal scan.

In the study group, the mean cervical length of the cervix measured with the transabdominal method was consistently smaller than those measured by transvaginal scan (Tab. 1). This observation is also consistent with other studies (Tab. 5).

Some authors have found that there are no statistically significant differences between the cervical length measured by transvaginal and transabdominal scan [11, 24, 25]. The longer cervix in transabdominal scan compared to transvaginal scan was observed when measuring with a full bladder (Tab. 5), [18, 19] and in the third trimester

over 36 weeks of pregnancy [15], as well as with a short cervix (< 25 mm) (Tab. 2) [15, 23, 27].

In the study group, the greatest cervical shortening was observed in the third trimester of pregnancy both in transvaginal measurement (10.8%) and in the transabdominal measurement method (6.2%). In the literature, a considerable shortening of the cervix (even above 20 mm) is usually observed after 32 weeks of pregnancy [28] and is usually associated with the maturation of the vaginal part of the cervix for delivery. The data obtained are consistent with the study results by other authors [15, 29, 30]. There is also evidence of a linear cervical shortening after 24 weeks of pregnancy, with the cervical length decreasing by 0.74 mm per week in transvaginal assessment [15].

The study also found that the cervical length showed minimal changes between the first trimester and the second trimester in both transabdominal (5%) and transvaginal (4.3%) scan, which is confirmed by most literature data [30, 31]. For this reason and due to the lack of patients in the first trimester with the cervix shorter than 25 mm, no ROC curves were determined for the study between 11–13 weeks of pregnancy.

The study group also showed that cervical shortening during the three trimesters of pregnancy is greater in transvaginal assessment (15.1%) than in the transabdominal measurement method (11.2%), due to overestimation of the cervical length by transabdominal scan in the third trimester. These observations are consistent with reports from the literature [15].

In the studies by other authors, the percentage of patients who need transvaginal reassessment of the cervix differs and depends on the visualization of the cervix and the percentage of short cervix found by transabdominal ultrasound in each population [13, 14, 16, 25].

Numerous studies have shown that progesterone administration effectively reduces the risk of spontaneous premature delivery in women with the short cervix in the second trimester of pregnancy [2, 9, 32]. However, the percentage of women meeting the criteria for implementing this prevention in the general population is relatively small [4, 33, 34]. Identification of these women requires a routine transvaginal cervical length measurement during fetal examination in the second trimester, which increases the time and costs of the examination and creates additional discomfort for the patient. Considering the high costs associated with preterm delivery and the savings obtained with its prevention, it has been found that the common transvaginal measurement of cervical length is economically justified in groups at high-risk of preterm delivery, but has limited rationale in groups at low-risk of preterm delivery [35]. However, since the majority of preterm deliveries occur in the low-risk group, it seems appropriate to use the transabdominal measurement of cervical length during routine ultrasound scans in the second trimester of pregnancy, and to use a cut-off point below which the risk of a short cervix (< 25 mm) is extremely low. Doing so would increase the number of screenings carried out with greater acceptance by pregnant women and ensure more effective prevention of premature delivery without increasing the cost of the scan [13].

CONCLUSIONS

Second and third trimester screening by transabdominal cervical length measurements in a group of pregnant women with low risk for preterm birth is useful to determine which patients require transvaginal measurement.

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Statement of ethics

All procedures performed in the study were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

The study protocol has been approved by the Bioethics Committee of Medical University of Warsaw (Statement No: KB 56/2017).

Authors contribution

AK: data acquisition, conception of the work, manuscript writing; PK conception of the work, statistical analysis, manuscript writing, critical review; PD: statistical analysis; MW: conception of the work, statistical analysis; critical review.

Conflict of interest

The authors declare no conflict of interest.

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Our clinical experience in pelvic magnetic resonance imaging with vaginal contrast

Fatma Öztürk Keleş[1], Inan Korkmaz[1], Esin Dogan[2], Sibel Hakverdi[2], Kenan Dolapcioglu[3], Sinem Karazincir[1]

[1]*Department of Radiology, Faculty of Medicine, Hatay Mustafa Kemal University, Antakya, Turkey*
[2]*Department of Pathology, Faculty of Medicine, Hatay Mustafa Kemal University, Hatay, Turkey*
[3]*Department of Obstetrics and Gynecology, Faculty of Medicine, Hatay Mustafa Kemal University, Hatay, Turkey*

ABSTRACT

Objectives: Magnetic resonance imaging (MRI) is an important modality for pelvic imaging. Vaginal distension is provided by the use of vaginal contrast in pelvic MRI, and it plays an important role in staging especially cervical and vaginal cancer. The aim of this study is to show whether the use of vaginal contrast material contributes to the diagnosis in pelvic examination.

Material and methods: Between October 1, 2016 and December 30, 2020, a total of 57 patients who underwent pelvic magnetic resonance imaging with vaginal contrast in the radiology clinic were included in the study and evaluated retrospectively.

Results: Cervical cancer was detected in 38 of the 57 patients included in the study, and when the vaginal pre- and post-contrast staging of the patients was performed, the pre-contrast stage was found to be high in six patients (15%). Eight of 38 patients diagnosed with cervical cancer underwent surgery. When the pathological and radiological staging of the patients who underwent surgery were compared, they were 100% compatible.

Conclusions: The use of vaginal contrast material increases the diagnostic value of MRI in various pelvic pathologies, especially in cervical cancer staging.

Key words: vaginal contrast; magnetic resonance imaging; ultrasound gel; pelvic pathologies

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INTRODUCTION

Imaging plays an important role in the evaluation of gynaecological pathologies. Magnetic resonance imaging (MRI) is a non-invasive imaging technique with high spatial and contrast resolution and is the most reliable diagnostic imaging method in the evaluation of pelvic pathologies. MRI is especially useful in evaluating the spread of the disease in gynaecological diseases. In addition, some studies have shown that creating vaginal opacification with intraluminal contrast material increases the diagnostic value and performance of MRI [1–3]. Vaginal opacification is important in evaluating parametrium and fornix invasion in cervical cancer and vaginal cancer, since the vagina collapses in the normal anatomical position [1].

Various liquid and solid materials have been used to visualize the inner contour of the vaginal wall to reduce false-negative MRI results. Solid materials such as tampons are more uncomfortable than liquid ones. They can also cause distension, deformation of surrounding structures, artifacts, and deterioration of image quality. Liquid ones such as ultrasound gel provide better imaging qualities than solid materials by providing vaginal distension without causing deformation of surrounding structures and creating hyperintensity in T2-weighted (T2W) sequences [1, 4, 5]. The sonographic gel is the most preferred intraluminal contrast agent due to its easy availability, well-tolerability, high viscosity, and absence of backflow during intravaginal administration [4].

In this study, the aim is to demonstrate whether the use of vaginal contrast material contributes to the diagnosis in pelvic imaging, especially in cancer staging, based on our own clinical experience.

Corresponding author:
Fatma Öztürk Keleş
Department of Radiology, Faculty of Medicine, Hatay Mustafa Kemal University, Antakya, Turkey
e-mail: fatma4083@hotmail.com

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MATERIAL AND METHODS

Between October 1, 2016 and December 30, 2020, a total of 57 patients referred to the obstetrics and gynaecology outpatient clinic of our hospital with a preliminary diagnosis of cervical pathology and underwent pelvic magnetic resonance imaging with vaginal contrast in the radiology clinic were included in the study and evaluated retrospectively.

MRI technique

Images of all patients were taken with an abdominal coil in the 1.5 T MRI system (Philips Ingenia; Philips Medical Systems, Best, Netherlands) available in our unit. Routine imaging protocol includes sagittal-axial and coronal T2W without vaginal contrast, sagittal and axial T2W with vaginal contrast, axial VISTA, non-fat suppressed and suppressed T1W, axial-sagittal and coronal fat-suppressed T1W with intravenous contrast. Axial images are obtained parallel to the long axis of the cervix.

Vaginal contrast protocol

After the standard pelvic MRI was done, 50 ml of ultrasound gel was applied into the vagina with a foley catheter by a gynaecologist without changing the patient's position. After the gel application, the MRI scan was continued.

Evaluation of images

The images obtained were evaluated retrospectively by a radiologist with seven years of abdominal and pelvic imaging experience with the Osirix MD (Pixmeo Labs, Geneva, Switzerland) software on the imaging monitors in our unit. Images before and after the gel were evaluated for the presence of malignancy, 1. tumour size if any, 2. parametrial invasion, 3. fornix and vaginal wall extension, 4. pelvic wall, bladder, and rectum invasion. Cervical cancer staging was performed according to the staging guideline published by the International Federation of Gynecology and Obstetrics (FIGO) in 2009, and cervical cancer staging for patients after 2018 was performed according to FIGO 2018.

RESULTS

The ages of the 57 patients who underwent pelvic MRI with vaginal contrast were between 31 and 81 years, with a mean age of 55.63 ± 12.45 years. Based on radiological imaging, 38 of 57 patients were diagnosed with cervical cancer and four with endometrial cancer (Fig. 1). Of the patients, six were previously diagnosed with cervical cancer and four of these patients were control patients after radiotherapy and two were control patients after conization, and no pathologies were detected in control imaging. Radiologically, the cervix was normal in seven patients. Biopsy was not performed in one of the normal patients, chronic cervicitis was detected in two patients, and the cervix was normal in four patients. Pathology results were available for all patients after the treatment, except for control patients (number of patients: 6) and one of the patients who were considered normal. Suspected cervical cancer was diagnosed in one of the patients on pelvic MRI, and the biopsy result was chronic cervicitis. In one patient, there was vaginal prolapse of a myoma uterine. In this case, the cervix could not be evaluated due to the uterine myoma. In this patient, the result of the cervical biopsy was cervical cancer. Eight of 38 patients diagnosed with cervical cancer underwent surgery, and the biopsy results of other patients have confirmed their diagnosis of cervical cancer. When the pathological and radiological staging of the patients who underwent surgery were compared, they were 100% compatible. Thirty patients diagnosed with cervical cancer were receiving treatment in the oncology clinic because they were clinically-radiologically Stage IIA2 and higher. When the images of patients with cervical cancer before and after the gel are evaluated in terms of staging, images before gel lead to overdiagnosis in 15% (6 patients) of the patients, increasing the stage of the patients (Tab. 1).

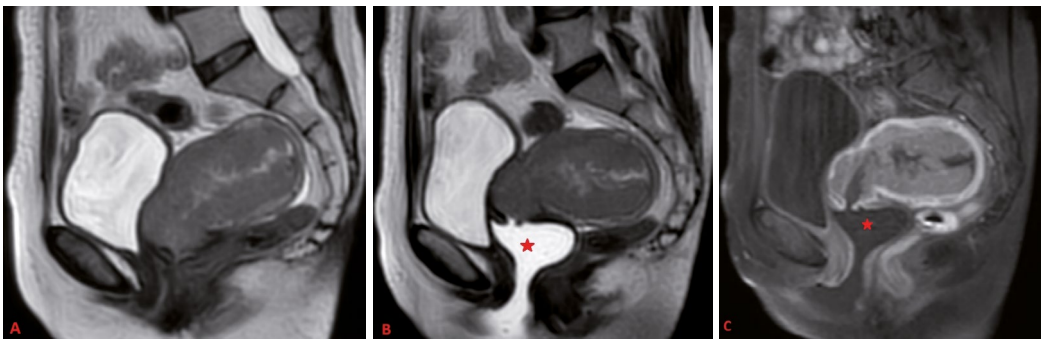

Figure 1. Endometrial cancer. Before vaginal gel (**A**), after vaginal gel (**B**) sagittal T2W and after vaginal gel with post-contrast sagittal T1W MRI (**C**). Vaginal and cervical anatomical structures and cervical extension of endometrial cancer can be seen more clearly in after gel images (asteriks: vajinal ultrasound gel)

Table 1. Patients whose pre-gel and post-gel stages do not match in cervical cancer cases

Number of patients	Pre-gel staging	After-gel staging	Pathological staging
1	IIIB	IIA	
1	IIB	IB1	IB1
1	IIIA	IIA1	
2	IIB	IB2	IB2
1	IIB	IIA1	
6	Total		

Table 2. Pelvic pathologies detected on pelvic magnetic resonance imaging with vaginal contrast

Number of patients	Radiological diagnosis	Pathological diagnosis
38	Cervical cancer	Cervical cancer
4	Endometrial cancer	Endometrial cancer
1	Cervical cancer	Chronic cervicitis
1	Vaginal prolapsus of a myoma uterine	Vaginal prolapsus of a myoma uterine, cervical cancer
7	Normal	Chronic cervicitis (2), normal (4)
4	After radiotherapy	
2	After conization	
57	Total	

In Table 2, the radiological and pathological diagnoses of the patients who underwent pelvic MRI with vaginal contrast.

DISCUSSION

In recent studies, the use of luminal contrast material in pelvic region MRI has been employed in cervical cancer staging, vaginal cancer, endometriosis patients, and distal rectal cancer staging [1, 4, 6, 7].

Cervical cancer is the 4th most common type of cancer in women and constitutes 6.6% of all cancers [8]. Clinical staging is limited in identifying tumour size, parametrial invasion, and nodal status, which have an important role in determining the overall treatment protocol and prognosis. Imaging plays an important role in staging. FIGO is the basic staging system for the prognostic classification of patients with cervical cancer and planning the treatment strategy. It was last updated in 2018 [9, 10]. Early-stage cervical cancer (IA, IB, and IIA1) is treated with conization, radical hysterectomy, and lymphadenectomy, while radiotherapy is another option in IB2 and IIA1. In the locally advanced stage (IIA2 and higher), platinum-based chemotherapy and radiotherapy are applied simultaneously. MRI has an important role in patient selection for fertility-sparing treatment in the form of radical trachelectomy [11]. This procedure consists of resection of the cervix, parametria, vaginal cuff, and cerclage of the isthmus. Patients are eligible for this treatment if they have tumour confined to the cervix (stage I disease), with no extension to the uterine body, and this evaluation can be accurately made using MRI. MRI has an accuracy rate of 78% in detecting tumours [12]. In the study by Shaker et al. [5], the detection rate of cervical cancer was 70% in MRI without gel, whereas this rate increased to 95% when the intravaginal gel is used. Parametrial invasion causes the patient to lose the chance of surgery. Studies have shown that parametrial invasion is evaluated better with vaginal opacification [1, 4]. The tumour stage may appear higher in MRI due to oedema, inflammation, or compression [13]. In our study, the majority of the cases consisted of cervical cancer cases, and when the images of these cases that were obtained before and after the gel were evaluated, over-stage cancer was detected in six patients (15%) based on before gel images. In these patients, the stage was increased, considering that there was parametrial invasion in the before gel images.

In the normal anatomical position, since the vaginal walls face each other and the vaginal fornix is found collapsed around the cervix, it is difficult to draw the borders of the vagina and cervix and to determine the tumour contours in MRI. Vaginal contrast material shows high signal intensity on T2W MRI and provides a clear assessment of the inner contours of the cervix, vaginal wall and fornix (Fig. 2, 3). In addition, it is useful in evaluating the vaginal and parametrial invasion of the tumour by distending the vaginal lumen and separating the vaginal walls from each other [1, 5]. Tumour staging is important in deciding the patient's treatment protocol.

In the literature, various solid and liquid materials have been used to provide vaginal distension in pelvic MRI examinations. Solid materials such as tampons can cause deformation of surrounding structures and lead to air artefacts. In addition, due to their stiffness, they cannot completely fill all anatomical spaces [14]. On the other hand, water-based composite materials completely fill the vaginal lumen and provide a clear evaluation of the vagina and cervix contours without causing anatomical distortion. These materials also provide high signal intensity in T2-weighted sequences and provide more comfort to the patient than other materials [15]. In patients with pelvic cancer, as liquid material, Van Hoe et al. [2] used barium, water and maltodextrin/calcium lactate mixture, Akata et al. [1] used barium and saline mixture, and Young et al. [3] and Atcı et al. [4] used ultrasound gel. In these studies, it was determined that the use of vaginal contrast increases the diagnostic value. In a meta-analysis by Unlu et al. [15] investigating the effectiveness of MRI with vaginal contrast in pelvic pathologies, they found that the use of vaginal contrast increased the diagnostic value by 54%. The sonographic gel was used not only in the gynaecological examination

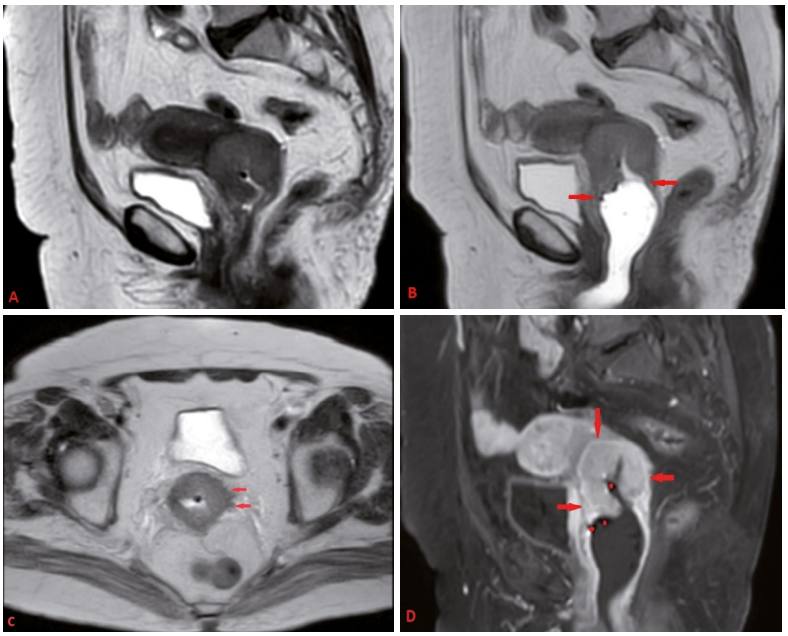

Figure 2. Stage IIB cervical cancer. Before vaginal gel sagittal T2W image (**A**). After vaginal gel sagittal T2W MR (**B**), anterior and posterior fornix involvement is better evaluated (red arrows). Axial T2W (**C**), tumor is seen to invade the parametrium (red arrows). Tumor borders are clearly observed on sagittal post-contrast T1W image (**D**). (asterix: air bubbles in intravaginal gel)

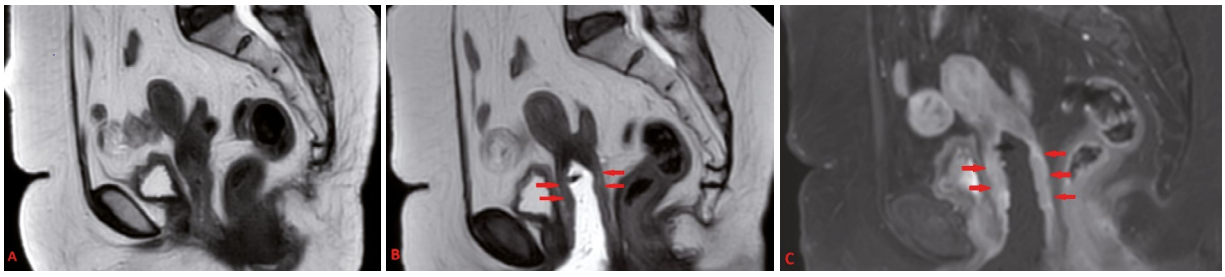

Figure 3. Cervical cancer. While the vagina collapsed in the sagittal T2W image before vaginal gel (**A**), the anterior-posterior vaginal wall thickness (red arrows) showing invasion is seen in the sagittal T2W image after vaginal gel (**B**). Vaginal wall contrast is seen in sagittal T1W (**C**)

but also in rectal examination. In the study of Palmucci et al. [7], in which they performed apparent diffusion coefficient (ADC) measurements before and after ultrasonographic gel for the staging of patients with rectal cancer, a positive correlation was found between the ADC values obtained after the gel, although the cause could not be determined. In another similar study, a statistically significant difference was found in intravoxel incoherent motion parameters of rectal tumours before and after the gel in patients in whom rectal distension was achieved with sonographic gel [16]. In a study of 63 patients with deep endometriosis, the use of gel increased the sensitivity and specificity of pelvic MRI when transvaginal ultrasonography, non-gel pelvic MRI, and gel pelvic MRI were compared in terms of detecting endometriosis [6].

Various guidelines, such as those of the European Society of Urogenital Radiology, European Society of Gastrointestinal and Abdominal Radiology, and American College of Radiology define vaginal opacification on pelvic MRI as optional, especially for the diagnosis of gynaecological disorders, including vaginal and cervical cancers [17, 18]. We routinely use vaginal gel in patients presenting with a preliminary diagnosis of cervical cancer in our clinic.

The limitations of our study are that it is retrospective, has a low variety of pelvic pathology, and involves the use of sonographic gel alone as a vaginal contrast material.

CONCLUSIONS

The use of vaginal contrast material increases the diagnostic value of MRI in various pelvic pathologies, especially in cervical cancer staging and post-op treatment follow up.

Contribution to authorship

FOK and IK conducted literature search and provided study design. FOK and İK examined the radiological images. ED

and SH examined the pathological evaluation. KD examined the gynecological examination. FOK wrote the manuscript and, SK reviewed it. All authors read and approved the final manuscript.

Details of ethics approval

This research complied with the guidelines for human studies and was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. Ethics Committee approval was obtained from Faculty of Medicine, Mustafa Kemal University (18/02/2021, meeting number 3, decision number 25).

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Conflict of interest

The authors declare no conflict of interest.

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Is there association between thyroid stimulating hormone levels and the four phenotypes in polycystic ovary syndrome?

Hyun Nyung Jo[1*], Hyun Joo Lee [2*], Hye Kyung Noh[3], So Hee Kim[2], Jong Kil Joo[2]

[1]Yeonje Ilsin Medical Center, Busan, Korea
[2]Department of Obstetrics and Gynecology, Pusan National University School of Medicine, Biomedical Research Institute, Pusan National University Hospital, Busan, Korea
[3]Mama Papa & Baby Clinic, Ulsan, Korea
**these authors contributed equally to this work*

ABSTRACT

Objectives: The aim of this study was to determine whether the incidence of subclinical hypothyroidism (SCH) is higher in polycystic ovary syndrome (PCOS) group than the control group. Additionally, the study investigated whether serum thyroid stimulating hormone (TSH) level is associated with various clinical parameters of PCOS regarding different phenotypes of the disease.

Material and methods: This retrospective, case-control study included 329 PCOS patients and 162 control women who were aged between 20 and 42 years and visited the Gynecology outpatient clinic in Pusan National University Hospital from January 2014 to December 2017. PCOS patients were further classified according to their phenotypes: phenotype A as the combination of all hyperandrogenism (HA), ovulatory dysfunction (OD), and polycystic ovarian morphology (PCOM); phenotype B as the combination of HA and OD; phenotype C as the combination of HA and PCOM; and finally, phenotype D as the combination of OD and PCOM. Laboratory blood tests included follicle stimulating hormone (FSH), luteinizing hormone (LH), TSH and anti-mullerian hormone (AMH). The ovarian volume was calculated using three diameters by gynecologic ultrasonography.

Results: Serum TSH level was significantly higher in PCOS patients than in the control group after adjusting for age and body mass index (BMI). Serum TSH level was not related to HA and OD, but its significant association with PCOM was confirmed in comparative analysis in quartiles. The proportion of phenotype A patients increased as serum TSH level increased, while the proportion of phenotype B and D decreased. Phenotype C stayed relatively consistent with varying TSH levels.

Conclusions: More numbers of patients showed elevated TSH level satisfying SCH diagnosis in PCOS group than the control group. In addition, a significant correlation between serum TSH level and different PCOS phenotypes has been observed; especially, PCOS patients with phenotype A, which displays all of HA, OD, and PCOM, tended to have the higher TSH levels than the PCOS patients with other phenotypes, requiring proper and thorough evaluation for potential endocrine disparity and according to management in such patient group.

Key words: PCOS; phenotypes; subclinical hypothyroidism; TSH

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INTRODUCTION

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders in reproductive women, characterized by chronic ovulatory dysfunction (OD), clinical and/or biochemical signs of hyperandrogenism (HA), and/or ultrasound characteristics for polycystic ovarian morphology (PCOM) [1]. Accordingly, PCOS can exhibit clinical features such as infertility, hirsutism, weight gain, central obesity and acanthosis nigricans [2–4]. Pathologic hormonal profile of the disease includes elevated luteinizing hormone (LH) levels with normal or slightly decreased levels

Corresponding author:
Jong Kil Joo
Pusan National University Hospital, Department of Obstetrics and Gynecology. 179, Gudeck-ro, Seo-Gu, Busan, Republic of Korea. Postal Code 49241, phone: + 82-51-240-7287
e-mail: jongkilj@hanmail.net

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of follicle-stimulating hormone (FSH), hyperandrogenemia, and hyperinsulinemia [5].

Among such disturbed metabolic pathways underlying PCOS, insulin resistance appears to be the major etiological characteristic in most patients [6–8]. In women with PCOS, approximately 50–70% of the patients have been reported to have insulin resistance and metabolic syndrome [9–12]. Similar features are seen in patients with hypothyroidism; the patients with hypothyroidism may present with menstrual disorders, infertility, signs of hyperandrogenism, weight gain, dyslipidemia and insulin resistance [13, 14]. Regarding the thyroid function of PCOS patients, Yu and Wang have concluded that PCOS is associated with the higher incidence of subclinical hypothyroidism (SCH) compared to the normal population [13]. SCH, defined as an elevated thyroid-stimulating hormone (TSH) level with normal thyroid hormone levels and lack of signs or symptoms of hypothyroidism, also results in these features [10, 15]. The prevalence of SCH in women with PCOS is variable, ranging from 11 to 36% [16, 17]. Pathophysiological connection between the two disorders has not been established until now; yet, Singla et al. suggest that multiple factors, including adiposity, increased insulin resistance, high leptin and evidence of deranged autoimmunity, contribute individually and interconnectedly to both of SCH and PCOS [18].

Composing such complicatedly mixed endocrine abnormalities within the disease, PCOS patients present diverse clinical characteristics and phenotypes. As an attempt to facilitate the understanding of the disease in both research purpose and clinical setting, the NIH consensus panel recommended four types of phenotype classification in PCOS as a systematic effort: phenotype A as the combination of all HA, clinical or biochemical presence, OD and PCOM; phenotype B as the combination of HA and OD; phenotype C as the combination of HA and PCOM; and finally, phenotype D as the combination of OD and PCOM [19]. Previous literature has thoroughly explored the significant relationship between serum TSH level and PCOS itself; however, as far as we know, only a limited number of studies have discussed the association between TSH and specific PCOS phenotypes [20, 21]. Thus, it is necessary to compare the possibly different association of each PCOS phenotype and TSH in pursue of providing patients with more individualized, efficient therapeutic and disease management plan.

Objectives

in this study, serum TSH levels of the PCOS patients and control were first compared to determine whether the incidence of SCH is higher in PCOS group. Next, the study investigates the possible, significant association of TSH level in PCOS patients with their clinical parameters and PCOS phenotypes.

MATERIAL AND METHODS

Patients and diagnostic criteria of PCOS

This study was a retrospective, case-control study, analyzing electronically charted patient records of the Gynecology outpatient clinic in Pusan National University Hospital. The study included a total of 329 patients, composed of 162 patients in the control group and 167 patients in PCOS group with the age group of 20 to 42 years, who visited the clinic between January 2014 and December 2017. All patients in this study were non-smokers, were not indicated with levotyroxin supplementation and had never taken hormonal contraceptives and/or analgesics at the time of patient selection. Those patients with underlying diseases regarding thyroid or pituitary, abnormal autoimmune antibody levels and/or thyroid ultrasonographic findings, TSH level out of reference range (0.25–5.0 mIU/L) and other related disorders such as congenital adrenal hyperplasia (CAH), Cushing's syndrome or virilizing tumors were excluded [1, 22, 23].

PCOS diagnosis was based on revised 2003 Rotterdam criteria, which confirms PCOS when the patient presents with two out of the following three features: first, OD represented as abnormal menstrual cycle such as amenorrhea, which was defined as the absence of menstrual cycles in the last six months, or oligomenorrhea, which was defined as having the cycle interval of 35 days or more; second, clinical HA, such as hirsutism, alopecia and/or acne or biochemical HA of serum testosterone higher than 2.0 nmol/L; last, the presence of PCOM on gynecologic ultrasonography, showing 12 or more follicles with 2 to 9 mm in diameter and/or ovarian volume of larger than 10 cm^3 on either ovary. Each presentation of clinical HA was determined using previously established diagnostic criteria — for hirsutism, modified Ferriman Gallway score with cut-off score of ≥ 6; for alopecia, the Ludwig visual score; and for acne, despite the absence of universal agreement on visual assessments for its evaluation, the term "acne vulgaris" (AV**)** applied when the patient had a pilosebaceous unit that causes noninflammatory comedones, inflammatory lesion containing red papules, pustules or nodules, and varying degrees of scarring [24–26]. The diagnosed PCOS patients were further categorized into four groups according to their phenotypes: phenotype A as the combination of all HA, OD, and PCOM; phenotype B as the combination of HA and OD; phenotype C as the combination of HA and PCOM; and finally, phenotype D as the combination of OD and PCOM [19].

The control group included age-matched healthy women without any of HA, OD or PCOM who had performed blood thyroid function test (TFT) for other non-related surgical indications such as ovarian endometrioma, mature cystic teratoma and/or cystadenoma.

Table 1. Comparative description of FSH, LH, ovarian volume and clinical presentations of PCOS patients according to the varying ranges of serum TSH levels

		Overall (n = 167)	TSH < 2.0 (n = 76)	2.0 ≤ TSH < 4.5 (n = 77)	TSH ≥ 4.5 (n = 14)	p value
FSH[a] [mIU/mL]		6.21 ± 2.35	5.99 ± 2.53	6.48 ± 2.26	5.92 ± 1.67	0.394
LH[b] [mIU/mL]		6.52 [3.68, 10.16]	6.17 [2.47, 10.43]	6.58 [4.11, 9.79]	6.12 [4.81, 7.95]	0.887†
LH:FSH ratio[b]		1.11 [0.64, 1.57]	1.13 [0.59, 1.69]	1.08 [0.64, 1.56]	1.07 [0.67, 1.25]	0.914†
Ovarian volume[a] [cm^3]		13.57 ± 16.84	11.29 ± 15.12	14.32 ± 17.50	21.83 ± 20.13	0.085
Clinical presentations[a]						
HA (%)	No	66 (39.5)	35 (46.1)	29 (37.7)	2 (14.3)	0.074
	Yes	101 (60.5)	41 (53.9)	48 (62.3)	12 (85.7)	
OD (%)	No	4 (2.4)	2 (2.6)	2 (2.6)	0 (0.0)	1.000‡
	Yes	163 (97.6)	74 (97.4)	75 (97.4)	14 (100.0)	
PCOM (%)	No	36 (21.6)	20 (26.3)	14 (18.2)	2 (14.3)	0.829
	Yes	131 (78.4)	56 (73.7)	63 (81.8)	12 (85.7)	
Phenotypes[a] (%)						
A: HA-OD-PCOM		61 (36.5)	19 (25.0)	32 (41.6)	10 (71.4)	0.039*/+0.004‡
B: HA-OD		36 (21.6)	20 (26.3)	14 (18.2)	2 (14.3)	
C: HA-PCOM		4 (2.4)	2 (2.6)	2 (2.6)	0 (0.0)	
D: OD-PCOM		66 (39.5)	35 (46.1)	29 (37.7)	2 (14.3)	

[a]Data are presented at the means ± SD; [b]data are presented at the median [IQR]; independent t-test or Wilcoxon rank-sum test(†) was used for continuous variable; Fisher's exact test(‡) was used for categorical variable. +p value for trend; *p < 0.05 was considered significant; FSH — follicle stimulation hormone; HA — hyperandrogenism; LH — luteinizing hormone; OD — ovulatory dysfunction; PCOM — polycystic ovarian morphology; TSH — thyroid stimulating hormone

Measurement of laboratory tests and ovarian volume

Laboratory blood tests were performed with the venous blood sampling at the time of PCOS diagnosis, and the tests included following measurements: FSH and LH using Dream Gamma-10 radioimmunoassay (RIA) (Shin Jin Medics Inc., Korea) of which measurements were used to calculate LH/FSH ratio; TSH using Coat-A-count TSH IRMA Kit (SIMENS, Ireland); and anti-mullerian hormone (AMH) using an Anti-Mullerian Hormone/Mullerian Inhibiting Substance Enzyme Immuno Assay (AMH/MIS EIA) kit (Beckman Coulter, France). Body mass index (BMI) was calculated as the patient's weight in kilograms divided by her height in meters squared. All PCOS patients underwent transvaginal or transrectal ultrasonography to determine the volume of both ovaries and the size of ovarian follicles using a 5–9 MHz transvaginal transducer or transrectally for virgin patients (Voluson E6 General Electric, Milwaukee, Wauwatosa, WI, USA). The ovarian volume was calculated using the longest longitudinal (d1), anteroposterior (d2), and transversal diameters (d3): volume in cm^3 = d1 x d2 x d3 x 0.523. Patients were examined at a random day during the menstrual cycle because ultrasonography was performed on the first day of their visit to the hospital.

Arbitrarily, the related factors were identified by dividing the TSH levels into three groups according to their range: TSH < 2, 2.0 ≤ TSH < 4.5, TSH ≥ 4.5. The total volumes of ovaries, FSH and LH were found to be unrelated (Tab. 1). Since the patients were divided randomly only according to their TSH levels, as shown in Table 1, distribution of the number of subjects in each group was uneven. As a result, the possible factors related to the uneven distribution of the patients which could have influenced the results of the study were evaluated by dividing the total number of subjects in quartiles based on TSH level, as described in Table 2: 0.11 ≤ quartile 1 < 1.40; 1.40 ≤ quartile 2 < 2.14; 2.14 ≤ quartile 3 < 3.41; and 3.41 ≤ quartile 4 ≤ 6.86.

Statistical analysis

Data were analyzed according to their patterns of distribution using parametric or nonparametric test. Continuous variables were expressed as mean ± SDs, and categorical variables as numbers and percentages. When comparing the two groups as in Tables 1 and 3, independent t-test or Wilcoxon rank-sum test was used to assess the continuous variable, and Chi-square test or Fisher's exact test was used to assess the categorical variable. As shown in Table 4, one-way ANOVA or Kruskal-Wallis test was performed for comparing multiple groups. The logistic regression analysis was performed to assess the effect of various factors on PCOS. In multivariable analysis, factors with the potential to affect PCOS — age and BMI — were adjusted and included

Table 2. Comparative description of FSH, LH, ovarian volume and clinical presentations of PCOS patients according to the quartiles of serum TSH level

	Overall	Quartile 1	Quartile 2	Quartile 3	Quartile 4	p value
	(n = 167)	(n = 42)	(n = 42)	(n = 42)	(n = 41)	
FSH[a] [mIU/mL]	6.21 ± 2.35	6.18 ± 2.62	5.77 ± 2.53	6.55 ± 2.35	6.34 ± 1.81	0.489
LH[b] [mIU/mL]	6.52 [3.68, 10.16]	5.78 [2.30, 10.29]	6.88 [4.18, 10.99]	7.26 [4.28, 9.65]	5.47 [4.09, 8.67]	0.755†
LH:FSH ratio[b]	1.11 [0.64, 1.57]	1.00 [0.55, 1.64]	1.25 [0.80, 2.12]	1.20 [0.62, 1.48]	0.82 [0.67, 1.24]	0.245†
Ovarian volume[a] [cm^3]	13.57 ± 16.84	12.95 ± 15.73	10.85 ± 15.06	14.99 ± 17.92	15.53 ± 18.65	0.574
Clinical presentations[a]						
HA (%)	66 (39.5)	17 (40.5)	21 (50.0)	11 (26.2)	17 (41.5)	0.162
	101 (60.5)	25 (59.5)	21 (50.0)	31 (73.8)	24 (58.5)	
OD (%)	4 (2.4)	1 (2.4)	1 (2.4)	1 (2.4)	1 (2.4)	1.000‡
	163 (97.6)	41 (97.6)	41 (97.6)	41 (97.6)	40 (97.6)	
PCOM (%)	36 (21.6)	16 (38.1)	6 (14.3)	9 (21.4)	5 (12.2)	0.017*
	131 (78.4)	26 (61.9)	36 (85.7)	33 (78.6)	36 (87.8)	
Phenotypes[a] (%)						
A: HA-OD-PCOM	61 (36.5)	8 (19.0)	14 (33.3)	21 (50.0)	18 (43.9)	0.022*/+0.148‡
B: HA-OD	36 (21.6)	16 (38.1)	6 (14.3)	9 (21.4)	5 (12.2)	
C: HA-PCOM	4 (2.4)	1 (2.4)	1 (2.4)	1 (2.4)	1 (2.4)	
D: OD-PCOM	66 (39.5)	17 (40.5)	21 (50.0)	11 (26.2)	17 (41.5)	
TSH quaternary						
	0%	25%	50%	75%	100%	
	0.11	1.40	2.14	3.41	6.86	

[a]Data are presented at the means ± SD; [b]Data are presented at the median [IQR]; One-way ANOVA or Kruskal-Wallis test(†) for continuous variable; Chi-square test or Fisher's exact test(‡) for categorical variable; +p value for trend; *p < 0.05 was considered significant; FSH — follicle stimulation hormone; LH — luteinizing hormone; HA — hyperandrogenism; OD — ovulatory dysfunction; PCOM — polycystic ovarian morphology; TSH — thyroid stimulating hormone

Table 3. Characteristics of the study population

	Overall (n = 329)	PCOS (n = 167)	Control (n = 162)	p value
Age (years)	27.43 ± 6.16	25.38 ± 4.98	29.55 ± 6.55	< 0.001*
BMI [kg/m^2]	22.33 ± 4.50	22.75 ± 4.57	21.91 ± 4.39	0.088
AMH [ng/mL]	7.43 ± 5.81	11.19 ± 5.60	3.55 ± 2.60	< 0.001*
TSH [mIU/mL]	2.27 ± 1.23	2.39 ± 1.34	2.15 ± 1.09	0.085

Data are presented at the means ± SD. *p < 0.05 was considered significant.; AMH — anti-Mullerian-hormone; BMI — body mass index; PCOS — polycystic ovary syndrome; TSH — thyroid stimulating hormone.

TSH. All statistical analyses were conducted using R 4.0.1., and p value < 0.05 was considered statistically significant.

RESULTS

Table 3 features the basic characteristic of the patients included in the study. The mean age of the study population was 25.38 ± 4.98 years in the PCOS group and 29.55 ± 6.55 years in the control group (described as means ± standard deviation [SD], p < 0.001). BMI was not statistically different in overall patients, with mean ± SD of 22.33 ± 4.50 kg/m^2. As observed in previous literature, AMH level of the PCOS group was statistically higher than the control group which included patients with benign ovarian cysts such as endometrioma, mature teratoma and/or cystadenoma (11.19 ± 5.60 ng/mL in the PCOS group and 3.55 ± 2.60 in the control group, described as means ± SD with p < 0.001, respectively) [27].

Logistic regression analysis, adjusted for age and BMI, was performed to compare TSH levels between the control and PCOS groups, as described in Table 4. Multivariable analysis showed that TSH level was significantly higher in the PCOS group compared to the control group, with odds ratio (OR) of 1.226 and 95% confidence interval (CI) of 1.006, 1.493 (p < 0.05). In the univariable analysis, the comparison

Table 4. Logistic regression analysis of patient characteristics for PCOS diagnosis including varying ranges of TSH levels, adjusted for age and BMI

	Univariable analysis		Multivariable analysis	
	OR [95% CI]	p value	OR [95% CI]	p value
Age [years]	0.884 [0.848, 0.921]	< 0.001*	0.878 [0.841, 0.916]	< 0.001*
BMI [kg/m^2]	1.044 [0.993, 1.096]	0.090	1.049 [0.995, 1.106]	0.075
AMH [ng/mL]	1.762 [1.555, 1.997]	< 0.001*		
TSH [mIU/mL]	1.170 [0.978, 1.400]	0.087	1.226 [1.006, 1.493]	0.043*
< 2 (%)	Reference value			
2–4.5 (%)	1.196 [0.766, 1.868]	0.431		
≥ 4.5 (%)	3.132 [1.077, 9.102]	0.036*		

*p < 0.05 was considered significant; AMH — anti-Mullerian-hormone; BMI — body mass index; CI — confidence interval; OR — odds ratio; TSH — thyroid stimulating hormone.

of TSH levels was performed using the randomly divided three groups according to their range. The analysis showed that groups with TSH levels of 4.5 mIU/mL or higher had significantly higher rates of PCOS than those with TSH levels of less than 2 mIU/mL [OR (95% CI) of 3.132 (1.077, 9.102), p < 0.05].

As represented by Table 1, FSH, LH, LH:FSH ratio and the ovarian volumes of PCOS patients were not significantly associated with the varying ranges of their serum TSH levels. Also, regarding their clinical presentations, the results confirmed that serum TSH level was not specifically related to each of HA, OD and PCOM. However, significant relationships between the four types of PCOS phenotype and TSH have been identified (p < 0.05). As TSH level increased, the proportion occupied by phenotype A increased, while the proportion occupied by phenotype B decreased. Phenotype C stayed similar, and phenotype D also decreased with the increasing TSH level (p value for trend < 0.05).

According to Table 2, FSH, LH, LH:FSH ratio and the volumes of ovaries did not display significant relationship with the different quartiles of serum TSH levels, but PCOM did (p < 0.05). In addition, significant relationships between TSH level quartiles and different PCOS phenotypes were identified; however, unlike in Table 1 with varying ranges of TSH levels, the analysis did not observe a statistically significant trend (p = 0.148).

DISCUSSION

Over the decades, many studies have investigated the prevalence of SCH in PCOS. Consequently, it has been observed that PCOS and SCH are closely related, with thoroughly examined underlying mechanisms. However, only a few studies have been evaluated the relationship between TSH level and each different phenotype in patients with PCOS. To our knowledge, this is the first analysis to evaluate the relationship and its trends between the patient's TSH level and PCOS phenotype.

In order to evaluate such relationship, general characteristics of the overall patients – both PCOS and control – were first investigated. As one of the important biomarkers for ovarian function and reserve, serum AMH levels of the patients were routinely measured to evaluate their general and clinical characteristics when diagnosis in the PCOS group or planning for surgical treatments in the control group was made. As previously established, the current study observed significantly increased AMH level in PCOS patients compared to the control group [27]. It has been reported that elevated TSH could be associated with decreased AMH in infertile women, but those women were without PCOS or ovary-related surgical histories, which does not apply to the scope of the current study [28]. Moreover, the control group of the current study included patients with benign ovarian tumors such as endometriosis, mature cystic teratoma and/or cystademona; serum AMH levels among these patients with such various ovarian pathologies were diverse and all equally included in the statistical analysis, which resulted in 3.55 ± 2.60 ng/mL (mean ± SD). Such approach could have possibly nullified the possibly decreased AMH level of included endometriosis patients. Another important biomarkers for PCOS include serum LH, FSH and LH:FSH; especially, LH:FSH ratio has been known to be significantly different between the general population and PCOS patients [29]. In the current study, only those PCOS patients were evaluated for LH, FSH and LH:FSH ratio, and the results showed no significant differences in LH, FSH and LH:FSH ratio according to varying TSH levels, agreeing with the previous study of Cai et al. [30]. Lastly, BMI was evaluated as it could have possibly affected the physiologic status of the patients, and BMI was not significantly different between the control and PCOS patients, all lower than 25 kg/m^2. Generally speaking, the prevalence of obesity in PCOS women has been reported to be 30–75%, according to varying ethnicities [31]. Although a majority of PCOS patients are obese or overweight, a small but significant proportion of PCOS patients, termed with "lean" PCOS patients, do present with normal BMI, requiring different

therapeutic approach [32]. When comparing Asian and Caucasian PCOS patients, it has been reported that the Caucasian patients had a statistically greater increase in obesity prevalence than their Asian counterparts [33]. In the current study of Korean PCOS patients, it was not completely surprising to see that the included patients with Korean ethnicities had BMI lower than 25 kg/m^2. Moreover, as LH:FSH ratio dose not differ between obese and lean PCOS patients, the possible influence that lean status of PCOS patients in this study might have exerted on their TSH levels could have been minimal [34].

According to the current study, adjusting for age and BMI resulted in higher TSH levels in PCOS patients compared to the control group, as shown in Table 4. Similar results have been found in many other studies on the close relationship between PCOS and SCH. In the study by Qun Yu et al., in China, 27% of their PCOS patients had comorbid SCH, whereas only 8% of the control group did so [35]. Furthermore, the current study investigated whether such comorbidity was differently associated with TSH according to the PCOS features. In previous literature, Jie Cai et al. reported that the increased prevalence of HA was associated with the higher TSH level than other features, independent of age, BMI and thyroid autoimmunity in euthyroid PCOS patients [30]. On the other hand, according to the results of this study, the association between TSH and PCOS features such as HA, OD and PCOM was not statistically confirmed ($p = 0.074$). Other than the small number of patients included in this study, possible explanations include inevitable recall bias since the decision of OD was dominantly based on the patient's memory; in fact, the most common chief complaint of PCOS patients at the research facility was irregular menstruation. In addition, no significant difference in the PCOM prevalence was observed ($p = 0.829$).

However, the proportion of each phenotype turned out to be closely related to TSH according to the study; the higher the TSH level was, the higher the percentage of phenotype A in HA, OD and PCOM. Conversely, phenotype B, which represented HA and OD, decreased with higher TSH level. Phenotype C, representing HA and PCOM, was restrictively difficult to compare because the number of subjects was only four; in case of phenotype D, representing OD and PCOM, showed rather smaller percentage with the higher TSH level. In the group of PCOS patients with TSH level of 4.5 or higher, 71.4% showed phenotype A. Hence, it could be logically interpreted that when the TSH level increased, the probability of occurrence of all HA, OD and PCOM also increased, probably suggesting the pathophysiology between thyroid hormones and androgen played an important, causal role. As previously known, GnRH regulates the biosynthesis and secretion of LH and FSH, which are usually upregulated in PCOS; it is assumed that such GnRH could have modulated thyroid hormones at the pituitary level [30]. Indeed, there is evidence that thyroid hormones are involved in gonadal differentiation and reproductive function [36]. Thyroid hormones regulate androgen biosynthesis and signaling through direct and indirect regulation of the expression and activity of associated steroidogenic enzymes [37, 38].

Further investigating the association of TSH with PCOS features, Table 2 describes the total number of subjects divided in quartiles based on TSH level, showing somewhat slightly different results from Table 1; there was no significant difference in HA for each group, but PCOM was significantly different among the quartiles ($p = 0.017$). As in Table 1, there was a significant difference in phenotypes ($p = 0.022$), but, in Table 2, it was unreasonable to interpret that it had a certain tendency depending on the TSH level (p value for trend = 0.148). Despite that the same patient group was investigated, the reason for different results between Tables 1 and 2 could have been that in Table 2 the classification of the patient group was based on quartiles; the number of patients in each group was similarly distributed, but the range of their TSH levels were significantly different from each other. Therefore, according to the current study, it could be presumed that the TSH levels of 2.0 and 4.5 are statistically meaningful.

The current study still has several limitations. First, due to the retrospective nature of the current study, no useable data could have been newly obtained from the study population. Consequently, certain biochemical markers for HA were missing for example, sex hormone binding globulin (SHBG) and dehydroepiandrosterone (DHEA), as SHBG and DHEA measurements were limited due to the National Insurance Coverage restrictions in some cases. Instead, serum testosterone levels were measured to satisfy biochemical presentation of HA when a patient did not fulfill previously established diagnostic criteria but had symptoms of highly suggestive HA [24–26]. Last but importantly, as previously mentioned, the number of subjects included in the study was relatively small. Subgroups were divided based on TSH level, but the total number of subgroups with high TSH level was too small, possibly limiting the thorough analysis of the results. Further studies with prospective nature and larger population to strengthen the regarding statistical analysis of data character are required.

CONCLUSIONS

In conclusion, the current study confirmed higher prevalence of SCH in PCOS patients compare to the control group, and in such PCOS patients, the significant correlation between serum TSH level and specific PCOS phenotype was observed, with statistically confirmed tendency of elevating TSH level in increasing proportion of PCOS phenotype

A which included all of HA, OD and PCOM. Proper screening and patient guidance considering the hormonal status and phenotype of the patient at the same time could substantially accommodate clinicians to provide PCOS patients with more individualized, efficient therapeutic and management planning in clinical setting.

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None.

Conflict of interest

All authors declare no conflict of interest.

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Fetal kidney measurement — additional biometric parameter for accurate gestational age assessment

Agnieszka Zalinska[1, 2, 3], Oskar Sylwestrzak[3], Arkadiusz Papis[2], Przemyslaw Oszukowski[1, 2], Agnieszka Pieta-Dolinska[1, 2]

[1]Delivery Ward, Polish Mother's Memorial Hospital Research Institute, Lodz, Poland

[2]Department of Obstetrics and Perinatology, Chair of Obstetrics, Gynecology and Oncological Gynecology, Medical University of Lodz, Poland

[3]Department of Prenatal Cardiology, Polish Mother's Memorial Hospital Research Institute, Lodz, Poland

ABSTRACT

Objectives: Ultrasound examination — recommended in the prenatal period — allows for an assessment of fetal anatomy and well-being and for monitoring its growth trend. Determining gestational age is important in monitoring the developing fetus. Research is increasingly being conducted in search of further biometric components that may improve ultrasound techniques in terms of predicting the gestational age. It should be noted that a fairly large number of publications focus on the accessibility of fetal kidneys to diagnostic imaging during routine ultrasound examination. The reported study was an attempt to answer the question whether fetal kidney dimensions correlated with gestational age. The obtained results are presented as fetal kidney normograms for particular weeks of gestation.

Material and methods: The study covered by dissertation was conducted among patients hospitalized at the Provincial Specialist Hospital in Zgierz, Department of Gynecology, Obstetrics and Endoscopic Therapy, in the period from 1st April 2019 to 30th November 2019. The study group included patients in a single pregnancy. The control group was not included in the study. The ultrasound examinations, which are the basis of the study, were carried out using the PHILIPS Affiniti 70 ultrasound device, with a frequency of 3.5 MHz transabdominal transducer. All data were subjected to statistical analysis using the Statistica 13.1 program.

Results: The study involved 265 pregnant women with an average age of 29 years. The ultrasound examination was performed between the 17 th and 42 nd weeks of pregnancy and the mean gestational age of the examined population was 29 + 5. Female sex was identified in 122 fetuses and male sex in 143 ones. Based on the results of Mann-Whitney U test, no statistical difference was found between the weeks of gestation in the group of male and female fetuses ($p > 0.05$). The same test showed no difference between male and female fetuses in terms of particular kidney dimensions during pregnancy.

Conclusions: Kidney dimensions strongly correlated with gestational age. Fetal kidney growth was a linear process in normal pregnancy. Fetal kidney measurements can provide additional biometric parameters for accurate gestational age assessment.

Key words: fetal anatomy; determining gestational age; fetal kidney; fetal kidney normograms; kidney dimensions; fetal kidney growth

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INTRODUCTION

Ultrasound examination — recommended in the prenatal period — allows for an assessment of fetal anatomy and well-being and for monitoring its growth trend. Prenatal sonography is increasingly being used as a tool to determine the advancement of gestational age in unclear cases, such as those related to the unknown date of the last menstrual period. Determining gestational age is important in monitoring the developing fetus [1, 2].

In the absence of the ability to accurately determine the stage of pregnancy, a reliable prediction of the prenatal and postnatal fate is rather difficult to establish. The lack of both reliable data and precise and clear eligibility criteria in the area directly translates into higher rates of

Corresponding author:
Agnieszka Zalinska
Department of Obstetrics and Perinatology, Chair of Obstetrics, Gynecology and Oncological Gynecology, Medical University of Lodz, Poland
e-mail: aga_zalinska@wp.pl

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perinatal mortality, increased incidents of low birth weight or an elevated risk of preterm birth. Research is increasingly being conducted in search of further biometric components that may improve ultrasound techniques in terms of predicting the gestational age. Examples of such parameters include the transverse dimension of the cerebellum, the length of the foot or the width of the palate [3–5].

It should be noted that a fairly large number of publications focus on the accessibility of fetal kidneys to diagnostic imaging during routine ultrasound examination. Numerous efforts are underway to develop fetal renal normograms for different stages of pregnancy [6].

Aim of the study

The reported study was an attempt to answer the question whether fetal kidney dimensions correlated with gestational age. The obtained results are presented as fetal kidney normograms for particular weeks of gestation.

MATERIAL AND METHODS

The study was conducted at the Regional Specialist Hospital in Zgierz, Poland, Department of Gynecology, Obstetrics and Endoscopic Therapy, among female patients hospitalized between the 1st of April 2019 and 30th of November 2019, using a PHILIPS Affiniti 70 ultrasound system with a transabdominal 3.5 MHz probe. The concept of the study received approval of the Bioethics Committee. All examinations were performed individually by the author of the study during a routine ultrasound assessment of the fetus. Each patient was examined only once, not in individual trimesters.

The study group included patients with single pregnancy, in whom the duration of pregnancy had been calculated based on the first trimester examination, using the crown rump length (CRL) parameter or considering the date of the last menstrual period [7]. The exclusion criteria comprised undetermined pregnancy duration, multiparous pregnancies, pregnancies complicated by chronic diseases in an uncompensated phase, *i.e.*, diabetes (including gestational diabetes), hypertension and collagenosis.

In addition, patients with congenital fetal anomalies and those with any sonographic abnormalities identified in the fetal kidneys were not included in the study. Sonographic examinations were performed in the enrolled pregnant women between the 18th and 40th weeks of gestation. No control group was considered in the study. First, fetal well-being was determined (with an assessment of fetal growth trend, peripheral flows and amniotic fluid volume). In a subsequent stage of the study, an attempt was made to visualize fetal kidneys, which was carried out according to the accepted standard for studies of indicated structures, used, among others, in the publication by Edevbie JP et al. [8]. A satisfactory transverse plane of the fetus was first defined at the level of four chambers of the heart, followed by a transverse scanning continued caudally until fetal kidneys were visualized, often at the level of the stomach or immediately below it. The probe was then rotated by 90° to obtain the longitudinal axis of each kidney on either side of the midline tubular anechoic abdominal aorta. The largest longitudinal image showing both superior and inferior outer poles of each kidney was meticulously obtained and frozen on screen [8]. Using electronic calipers, kidney length was measured from the superior outer pole to the inferior outer pole — KD 1 (Kidney Dimension 1) as the greatest kidney dimension in longitudinal axis and KD 2 (Kidney Dimension 2) as the greatest dimension perpendicular to the previous axis. As a rule, three measurements per kidney were taken. The average value in millimeters was recorded in a worksheet (Fig. 1). It is important to notice that once the measurement in the longitudinal axis is taken, it is necessary to obtain a transverse scan of the spine and both kidneys (spine located at 6 or 12 o'clock) in order to record the largest dimension of the fetal kidneys (KTD — kidney transverse dimension) in an axis parallel to a hypothetical line between the spine and the sternum.

In order to eliminate erroneous measurements, US imaging was repeated three times in each patient and for each fetal kidney separately. To receive the most reliable results, the study population was divided into relatively homogeneous subpopulations.

Statistical analysis

A statistical analysis was performed by means of the Statistica 13.1 software. The received results were expressed as arithmetic means ± standard deviations and minimum and maximum values. The Shapiro-Wilk test ($\alpha < 0.05$) was applied to check the normality of the distribution of variables. The Pearson correlation analysis was used for continuous variables with normal distribution. Student's t-test was used to compare the values of variables with normal distributions in two groups. If normal distribution was not found, further analysis was performed, using non-parametric tests. The Spearman correlation analysis was employed for continuous variables without normal distribution.

RESULTS

The study involved 265 pregnant women with an average age of 29 years. The ultrasound examination was performed between the 17th and 42nd weeks of pregnancy and the mean gestational age of the examined population was 29 + 5. Female sex was identified in 122 fetuses and male sex in 143 ones. See Table 1 for mean kidney dimensions at particular weeks of gestation (Tab. 1). See Tables 2–7 for normal kidney dimensions, expressed as the 5th, 10th, 50th,

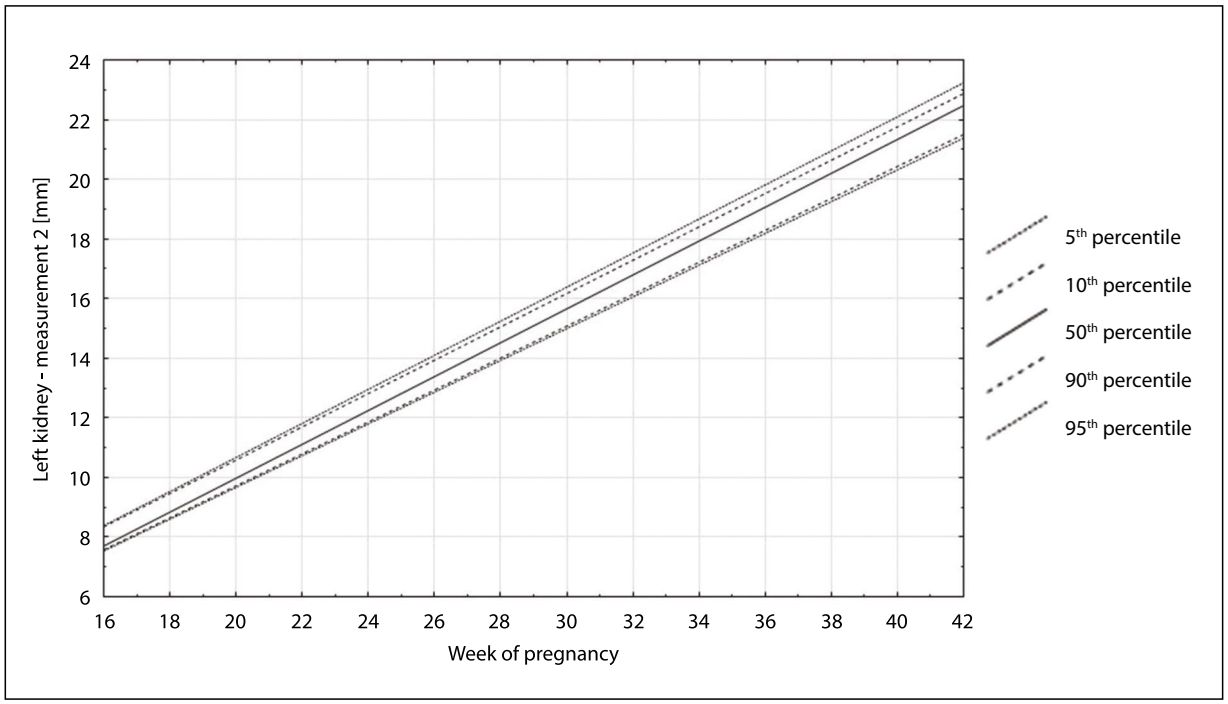

Figure 1. Percentile grid of left kidney dimension 1

Table 1. Kidney dimensions in particular gestation weeks

Gestational age		LKD 1	LKD 2	LKTD	RKD 1	RKD 2	RKTD
17–18	Mean average	18.63	8.70	8.38	18.30	8.14	8.85
	STD	0.30	0.68	0.95	0.34	0.97	0.84
19–20	Mean average	20.15	10.96	11.83	20.19	11.23	11.72
	STD	0.63	0.30	0.34	0.49	0.34	0.50
21–22	Mean average	22.11	10.56	11.44	22.35	11.05	11.56
	STD	0.47	0.46	0.39	0.54	0.36	0.51
23–24	Mean average	24.89	11.90	13.23	24.60	12.14	12.67
	STD	0.46	0.37	0.47	0.56	0.42	0.48
25–26	Mean average	27.24	13.37	16.15	27.08	13.28	14.77
	STD	0.44	0.13	0.75	0.30	0.09	0.29
27–28	Mean average	28.55	14.89	17.33	28.51	15.03	16.26
	STD	0.46	0.64	0.69	0.54	0.62	0.61
29–30	Mean average	31.08	16.01	18.85	31.09	15.96	17.43
	STD	0.90	0.40	0.72	0.75	0.38	0.46
31–32	Mean average	32.25	17.13	19.53	32.42	17.12	18.47
	STD	0.81	0.25	0.56	0.66	0.28	0.27
33–34	Mean average	34.57	17.53	19.42	34.32	17.35	18.72
	STD	0.60	0.50	0.46	1.12	0.36	0.40
35–36	Mean average	36.79	18.41	21.16	37.02	18.47	19.91
	STD	0.61	0.59	0.41	0.75	0.60	0.40
37–38	Mean average	38.61	19.82	21.70	38.73	20.09	21.03
	STD	0.64	0.60	0.60	0.66	0.93	0.85
39–40	Mean average	40.65	21.78	23.28	40.81	21.65	22.30
	STD	0.98	0.73	0.64	1.00	0.65	0.66

LKD — Left Kidney Dimension; LKTD — Left Kidney Transverse Dimension; RKD — Right Kidney Dimension; RKTD — Right Kidney Transverse Dimension; STD — Standard Deviation

Table 2. Consecutive percentiles for left kidney dimension 1 during pregnancy

Gestational age	5. percentile	10. percentile	50. percentile	90. percentile	95. percentile
17–18	18.11	18.13	18.72	18.89	18.96
19–20	19.13	19.14	20.53	20.73	20.73
21–22	21.50	21.67	22.10	22.67	22.67
23–24	24.25	24.42	24.85	25.47	25.59
25–26	26.43	26.70	27.43	27.57	27.58
27–28	27.58	28.07	28.57	29.13	29.16
29–30	29.25	29.56	31.48	31.83	31.86
31–32	31.31	31.40	32.00	33.50	33.55
33–34	33.83	33.83	34.52	35.31	35.74
35–36	36.01	36.07	36.72	37.58	37.73
37–38	37.58	37.63	38.72	39.38	39.47
39–40	39.45	39.62	40.48	42.33	42.45

Table 3. Consecutive percentiles for left kidney dimension 2 during pregnancy

Gestational age	5. percentile	10. percentile	50. percentile	90. percentile	95. percentile
17–18	8.04	8.08	8.43	9.92	10.00
19–20	10.63	10.67	11.03	11.19	11.23
21–22	9.94	10.09	10.47	10.89	11.13
23–24	11.38	11.50	11.90	12.23	12.49
25–26	13.15	13.20	13.40	13.50	13.52
27–28	14.17	14.18	14.90	15.71	15.79
29–30	15.46	15.63	15.98	16.65	16.70
31–32	16.78	16.89	17.05	17.47	17.61
33–34	16.71	16.82	17.62	18.00	18.33
35–36	17.61	17.68	18.42	19.07	19.30
37–38	19.03	19.03	19.90	20.41	20.83
39–40	20.45	20.75	21.95	22.42	22.83

Table 4. Consecutive percentiles for the left kidney transverse dimension during pregnancy

Gestational age	5. percentile	10. percentile	50. percentile	90. percentile	95. percentile
17–18	7.66	7.77	7.93	10.16	10.24
19–20	11.30	11.31	11.90	12.26	12.35
21–22	10.94	11.06	11.45	11.86	12.02
23–24	12.76	12.85	13.10	13.75	14.33
25–26	14.58	14.65	16.50	16.60	16.65
27–28	16.43	16.57	17.20	18.21	18.71
29–30	17.73	17.96	19.08	19.71	19.93
31–32	18.87	18.90	19.68	20.12	20.33
33–34	18.90	18.95	19.33	19.85	20.28
35–36	20.46	20.65	21.10	21.58	21.80
37–38	21.05	21.10	21.58	22.52	22.68
39–40	22.24	22.53	23.25	24.13	24.35

Table 5. Consecutive percentiles for right kidney dimension 1 during pregnancy

GESTATIONAL AGE	5. percentile	10. percentile	50. percentile	90. percentile	95. percentile
17–18	17.90	17.95	18.22	18.80	18.88
19–20	19.29	19.77	20.17	20.70	20.70
21–22	21.77	21.79	22.03	23.15	23.17
23–24	23.95	24.02	24.35	25.33	25.44
25–26	26.62	26.80	27.10	27.27	27.50
27–28	27.64	27.68	28.50	29.20	29.20
29–30	30.03	30.38	31.23	31.92	32.06
31–32	31.52	31.56	32.20	33.43	33.51
33–34	33.47	33.69	34.43	35.67	35.74
35–36	35.96	36.20	36.93	37.75	38.37
37–38	37.73	37.76	38.65	39.64	39.68
39–40	39.48	39.83	40.55	42.15	42.43

Table 6. Consecutive percentiles for right kidney dimension 2 during pregnancy

Gestational age	5. percentile	10. percentile	50. percentile	90. percentile	95. percentile
17–18	7.36	7.37	7.70	9.91	9.96
19–20	10.69	10.93	11.20	11.57	11.60
21–22	10.67	22.53	11.07	11.27	11.45
23–24	11.73	11.83	12.07	12.43	13.14
25–26	13.17	13.17	13.23	13.40	13.42
27–28	14.15	14.35	14.97	15.87	16.03
29–30	15.41	15.63	15.93	16.39	16.43
31–32	16.63	16.91	17.07	17.51	17.60
33–34	16.76	16.95	17.40	17.80	17.84
35–36	17.58	17.73	18.63	19.10	19.31
37–38	19.12	19.16	19.93	21.46	22.04
39–40	20.56	20.80	21.73	22.43	

Table 7. Consecutive percentiles for the right kidney transverse dimension during pregnancy

Gestational age	5. percentile	10. percentile	50. percentile	90. percentile	95. percentile
17–18	7.86	7.95	8.63	10.17	10.29
19–20	10.96	11.05	11.80	12.29	12.30
21–22	10.93	11.10	11.65	11.99	12.20
23–24	12.10	12.10	12.65	13.05	13.76
25–26	14.55	14.55	14.65	15.05	15.30
27–28	15.22	15.46	16.25	17.04	17.44
29–30	16.77	16.92	17.50	18.07	18.23
31–32	18.11	18.30	18.45	18.82	19.00
33–34	18.23	18.25	18.80	19.08	19.31
35–36	19.36	19.40	19.85	20.53	20.64
37–38	20.10	20.19	20.83	21.90	22.82
39–40	21.08	21.23	22.48	22.95	23.00

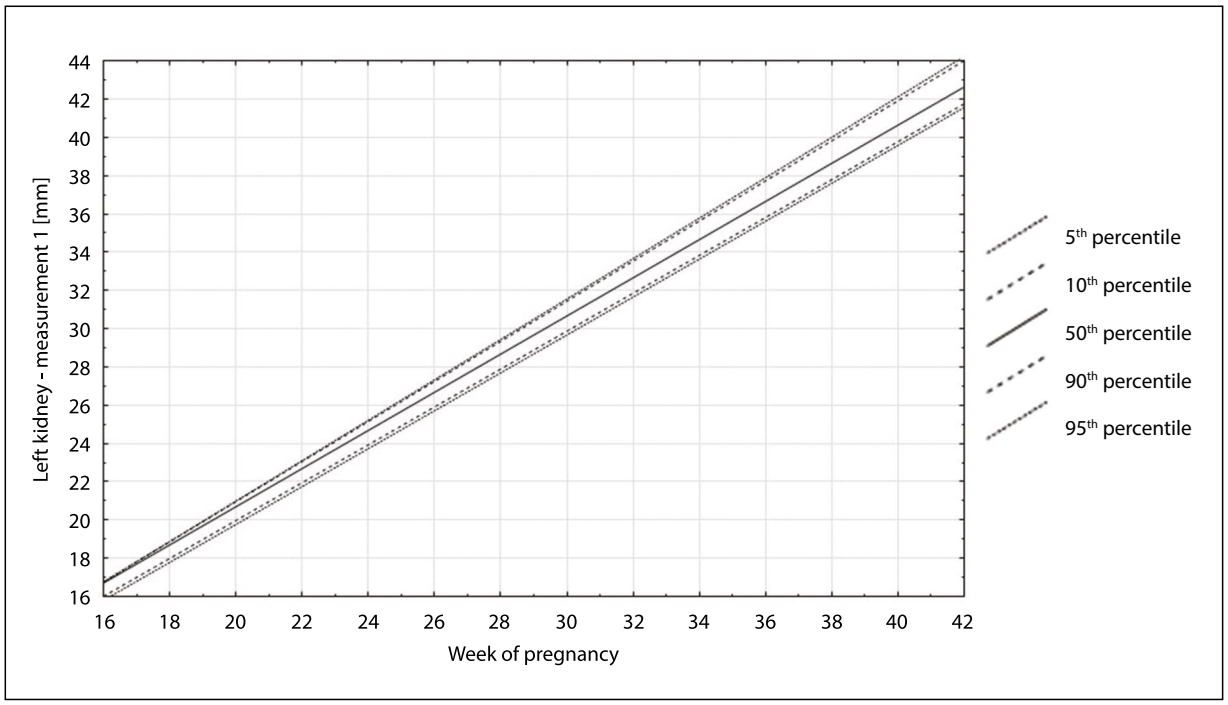

Figure 2. Percentile grid of left kidney dimension 2

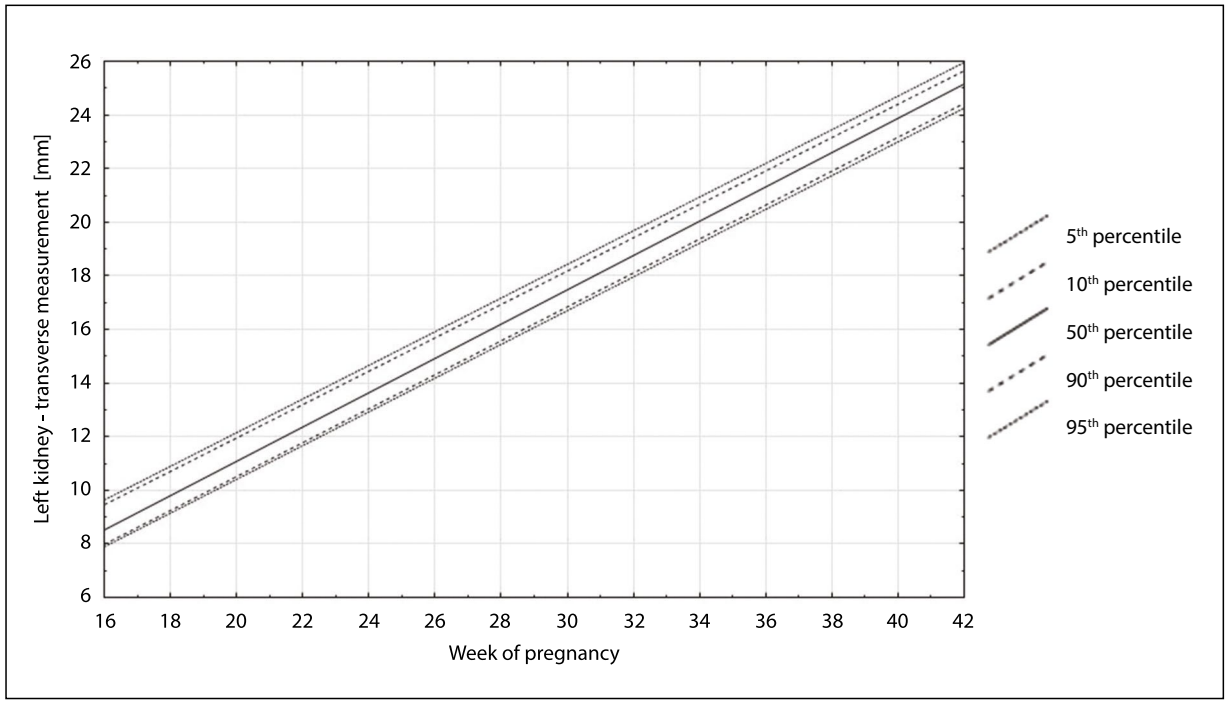

Figure 3. Percentile grid of the left kidney transverse dimension

90th and 95th percentile for each week of gestation (Tab. 2–7). The same data are also presented for the studied population in the form of percentile grids. The 5th, 10th, 50th, 90th and 95th percentiles were calculated for each week of gestation. Connecting simple regression lines were drawn for particular percentiles. The results are presented as percentile charts (Fig. 2–7). Based on the results of Mann-Whitney U test, no statistical difference was found between the weeks of gestation in the group of male and female fetuses ($p > 0.05$). The same test showed no difference between male and female fetuses in terms of particular kidney dimensions during pregnancy.

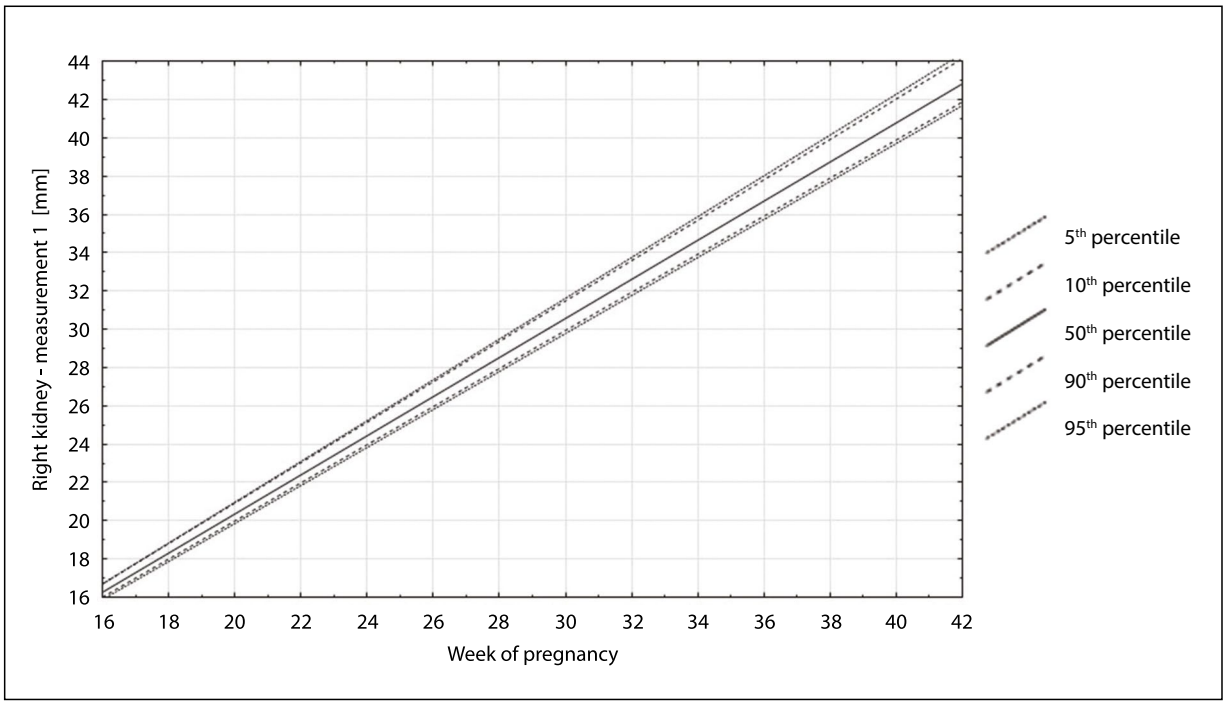

Figure 4. Percentile grid of right kidney dimension 1

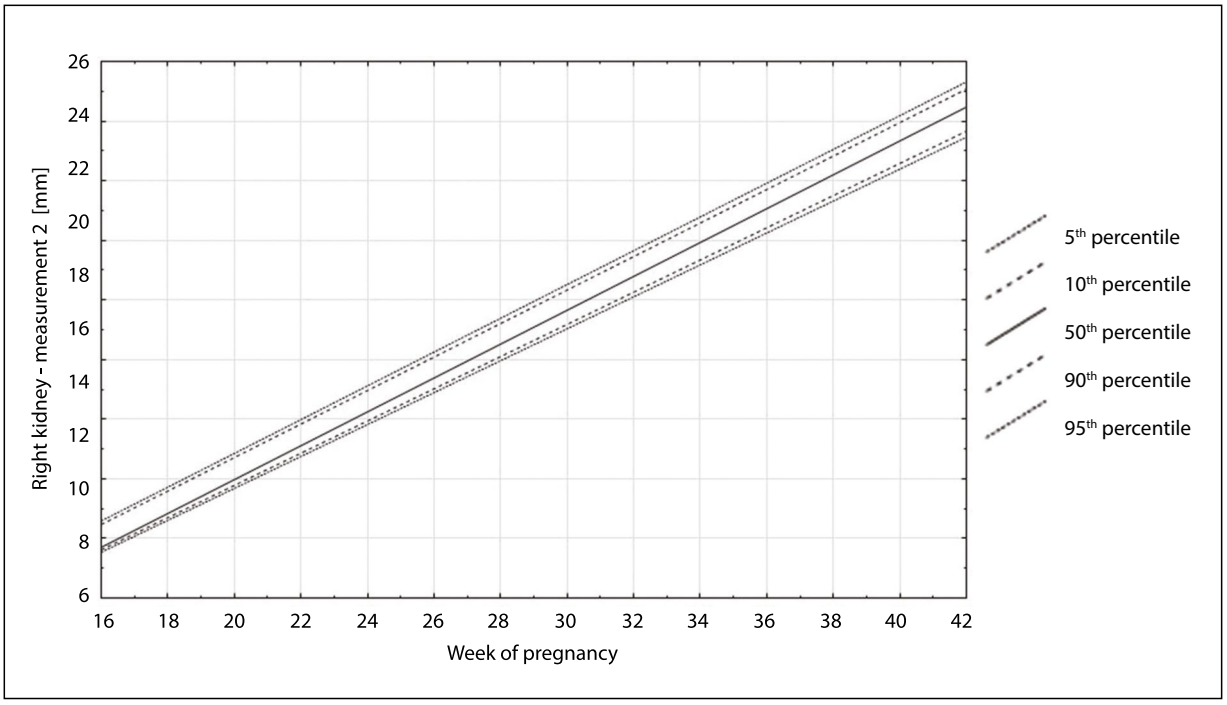

Figure 5. Percentile grid of right kidney dimension 2

DISCUSSION

Knowing the correct fetal age is crucial for prenatal management planning from the first trimester until delivery [9]. Three parameters are needed to determine the duration of pregnancy in the first trimester examination: the size of the gestational sac (GS), crown rump length (CRL) and detection of the yolk sac (YS) [10, 11]. In the case of the second and third trimesters, the following parameters are considered: the biparietal diameter (BPD), head circumference (HC), abdominal circumference (AC), femur length (FL) and humerus length (HL) [12].

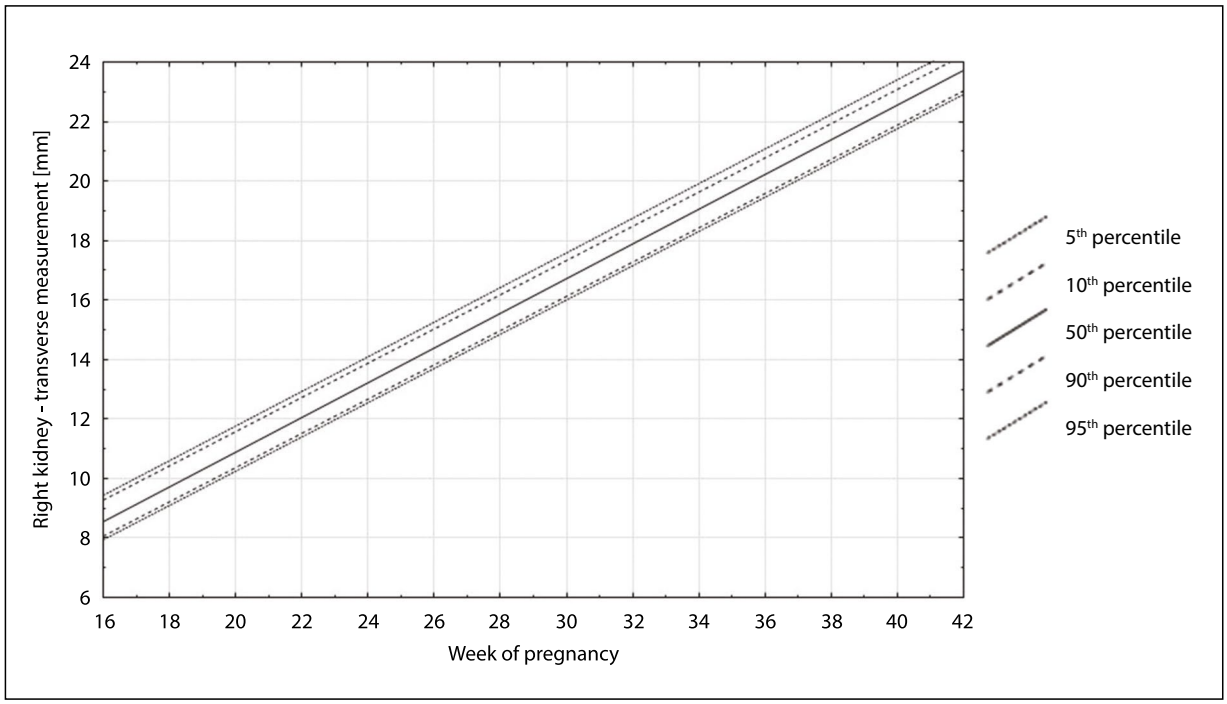

Figure 6. Percentile grid of the transverse dimension of the right kidney

It arises from available reports, that precise timing of pregnancy reduces unnecessary procedures, including the induction of labor for post-term pregnancy indications [13]. Exceeding specified time- frames in a particular medical procedure may result, among others, in ineffectiveness of therapeutic measures, such as prenatal stimulation of pulmonary respiratory system growth with recommended steroids, which should be administered between the 24th and 34th weeks of gestation [14–16]. The accuracy of establishing the gestational age is also important to determining delivery time. Some obstetric pathologies, such as gestational diabetes or untreatable hypertension, require induced labor [17]. Another advantage of accurate pregnancy timing is that it enables performing certain prenatal diagnostic tests. An example may be ultrasound imaging in the second trimester, which falls between the 18th and 22nd weeks of pregnancy [18, 19].

Additional biometric parameters helpful in determining the gestational age include: "floating particles" in the amniotic fluid — inhomogeneous amniotic fluid with hyperechoic inclusions, the cerebellar dimensions, visible ossification points in long bones, the scapula length, the foot length, the fetal chest to abdomen ratio, the sacral bone length, the hard palate width, echogenicity of the large intestine and the large bowel loop width. A complete diagnostic parameter should be characterized by easy detection, repeatability of measurements, independence from additional factors, *e.g.* chronic diseases accompanying pregnancy, and stability despite concomitant growth trend disorders. The innovative biometric parameters undoubtedly include the fetal kidney length, which correlates with the gestational age [20–25].

Romero R et al. [26] were among the pioneers of fetal kidney normogram development. The very few authors attempting to use the fetal kidneys for gestational age assessment not only provide evidence for a relationship between the fetal kidney linear growth and pregnancy duration, but also try to establish normograms for that organ [27]. In their publication, Lawson TL et al. [28] proposed methodology for the optimal measurement of fetal kidneys. They recommend that the whole procedure should individually visualize each of the kidneys; however, if it is difficult to visualize both fetal kidneys, the assessment may exceptionally address only one. Similarly, Edevbie JP et al. [8], due to subtle size differences between the left and right kidney, consider only one dimension in certain cases.

The size of the study population is undoubtedly of high significance to statistical reliability. In the study by Edevbie JP et al. [8], as many as 400 fetuses were examined, while in many reports, the number is below 100. In our study, 265 fetuses were assessed.

Similar findings were reported by Mete GU et al. [29] and Toosi FS et al. [30]. The above mentioned authors emphasize that fetal kidney measurements may be an excellent tool for pregnancy duration assessment in the third trimester. What is more, Konje JC et al. conducted observations between the 24th and 38th weeks of gestation and concluded that the fetal kidney length was a more predictive parameter for

determining pregnancy duration than other parameters, such as the biparietal dimension, head circumference, abdominal circumference or femur length [31].

Fetal kidney dimensions can be a useful parameter in situations where it is either difficult or simply impossible to calculate pregnancy duration based on standard parameters. Examples may include: the unknown date of the last menstrual period, low fetal head position, impeded measurements of head dimensions, the lack of ultrasound records (from the first and the second trimester), impossible assessment by routine parameters due to malformations, such as achondroplasia, phocomelia, amelia, hepato- and splenomegaly, agenesis of the cranial bones, *etc*. In many cases, measurements are either impossible for the lack of properly formed structures or distorted by pathological organ sizes.

Summing up, the results of our study, supported by a fair amount of medical evidence and conclusions of other authors, imply that precise pregnancy duration establishment is of the key importance for both entire perinatal care and reduction of neonatal morbidity and/or mortality rates. Biometric dimensions of fetal kidneys may constitute an additional tool for gestational age prediction.

The very high repeatability of measurements, with no impact of fetal sex or the latitude of the studied population, ensure homogeneous results in parallel studies. The development of normograms will perhaps enable percentile grids to be implemented in ultrasound systems to improve calculations in terms of time and reliability.

A strong positive correlation between the fetal kidney dimensions and pregnancy duration period may provide a basis for the measurements to be used as an isolated additional biometric parameter employed to calculate the gestational age, also in combination with other more common parameters, such as the biparietal diameter, head circumference, abdominal circumference or femur length.

CONCLUSIONS

Kidney dimensions strongly correlated with gestational age. Fetal kidney growth was a linear process in normal pregnancy.

Fetal kidney measurements can provide additional biometric parameters for accurate gestational age assessment.

Conflict of interest

All authors declare no conflict of interest.

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Prospective comparison of cervical ripening with double balloon Cook catheter, misoprostol or dinoprostone in term singleton pregnancies

Eliska Hostinska, Marek Lubusky, Radovan Pilka

Department of Obstetrics and Gynecology. Faculty of Medicine and Dentistry, Palacky University, University Hospital Olomouc, Olomouc, Czech Republic

ABSTRACT

Objectives: Induction of labor is indicated if the risk of continuing pregnancy is higher (either for fetus or mother) than the risk associated with the induction itself. The purpose of the present study was to compare the effectiveness of the double balloon Cook catheter and pharmacological preparations — prostaglandins (PGE), in our case it was misoprostol (PGE1) or dinoprostone (PGE2) for cervical ripening in pregnant women with gestational age at term.

Material and methods: The prospective observational study was conducted from March 2017 to December 2018. We used mechanical and pharmacological methods for cervical ripening. We compared the efficiency of methods and time to delivery from start of cervical ripening. We also evaluated the neonatal complications by Apgar score and neonatal intensive care unit admission in three different groups.

Results: Two hundred and nine women were chosen for cervical ripening. Double balloon Cook catheter and misoprostol were equally efficient in achieving vaginal delivery (76%). The shortest time for cervical ripening and successful vaginal delivery was shown in misoprostol (PGE1) group. In conclusion, no significant differences were found between groups in all neonatal outcomes.

Conclusions: Currently, many methods of delivery preinduction exist and the prevalence of their usage varies considerably between countries. As yet, there is no literature comparing these three methods for the preparation of cervix.

Key words: Bishop score; cervical ripening; prostaglandins

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INTRODUCTION

Induction of labor is one of the most common obstetric interventions. Its incidence is increasing worldwide [1]. The International Institute for Health and Care Excellence (NICE) from 2015 states that around 20% of women in the UK undergo the induction of labor each year [2]. Between 1990 and 2018, the overall frequency of induction of labor in the United States almost tripled, increasing from 9.5% in 1990 to 27.1% in 2018 [3].

At our department the average frequency of labor induction varied between 20–22% during last ten years.

Recent evidence shows that elective labor induction at term in low-risk nulliparous women is associated with lower risk of caesarean delivery, with no increase in adverse perinatal comorbidities [4]. Cervix maturation is a key to successful induction of labor. In absence of mature cervix, successful vaginal delivery is less likely [5]. To increase the success of vaginal delivery in adverse vaginal findings (usually defined as Bishop score < 6), we use effective mechanical and pharmacological methods. The use of oxytocin or artificial rupture of the membranes (ARM) is less likely to induce labor successfully in the absence of a favorable cervix. In such circumstances cervical ripening methods that soften, thin, and dilate the cervix are often needed to induce labor [6]. The ideal substance for cervical ripening should be effective, safe and easy to use [7].

Currently, many methods of delivery preinduction exist, and the prevalence of their usage varies considerably between countries. The purpose of the present single center prospective observational study was to compare the effectiveness of the double balloon Cook catheter with pharmacological preparations — prostaglandins, in our

Corresponding author:
Radovan Pilka
Department of Obstetrics and Gynecology. Faculty of Medicine and Dentistry, Palacky University, University Hospital Olomouc, I.P.Pavlova 6, 77900 Olomouc, Czech Republic
e-mail: radovan.pilka@fnol.cz

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Table 1. Indications — Comparison by Fisher's exact test

	Group	
	Cervical ripening	
	Count	%
Post-term pregnancy	66	31.58%
Growth restriction	36	17.22%
Pregestational DM	2	0.9%
Gestational DM	33	15.79%
Chronic hypertension	5	2.3%
Gestational hypertension	30	14.35%
Pre-eklampsia	13	5.9%
Intrahepatic cholestasis	7	3.2%
HDFN	23	10.5%
Stillbirth	5	2.3%
SGA	9	4.1%
Programmed childbirth	10	4.6%
Previous cesarean delivery	19	9.1%

case it was misoprostol (PGE1) or dinoprostone (PGE2) for cervical ripening in pregnant women with gestational age at term. As yet, there is no literature comparing these three methods for the preparation of cervix.

MATERIAL AND METHODS

In 2017 the double balloon Cook catheter was introduced to our clinical practice.

The aim of this prospective observational study was to show the non-inferiority of the double balloon Cook catheter compared to our standard of care represented by pharmacological methods. All eligible singleton pregnancies were grouped into double balloon Cook group (n = 72), misoprostol group (n = 67) and dinoprostone group (n = 70).

The study was approved by the Ethical Committee of University Hospital Olomouc. The informed consents were obtained from all participants before cervical ripening.

The study included 230 singleton pregnancies in the third trimester without signs of labor. Inclusion criteria were as follows: (1) 18–46 years old; (2) 37 + 0 to 42 + 1 weeks of pregnancy; (3) cervical Bishop score < 6; (4) singleton pregnancy; (5) head presentation; (6) no premature rupture of membranes; (7) physiological cardiotocograph monitoring before cervical ripening. The exclusion criteria were as follows: (1) any contraindication for vaginal delivery; (2) fetal anomaly; (3) multiple gestations; (4) non cephalic presentation; (5) history of two or more caesarean sections; (6) planned caesarean deliveries.

Pregnant women with the indication of a dead fetus and pregnant women with premature outflow of amniotic fluid before the due date were excluded from the study. Out of a total of 230 pregnant women, 209 women continued the study.

Two hundred and nine pregnant women in our study were fully informed of the advantages and disadvantages of diferent methods of cervical ripening.

According to the hospital protocol, all procedures were documented and the choice of pharmacological cervical ripening agent was made by individual provider, which resulted in an even distributive of both pharmacological agents in our study population. (dinoprostone in 33.49%, n = 70, misoprostol in 32.06% of cases, n = 67)

For high-risk pregnant women with a history of previous caesarean section, fetuses with growth restriction, small fetuses and suspect cardiotocograph monitoring cases we chose mechanical method, represented by double balloon Cook catheter (n = 72, 34.45% of cases).

In pregnant women with normal cardiotocograph monitoring, obese women, women with simple postmaturity, gestational hypertension, gestational diabetes mellitus, pre-eclampsia we chose one of two pharmacological methods.

The most common indications for cervical ripening were: postmaturity in 31.58% (n = 66), associated indications (2 or more) in 20.1% (n = 42), fetal growth restriction in 17.22% (n = 36), gestational diabetes mellitus in 15.79% (n = 33), gestational hypertensive disease in 14.35% (n = 30) and conditions after previous caesarean section in 9,1% (n = 19) (Tab. 1).

The double balloon Cook catheter was inserted into the cervix, each balloon on external and internal os was instilled with normal saline (80 mL). The proximal end of catheter was fixed to patient's thigh. If the spontaneous expulsion of catheter did not happen 24h after insertion, the catheter was removed artificially and Bishop score was assessed [8].

The vaginal insert misoprostol (PGE1) in dose of 200 µg withdrawal tape, was placed high in the vaginal posterior fornix and left there for a maximum of 24h, with a release rate of approximately 7 µg/h. The vaginal insert was removed with the onset of active labor (≥ 3 regular contractions/10 min) or painful contractions, cervical dilation of 2 cm or after the completion of maximum insertion time of 24 h [9].

Dinoprostone (PGE2) was inserted at the starting dose of 3 mg (1 tablet) high into the posterior vaginal arch. The second tablet was introduced after 6–8 hours if labor did not occur. The maximum daily dose was 6 mg.

Statistical analysis

quantitative data were expressed as mean, standard deviation (SD), minimum and maximum, and median. Due to big range of samples, the comparison of two independent samples in quantitative quantities was performed using two-sample t-tests. Comparison of several independent groups was per-

Table 2. Results of Kruskala-Wallis for maternal characteristics — age, body mass index (BMI), parity, epidural analgesia and success of vaginal labor

		Methods of cervical ripening						p
		Double balloon Cook catheter (n = 72)		Misoprostol (n = 67)		Dinoprostone (n = 70)		
		Count	%	Count	%	Count	%	
Age	< 35	48	66.70%	52	77.60%	52	74.30%	0.246[a]
	35–40	18	25.00%	14	20.90%	16	22.90%	
	> 40	6	8.30%	1	1.50%	2	2.90%	
BMI	< 25	47	65.30%	39	58.20%	36	51.40%	0.198[a]
	25–29.9	15	20.80%	19	28.40%	18	25.70%	
	30–34.9	7	9.70%	4	6.00%	10	14.30%	
	> = 35	3	4.20%	5	7.50%	6	8.60%	
Parity	0	37	51.40%	49	73.10%	47	67.10%	0.013[a]
	1	23	31.90%	15	22.40%	16	22.90%	
	2	10	13.90%	3	4.50%	5	7.10%	
	3	1	1.40%	0	0.00%	2	2.90%	
	4	1	1.40%	0	0.00%	0	0.00%	
Epidural analgesia	NO	36	50.00%	32	47.80%	36	51.40%	0.910[b]
	YES	36	50.00%	35	52.20%	34	48.60%	
Delivery	SC	17	23.60%	16	23.90%	28	40.00%	0.168[b]
	vaginal	50	69.40%	44	65.70%	38	54.30%	
	VEX	5	6.90%	7	10.40%	4	5.70%	

formed (due to big differences in file sizes) by non-parametric Kruskal-Wallis ANOVA. The correlation of quantitative quantities was verified by Pearson's correlation coefficient. Comparison of groups in qualitative quantities was performed using Fisher's exact test. The probability of vaginal delivery in time was plotted by using Kaplan-Meier curves. All tests were performed at the level of statistical significance of 0.05. IBM SPSS Statistics for Windows, Version 23.0 Armonk, NY: IBM Corp. statistical software was used for statistical processing.

RESULTS

From March 2017 to December 2018 we proceeded to cervical ripening in 209 women (4.8% out of all deliveries). With respect to gestational age in our study group 41 patients (19.62%) were in 37 weeks of pregnancy, 37 patients (17.7%) were in 38 weeks of pregnancy, 31 patients (14.83%) were in 39 weeks of pregnancy, 38 patients (18.18%) were in 40 weeks of pregnancy, 66 patients (31.58%) were in 41 weeks of pregnancy and one patient (0.48%) was in 42 weeks of pregnancy.

Seventy-two patients (34.45%) were allocated to the double balloon Cook catheter group, 70 patients (33.49%) into the dinoprostone (PGE2) group and 67 patients (32.06%) to misoprostol (PGE1) groups respectively. The demographic characteristics of the groups are shown in Table 2.

In double balloon Cook catheter group 48 patients (66.7%) were younger than 35 years, 18 patients (25.0%) were in the age group 35–40 years and 6 women (8.3%) were older than 40 years.

In misoprostol (PGE1) group 52 women (77.6%) were younger than 35 years. Between 35–40 years were 14 women (20.9%) and 1 woman was older 40 years (1.5%).

In Dinoprostone (PGE2) group 52 patients (74.3%) were younger 35 years, 16 patients (22.9%) were in the group 35–40 years and 2 women were older 40 years (2.9%).

The mean age of women was 31 (SD ± 5.31) years. There was no statistically significant difference in age categories between groups.

In double balloon Cook catheter group 47 patients (65.3%) had Body Mass Index (BMI) under 25 years old, 15 patients between 25–29.9 (20.8%), 7 patients (9.7%) between 30–34.9 and three patients (4.2%) had BMI 35 or more.

In misoprostol (PGE1) group 39 women (58.2%) had BMI under 25, nineteen women (28.4%) betweeen 25–29.9, 4 patients (6.0%) between 30–34.9 and 5 patients (7.5%) BMI 35 or more.

In dinoprostone (PGE2) group 36 women (51.4%) had BMI below 25 years old, 18 women (25.7%) between 25–29.9 years old, 10 women (14.3%) between 30–34.9 and 6 women (8.6%) 35 or more. Mean BMI was

Table 3. The time periods from the start of cervical ripening to first contractions (hours)

		The time from the start of cervical ripening to the start of first contraction (hours)					p
		Mean	SD	Minimum	Maximum	Median	
Methods of cervical ripening	Double ballon Cook catheter	22.89	14.28	4.00	76.00	23.25	0.005
	Misoprostol	15.68	11.03	3.50	47.50	13.25	
	Dinoproston	22.06	17.35	4.00	72.00	15.00	

The Kruskal-Wallis test showed statistically significant differences, p = 0.005. Subsequent post hoc tests with Bonferroni correction showed that there was a statistically significant difference only between the double balloon Cook catheter and misoprostol groups, p = 0.003.
The differences between the other pairs of groups are statistically insignificant

25.29 (SD ± 5.86). There was no statistically significant difference in age categories between groups. Mean gestation age at cervical ripening was 39.44 (SD ± 2.0 weeks).

In double balloon Cook catheter group 37 women (51.4%) were nulliparous, rest of cases were multiparous (n = 35, 48.6%).

In misoprostol (PGE1) group 49 patients (73.1%) had first pregnancy, in 18 cases (26.9%) it was a repeated pregnancy.

In dinoprostone (PGE2) group 47 women (67.1%) were nulliparous, rest of cases were multiparous (n = 23, 32.9%). There was statistically significant difference in age categories between groups — nulliparity and multiparity. (p = 0.013).

An epidural catheter was used in 105 cases (50.2%). In double balloon catheter group epidural catheter was inserted in 36 women (50.0%), of them 28 women (77.8%) had vaginal delivery, 6 women (16.7%) had caesarean section and 2 women (5.5%) operative delivery. In misoprostol (PGE1) group an epidural catheter was inserted in 35 women (52.2%), of them 23 women (65.7%) gave birth vaginally, 8 women (22.9%) had caesarean section and 4 women (11.4%) had operative delivery. In Dinoprostone (PGE2) group 34 women (48.6%) were treated with epidural analgesia (EDA), of them 18 patients (52.9%) gave birth vaginally, 12 patients (35.3%) by caesarean section and 4 patients (11.8%) by extraction vaginal delivery. The relationship between preinduction methods and EDA has not been shown.

We also chose a double-balloon Cook catheter in 26 cases of cervical ripening due to growth restriction of the fetus, where 23 women (88.5%) gave birth by vaginal delivery, 3 women by caesarean section (11.5%), also in conditions after caesarean section (n = 15), where 8 women gave birth spontaneous (53.3%) and 7 women had a caesarean section (46.7%).

There were no signifcant diferences in the spontaneous delivery rate in groups treated with different methods double balloon Cook catheter/misoprostol(PGE1)/dinoprostone (PGE2) (76.3% vs 76.1% vs 60%, p = 0.168) — or in rates of caesarean section (23.6% vs 23.9% vs 40.0%, p = 0.168).

Time to the first contractions from start of cervical ripening shows Table 3 and Figure 1. The Kruskal-Wallis test

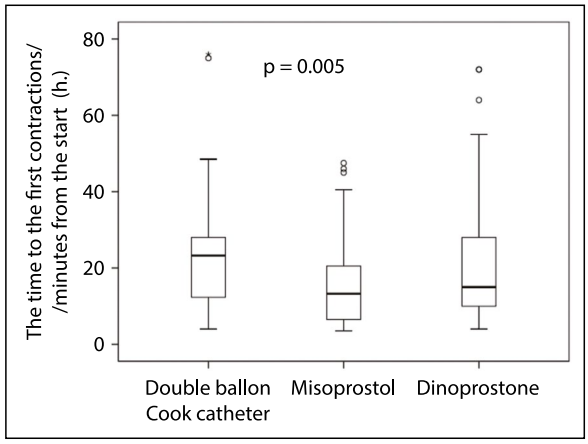

Figure 1. The time to the first contractions from the start in minutes
The distribution of the measured values was shown by a box graph. The horizontal line in the box shows the median value, the lower edge of the box the value of the 1st quartile (25th percentile), the upper edge the value of the 3rd quartile (75th percentile). The terminals show the maximum and minimum measured values. Outliers (values that are more than 1.5 times the interquartile range from the quartiles) are plotted in circles. Extremes (values that are more than 3 times the interquartile range from the quartiles) are plotted with asterisks

showed statistically significant differences, p = 0.005. Subsequent post hoc tests with Bonferroni correction showed that there was a statistically significant difference between the double balloon Cook catheter and misoprostol groups, p = 0.003. Dunn's test showed that time to delivery in double balloon Cook group (mean = 29.2 hours, median = 28.0 hours) was not different from the time in dinoproston group (mean 28.5 hours, median = 24.0 hours), but was longer than in misoprostol group (mean = 20.4 hours, median = 17.0 hours), p = 0.001 (Tab. 4 and Fig. 2).

Generally perceived advantages of mechanical methods over pharmacological ones include comparable efficacy, low risk of uterine hyperstimulation and fetal hypoxia, low risk of side effects such as nausea, vomiting, diarrhea, fever and potential economic and storage benefits [10, 11]. Side effects did not occur in our study.

Maternal complications or discomfort of mothers during cervical maturation with double balloon Cook catheter

Table 4. The time to delivery from start of cervical ripening (hours)

		Time to delivery from start of cervical ripening (hours)					p value
		Mean	SD	Min	Max	Median	
Methods of cervical ripening	Double balloon Cook catheter	29.19	14.85	4.50	77.00	28.00	0.001[d]
	Misoprostol	20.41	12.26	3.00	53.50	17.00	
	Dinoprostone	28.48	20.47	4.00	96.00	24.00	

Results of Kruskala-Wallis for time to delivery from start of cervical ripening. There was a statistically significant dependence of time to delivery on the methods of preinduction (p = 0.001)

were reported only in one percent of women. Postpartum infectious complications were not observed in any of the mothers. No cases of uterine rupture occurred during our study, but we reported three cases of scar dehiscence after catheter insertion were described perioperatively (0.5%) (Tab. 2).

As regards neonatological results in double balloon Cook catheter group the mean of birth weight was 2893 grams (g), median = 2930 g, in misoprostol group the mean of birth weight was 3383 g, median = 3440 g, in dinoprostone group the mean of birth weight was 3432 g, median = 3455 g (Tab. 3). There was a statistically significant difference between the groups due to preinduction of labor in small fetuses and fetuses with growth restriction by double balloon Cook catheter.

The median of pH of umbilical cord blood did not differ between groups (Tab. 5). Clinical status of newborns expressed as percentage of neonatal intensive care admissions did not differ between groups. We also evaluated the neonatal complications by Apgar score and neonatal intensive care unit admission in three different groups and no differences were found. In conclusion no significant differences were found between groups in all neonatal outcomes.

Comparison of mechanical (double-balloon Cook catheter) and pharmacological method — misoprostol (PGE1) revealed the same success of vaginal delivery (76.3% vs 76.1%), but more complications occurred with use of a pharmacological preparation due to more frequent occurrence of uterine hyperstimulation (n = 5, 2.39%) and fetal hypoxia (n = 31, 14.83%).

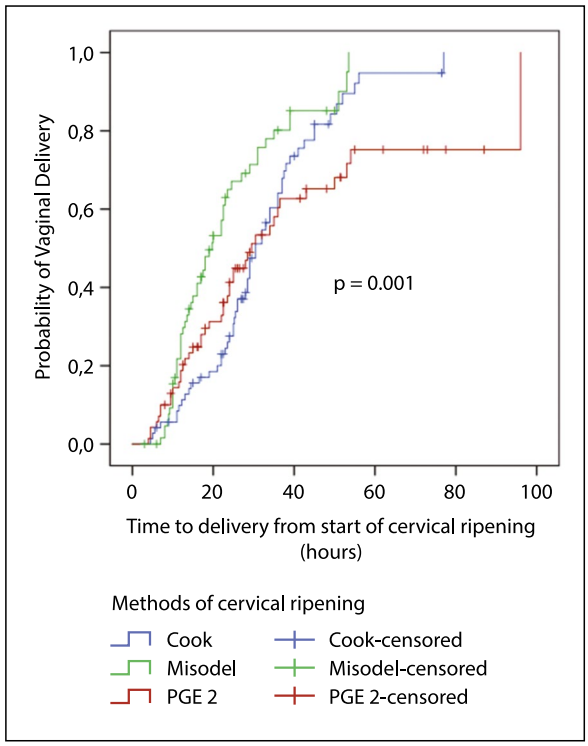

Figure 2. Kaplan-Meier curves ilustrating time to delivery from start of cervical ripening in hours

DISCUSSION

This prospective observational single-center study focuses on obstetrical and neonatal outcomes after cervical ripening with double balloon Cook catheter, misoprostol and dinoprostone and compares their efficacy and probability of vaginal delivery. Induction of labor is indicated if the risk of continuing of pregnancy is higher (either for fetus or for mother) than the risk associated with the induction itself [12].

Induction of vaginal delivery is generally associated with a decrease in caesarean sections regardless of gestational week, parity, or evaluation of vaginal findings. Maternal results reported fewer infectious complications, shoulder dystocia, and perineal injuries. Neonatal morbidity was reduced in induced births between 38 and 40 weeks [13]. The published work from 2017 states that induction of childbirth after the 39th week can reduce the risk of stillbirth. On the other hand, induction may be associated with increased hospitalization costs, reduced patient satisfaction, and slower onset of breastfeeding [14].

The use of cervical maturation methods has been shown to reduce the necessity of caesarean section when compared to initiating oxytocin induction in women with unfavorable cervix [15]. Induction of labor in the terrain of unfavorable cervix is associated with prolonged labor when compared to spontaneous onset of labor or induction of labor in a favorable cervix [16, 17].

Several methods have been proposed for cervical maturation, which are mainly divided into two groups —

Table 5. Newborns' characteristics and methods of cervical ripening

	Methods of cervical ripening															p
	Double balloon Cook (n = 70)					Misodel (n = 65)					PGE 2 (n = 70)					
	Mean	SD	Min	Max	Median	Mean	SD	Min	Max	Median	Mean	SD	Min	Max	Median	
birth weight (g)	2950	567	1940	4050	2945	3409	469	2200	4700	3440	3432	531	2340	4660	3455	< 0.0001
APGAR 1	9.09	1.73	1.00	10.00	10.00	9.25	1.48	4.00	10.00	10.00	9.07	1.54	3.00	10.00	10.00	0.564
APGAR 5	9.71	0.84	6.00	10.00	10.00	9.80	0.81	4.00	10.00	10.00	9.84	0.63	6.00	10.00	10.00	0.538
APGAR 10	9.96	0.20	9.00	10.00	10.00	9.98	0.12	9.00	10.00	10.00	10.00	0.00	10.00	10.00	10.00	0.180
PH	7.24	0.09	6.98	7.40	7.24	7.23	0.09	7.00	7.44	7.24	7.24	0.09	7.09	7.59	7.25	0.633
Lactate	5.06	2.19	0.40	10.90	4.70	5.05	2.54	0.50	11.80	4.40	4.66	2.02	0.50	9.60	4.50	0.663

Children born by the double balloon Cook method had significantly lower weight than newborns born by the misoprostol and dinoprostone methods ($p < 0.0001$)

mechanical and pharmacological. The ideal method should not be associated with adverse side effects neither in mother nor in fetus during cervical preparation 18].

The safety of prostaglandins for induction of labor in women with a preceding caesarean section has been questioned [19]. In 2001, Lydon Rochelle et al. described significantly more cases of uterine rupture in women whose birth was induced by prostaglandins after a prior caesarean section. Balloon catheters have been shown to be effective and safe even in women with a history of past caesarean section. According to Scandinavian authors in the publication from 2019, the success rate of vaginal delivery (using this method) ranges between 55.7–71.0% [20].

In our study, double balloon Cook catheter was most often used in the following indications: history of previous cesarean section (n = 19), intrauterine fetal growth restriction (n = 36). Our data showed 76.3% success rate of vaginal delivery (including extraction delivery). Spanish authors of a retrospective cohort study from 2017 state a 75.86% success rate of vaginal delivery in women with fetal growth restriction [21]. Our data showed 88.5% success rate of vaginal delivery in cases with fetal growth restriction, although this was a small subgroup.

A 2020 meta-analysis comparing vaginal misoprostol, dinoprostone, and a balloon catheter in small fetuses and growth-restricted fetuses states that mechanical methods are associated with lower incidence of adverse outcomes during pregnancy. However, there is limited evidence of the optimal type of labor induction in pregnancies with small fetuses [22].

Another parameter was the evaluation of the time from the start of induction to delivery.

In our study, the time from insertion of a double balloon Cook catheter to delivery was 29.19 ± 14.85 hours and sucess of vaginal delivery was 76%.

According to Chinese authors in a randomized study from 2019, time from double balloon catheter insertion to delivery was 21.8 ± 9.8 hours and success of vaginal delivery within 24 h from catheter insertion 52.8%, and within 48 h from catheter insertion 64.2% [8]. There was a significant difference in the time from double balloon catheter insertion to delivery due to the different length of catheter retention in situ. Chinese authors inserted the catheter for 12 hours, while we inserted it for 24 hours, but with higher success rate of vaginal labour.

Peng and al. in their retrospective study from 2021 compared the effects of double-balloon catheter within 12 h and within 12–24 h for the induction of labour in mid-trimester pregnancy. They found that the success rate of induction of labour was higher in the double balloon catheter group within 12–24 h (96.3%, 29/31) than in the double balloon catheter group within 12 h (71.0%, 18/27). Authors stated the time from induction to delivery in the 24h group was shorter than that in the 12 h group (median time, 27.0 h vs 29.8 h), but the difference was not statistically significant ($p > 0.05$). However, the time from double balloon catheter removal to delivery in the 12 h group (median time, 17.8 h) was longer than that in the 24 h group (median time, 3.0 h), indicating a significant difference ($p < 0.05$) [23].

Prostaglandins are the most used pharmacological agents in labor induction. Misoprostol (PGE1) and dinoprostone (PGE2) were shown to be equally effective in delivering success in case of preinduction. It is generally known that the use of PGE is associated with higher risk and earlier onset of uterine hyperstimulation and adverse changes in fetal heart rate [24].

Misoprostol is an often-used synthetic analog of PGE1 due to its low cost and ease of storage. Several publications have shown that the vaginal route of misoprostol is an effective method of inducing vaginal delivery comparable to oxytocin [25]. In the retrospective cohort study from 2020, Gornisiewicz et al. showed the success rate of vaginal delivery in 68.8% cases and time from vaginal misoprostol application to delivery to be 14.5 hours [26].

In our study, vaginal misoprostol (PGE1) administration resulted in successful vaginal delivery in 75.1% of cases ($p = 0.168$), and the time to delivery was 20.44 hours.

In the retrospective observational study of Mlodawski et al. [27] patients with misoprostol vaginal insert had significantly higher risk of caesarean section when compared to a Foley catheter cervical ripening (45.19% vs 27.72%, $p < 0.001$). The most common indication for operative delivery was, in cases of misoprostol use, nonreassuring fetal heart rate tracing.

Also, Nazanin et al. in a randomized controlled trial from 2021 described higher vaginal delivery success in Foley catheter group when compared to vaginal misoprostol group (85.0% vs 73.3%).

In their retrospective cohort study, Gornisiewicz et al. [26], authors reported 76.9% probability of vaginal delivery with dinoprostone gel use and time from drug application to delivery (vaginal and caesarean section) to be 35.6 hours.

In our study the success rate of vaginal delivery using dinoprostone tablets was 60% and time to delivery was 28.48 hours. In contrast with Gornisiewicz et al., where they were using dinoprostone gel, delivery success was highter in compare with our dinoprostone tablet.

According to Scottish authors from 2004, who compared dinoprostone gel with dinoprostone tablets, the success rate of vaginal delivery was equal (55.9% vs 50.3%) and time from start of induction to delivery was 25.2 hours versus 25.7 [28].

Papanikolaou et al. showed in misoprostol group more women delivered within 12 h in compared with dinoprostone tablets group (57.5% vs 32.5%, $p < 0.01$). The induction-delivery interval was significantly shorter in the misoprostol group (11.9 h vs. 15.6 h, $p < 0.001$) [29].

In case of cervical ripening with dinoprostone, this method proved to be the least effective of all methods, because it led to more frequent caesarean deliveries (60% vaginal delivery versus 40% caesarean section).

Our results in misoprostol and dinoprostone group correspond to the data published.

In our study we have shown double balloon Cook catheter to have comparable results in labor induction as pharmacological agents (commonly used prostaglandins — dinoprostone, misoprostol).

CONCLUSIONS

We have shown, that double baloon catheter is safe and effective method in labor induction. The time to first contractions with double balloon catheter and the time to delivery was equal to results of dinoprostone group, but longer than in misoprostol group. Hovewer, the indications for double balloon catheter clinical use were different from pharmacological methods. We did not observe any maternal and neonatological complications during the study. The aim of study was to show the advantage of mechanical double balloon catheter in labor induction in specificy subgroups of patients (growth restriction, uterine scar), further studies are needed.

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Conflict of interest

The authors declare no conflict of interest.

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Adropin in pregnancy complicated by hyperglycemia and obesity — a preliminary study

Lukasz Adamczak[1,2], Pawel Gutaj[1], Ewa Wender-Ozegowska[1]

[1]Department of Reproduction, Chair of Obstertics, Gynecology and Gynecological Oncology, Poznan University of Medical Sciences, Poland

[2]Doctoral School, Poznan University of Medical Sciences, Poznan, Poland

ABSTRACT

Objectives: According to the data, approximately 33–37% of women of reproductive age are obese. These numbers are reflected in the increasing number of complications in pregnancy, including gestational diabetes.

The study aims to assess the concentrations of adropin in the course of gestational diabetes and their possible relationship with the occurrence of obstetric complications characteristic for it.

Material and methods: The study included 65 obese and overweight pregnant patients (BMI > 27 kg/m^2) with glycemic disorders diagnosed during pregnancy. Blood samples we collected during visits: V0 — the first half of pregnancy V1 — 28–32 weeks of gestation, and V2 — 37–39 weeks of gestation. The concentrations of adropin were measured during V1 and V2 by ELISA tests. We analyzed the studied patients' anthropometric, metabolic parameters and obstetrical results.

Results: In the study group, at the visit V1, the mean level of adropin was 525.5 mmol/mL and 588.1 mmol/mL for the V2 visit. The comparison of adropin concentration between visits showed a statistically significant increase (p = 0.02). The concentration of adropin did not differ between obese and morbidly obese patients at V1, but at V2, there was a significant lover adropin level in morbidly obese patients.

Conclusions: In overweight and obese pregnant patients with gestational diabetes, the levels of adropin in serum increased significantly in the last trimester of pregnancy. The increase in concentration was significantly lower in the morbidly obese patients than in the obese group. The study provides the basis for further analyses of the role of adropin in pregnancies complicated by obesity and gestational diabetes.

Key words: adropin; gestational diabetes mellitus; obesity; pregnancy

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INTRODUCTION

Hyperglycemia in pregnancy, defined either as gestational diabetes mellitus (GDM) or overt diabetes/diabetes in pregnancy (DIP), is associated with adverse feto-maternal outcomes [1]. The Hyperglycemia and Pregnancy Outcomes (HAPO) study showed that the risk of adverse perinatal outcomes increased due to maternal glycemia, even within ranges considered normal for pregnancy [2]. Both GDM and even diabetes in pregnancy rarely present with symptoms. Diagnosis is made by screening and clinical risk factors used to identify it in early pregnancy or between 24 and 28 weeks. Gestational diabetes mellitus (GDM) has become more prevalent since the introduction of more stringent criteria for diagnosis [World Health Organization (WHO), 2013] and a constantly growing number of overweight and obese women of reproductive age. According to national guidelines every women in Poland should be screened for risk factors for hyperglycemia in pregnancy. In high-risk women, 75 g oral glucose tolerance test (OGTT) at first visit during gestation confirms or excludes the GDM [Polish Society of Obstetricians and Gynecologists (PSOG), Polish Diabetes Society (PDS)] [3].

Maternal hyperglycemia is a well-known risk factor for adverse neonatal outcomes. Nowadays, increasing evidence shows that non-glycemic risk factors for perinatal complications are still more frequent in diabetic pregnancies despite improved maternal metabolic control [4]. Among them, particularly maternal obesity has gained growing attention as an independent contributor to feto-maternal complications.

Body mass index (BMI) is a risk factor in pregnancy to identify women at risk of developing hyperglycemia

Corresponding author:
Lukasz Adamczak
Department of Reproduction, Chair of Obstertics, Gynecology and Gynecological Oncology, Poznan University of Medical Sciences, 33 Polna St, Poznan, Poland
e-mail: lukaszadamczak91@gmail.com

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and other perinatal complications. Several adipokines may also serve as factors confirming the role of adipose tissue in developing carbohydrate disturbances. Adropin is a peptide hormone involved in glucose and fatty acids metabolism [5]. It is produced mainly in the liver, CNS tissues, kidneys and pancreas. In mice, adropin promotes muscle glucose oxidation more than fatty acid oxidation. It increases glucose tolerance by reducing insulin resistance. In a mouse model, it has also been shown that adropin reduces blood glucose levels by inhibiting its production in the liver [6]. The role of adropin in pregnancy complicated by diabetes and obesity has not been extensively studied in humans.

We wanted to confirm that hyperglycemia detected in early pregnancy is related to the degree of maternal obesity and that severity of obesity is associated with feto-maternal complications. We assumed also that hyperglycemia detected in early pregnancy and its consequences together with other metabolic aterations, might be associated with changes in concentration of adropin.

MATERIAL AND METHODS

We analyzed 389 pregnant women with hyperglycemia detected during pregnancy, admitted to the Department of Reproduction at Poznan University of Medical Sciences in 2018–2020. The study included 65 patients who met the inclusion criteria: single pregnancy, age ≥ 18 years, BMI before pregnancy ≥ 30.0 kg/m^2 and hyperglycemia diagnosed during pregnancy.

The study protocol encompassed three visits: the enrolment visit (V0) — the first patient's admission to the Department immediately after diagnosing glycemic disorders, the first study visit (V1) between 28 and 32 gestational weeks (GW), and the second study visit (V2) between 37 and 39 GW. Finally, we analyzed the feto-maternal results. On the V1 and V2, anthropometric measurements and blood sample collection we performed in all patients. In the study group, hyperglycemia during pregnancy was diagnosed according to the diagnostic criteria of the Polish Diabetes Association of 2017 (4). Diabetes in pregnancy (DIP) was diagnosed according to the 2013 IADPSG and WHO classification and adopted in our country [7]. Upon the first admission, all referred women participated in the dietary treatment and glucose self-control training. In women with DIP, insulin therapy in a basal-bolus mode was initiated immediately after the admission. Women with GDM had their follow-up visits scheduled every two to three weeks in the outpatients' clinic. If glycemic targets were not met at the first follow-up visit, we added insulin therapy in a basal-bolus mode to the diet.

The study group was divided according to the severity of obesity based on the WHO classification [8]. The obese patients were compared with morbidly obese to find possible differences between patients with the first grade of obesity and morbid obesity.

Blood samples were taken overnight in the fasting state and immediately transported for analysis. Serum concentrations of adropin we determined during the V1 and V2, using the enzyme-linked immunosorbent assay (ELISA) [Commercial kits Human AD (Adropin) ELISA Kit]. Fetal weight diagnosed as LGA — large for gestational age or as SGA — small for gestational age were defined according to Fetal Medicine Foundation criteria [9].

We used Statistica 13.1 program. Descriptive statistics characterized parameters — the D'Agostino-Pearson test we used for testing the normality of data distribution. Student's t-test we used to check t the difference between two continuous variables If data fitted normal distribution. Comparisons of non-normally distributed data we performed using the Mann-Whitney test. The Chi-Square test was used to examine differences between categorical variables.

RESULTS

The study group was characterized by anthropometric and metabolic parameters, obstetric results, and neonatal outcomes. They are presented in Table 1.

Comparing patients with the first degree of obesity with patients with the third degree of obesity has shown a significant difference in HbA1c values between both groups, only during the V0 visit. There were also no differences in daily insulin doses between groups. In patients with lower stage of obesity, a more significant increase in HbA1c we noted than in morbidly obese patients both between individual visits and during the entire period of pregnancy. We noticed a significant increase in adropin concentrations measured at V1 and V2 ($p = 0.02$) (Tab. 1).

We also analyzed the correlations between adropin concentration with BMI, weight gain, HbA1c, triglycerides, CRP, placental weight. There were no significant correlations. Adropin did not differ between obese and morbidly obese patients at visit V1. At the end of pregnancy at V2, adropin's concentration was significantly lower in morbidly obese patients than in obese. Adropin concentration in the third trimester was significantly higher in obese patients than in the second one. There were no differences in neonatal outcomes between these two analyzed groups.

DISCUSSION

In our preliminary study, a significant increase in the concentration of serum adropin was observed in the third trimester among hyperglycemic women with obesity and but not in women with morbid obesity. We know from previous studies that adropin levels in women with gestational diabetes are lower than those in healthy pregnant women [10]. However, our study showed increased adropin concentration in the last

Table 1. Characteristics of the study group

	Study group (n 65)	Obese (n 20)	Morbidly obese (n 21)	p*
Maternal age [years]	32.4	32.2	32.2	0.9
Maternal BMI BP [kg/m^2]	36.9	32.6	43.7	0.02
Maternal BMI V1 [kg/m^2]	38	34.6	43.2	< 0.01
Maternal BMI V2 [kg/m^2]	38.8	35.5	44.2	< 0.01
Maternal weight change (BP to V1) [kg]	2.4	5.9	–1.4	< 0.01
Maternal weight change (V1 to V2) [kg]	2.5	2.5	2.5	0.9
Maternal weight change (BP to V2) [kg]	4.6	7.0	1.25	0.004
Metabolic parameters				
Gestational diabetes in previous pregnancy n [%]	15	3	6	0.3
Diabetes in I grade relatives n [%]	44	16	18	0.7
75g OGTT results 0 min [mg/dL] 60 min [mg/dL] 120 min [mg/dL]	 100 179.5 141	 100.1 188.7 148.2	 103.1 181.8 149.3	 0.2 0.3 0.5
Beginning of dietary treatment [week of pregnancy]	12	11	11	0.5
Beginning of insulin therapy [week of pregnancy]	16	15	14	0.6
Insulin therapy n (%)	56	16 (80)	18 (86)	0.6
HbA1c V0 [%]	5.3	5.1	5.4	0.02
HbA1c V1 [%]	5.1	52	5.0	0.3
HbA1c V2 [%]	5.5	5.3	5.5	0.9
HbA1c change V0–V1	–0.1	0.19	–0.38	< 0.01
HbA1c change V1–V2	0.3	0.2	0.34	0.2
HbA1c change V0–V2	0.2	0.37	0.03	0.01
CRP V0 [mg/dL]	8.12	5.0	14.0	0.001
CRP V1 [mg/dL]	7.48	6.1	13.4	0.008
CRP V2 [mg/dL]	8.3	5.2	7.1	0.2
Chronic hypertension n (%)	12	4 (20)	8 (38)	0.2
Gestational hypertension n (%)	8	4 (20)	3 (14)	0.7
Preeclampsia n (%)	7	2 (10)	3 (14)	0.4
Adropin concentration V1 [pg/mL]	525.5	557.8	534.7	0.7
Adropin concentration V2 [pg/mL]	588.1	690.2	551.5	0.04
Adropin concentration change V1–V2 [pg/mL]	62.6	143.4	10.6	0.04
Perinatal outcome				
Week of delivery median [week] (IQR)	38 (0)	38 (0)	38 (0)	
Premature birth n (%)	4 (6)	1 (5)	1 (5)	0.7
Cesarean section n (%) Elective Urgent	45 (68,5) 33 (73) 12 (27)	14 (70) 12 (86) 2 (14)	16 (76) 12 (75) 4 (25)	0.6 1 0.4
Neonatal birthweight median [g] (IQR)	3610 (680)	3540 (590)	3640 (675)	0.5
Birthweight centile acc. to FMF [centile] LGA > 90 n (%) SGA < 10 n (%)	89 30 (45.5) 2 (3)	70 8 (40) 1 (5)	74 14 (67) 0	0.2 0.2 0.1
Neonatal birthweight > 4000 g n (%)	8 (12)	3 (15	2 (10)	0.6
Neonatal birthweight > 4250 g n (%)	3 (4.5)	2 (10)	0	0,1
Apgar score 1st minute — median (IQR)	10 (1)	10 (1)	10 (1)	0.6
Apgar score 5th minute — median (IQR)	10 (1)	10 (0)	10 (0)	0.6

p* — the difference between obese and morbidly obese group; BMI — body mass index; BP — first visit in pregnancy; CRP — C-reactive protein; DBP — diastolic blood pressure; HbA1c — glycated hemoglobin; SBP — systolic blood pressure; TAG — triglyceride; $V_{0,}$ — inclusion visit; V_1 —28–32 GA visit; $V_{2,}$ — 37–40 GA visit; OGTT — oral glucose tolerance test; LGA — large for gestational age; SGA — small for gestational age; IQR — interquartile range

weeks of pregnancy, especially in the slimer subgroup, which has not been previously reported. It has been demonstrated in animal models that the exogenous administration of adropin promotes the reduction of insulin resistance and enhances glucose tolerance [11]. Our patients, in whom we observed an increase in adropin concentration, were well metabolically controlled and maintained low fat and low carbohydrate diet, as was evidenced by proper HbA1c values. Most of them were treated with insulin from the end of the first trimester. It might have affected the endogenous increased secretion of adropin, which regulates the glucose metabolism in the pregnant state. The available studies have reported that BMI significantly influences the concentration of adropin [12]. In the entire study group, during V1, the difference in adropin concentration was not significant; however, at the end of pregnancy concentration of adropin increased significantly in the slimer liner group of patients [15].

Adropin influences the expression of an inducible nitric oxide synthase, explaining its potential role in predicting endothelial dysfunction in patients with diabetes mellitus [13]. We would like to emphasize that both groups differed metabolically only in CRP concentrations aside from BMI and anthropometrics. We speculate that it might be the critical factor predisposing to lower adropin concentration in morbidly obese women, especially in late pregnancy when insulin resistance rises significantly. The literature described a reduction in adropin levels in obese people, as shown in our study [14]. We showed no correlation between the concentration of adropin and the newborns' birth weight.

Qiu et al. [15] assessed the correlation between adropin in the umbilical cord blood. They found no correlation with the birth weight of newborns, but a positive correlation occurred with the weight of the placenta what we also observed in our study. The available literature does not explain this phenomenon, but there are assumptions that adropin is also partly produced by the placenta.

CONCLUSIONS

Despite being morbidly obese, the patients were metabolically well-controlled, which probably resulted in the lack of significant differences in obstetric results in both groups. Interestingly, patients with the first degree of obesity in the third trimester experienced a significantly higher adropin concentration than patients with the third degree. We speculate that a lower BMI is conducive to endogenous adropin production and its protective effect on insulin resistance increase at the end of pregnancy.

To conclude, our study presents novel findings on the role of adropin in the pathomechanism of insulin resistance and carbohydrate disturbances in pregnancy complicated with obesity. In some cases, we have found that the ability to produce adropin in a higher amount reduces insulin resistance and might protect against hyperglycemia. However, it also has significant limitations such as relatively small sample size and lack of healthy controls. Addressing these issues in future studies could further explain the role of this adipokine in pregnancy-related complications.

Contribution statement

LA and EWO conceived the idea for the study. EWO contributed to the design of the research. LA was involved in data collection. LA and PG analyzed the data. All authors edited and approved the final version of the manuscript.

Conflict of interest

All authors declare no conflict of interest.

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Foetal macrosomia — incidence, determinants and neonatal outcomes: 10-years retrospective review, 2010–2019

Marta Buraczewska[1], Mateusz Bonin[2], Jaroslaw Meyer-Szary[3], Amelia Wawer[1], Patrycja Wieczorek[1], Olga Gapska[1], Karolina Filipczyk[1], Paulina Samusik[1], Ewa Michalik[1], Iwona Sadowska-Krawczenko[4]

[1]Neonatology Department with Intensive Care Unit, Wejherowo Specialistic Hospital, Pomeranian Hospitals, Gdynia, Poland
[2]Department of Paediatrics, Endocrinology and Diabetology, Voivodeship Children's Hospital in Bydgoszcz, Poland
[3]Department of Paediatric Cardiology and Congenital Heart Diseases, Medical University of Gdansk, Poland
[4]Department of Neonatology, Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University in Torun, Poland

ABSTRACT

Objectives: Prevalence of macrosomia differs worldwide according to studied population and has been variable over last few decades. The objective of the study was to determine the trends in incidence and clinical characteristics of infants with macrosomia born in two diverse Polish neonatal centres from 2010–2019.

Material and methods: Trends in the incidence of macrosomia, maternal age, delivery mode and neonatal complications were analysed over a 10 year period based on birth medical records.

Results: The total number of 43 165 term neonates were analysed with macrosomia incidence of 16.63% (n = 7179). The prevalence of macrosomia was stable from 2010–2019 irrespectively of referentiality and geographical area. Mean maternal age increased over the decade with higher age of mothers of macrosomic neonates. Recognizability of gestation diabetes among pregnant women increased from 9.61% in 2010 to 15.27% in 2019 and it was comparable in mothers of macrosomic infants. The percentage of caesarean sections was higher in macrosomic neonates and gradually increased over last decade. The highest percentage of birth injuries was observed in the first grade of macrosomia (4000–4499 g). The number of neonatal complications including lower Apgar score, respiratory and cardiology symptoms correlated with severity of macrosomia, with highest morbidity in children above 5000 g.

Conclusions: The prevalence of macrosomia in the studied cohort remained invariable over the last decade. Macrosomia is associated with an increased rate of caesarean sections, higher maternal age and increased neonatal morbidity. A higher macrosomia grade is related to a worse neonatal outcome. Further studies on other risk factors of macrosomia are needed.

Key words: foetal macrosomia; birthweight; growth acceleration; gestation diabetes

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INTRODUCTION

Foetal macrosomia is defined as birthweight of beyond 4000 g regardless of gestation age. Three grades of foetal macrosomia include: 1st grade 4000–4499 g, 2nd grade 4500–4999 g, 3rd grade of 5000 g and more.

The incidence of foetal macrosomia varies worldwide depending on studied population (Denmark: 20%, Australia 12.8%, USA 8.07%, China 7.83%, Israel 4.4%, Japan 0.9%) [1–7].

Global growth acceleration and increased incidence of foetal macrosomia have been observed over the past several decades. Long-term reviews describe the increase of macrosomia over the years due to improved maternal nutrition, reduced nicotine intake during pregnancy, raised maternal age, higher pre-gestational body mass index (BMI) and considered to be most relevant — increased gestational weight gain [8, 9]. Significant birth weight acceleration and increasing prevalence of foetal macrosomia has been observed particularly in Nordic countries [2]. For instance, in Aarhus, Denmark the percentage of children born with birth weight above 4000 g increased from 16.7% in 1990 to 20%

Corresponding author:
Marta Buraczewska
Neonatology Department with Intensive Care Unit, Wejherowo Specialistic Hospital, Pomeranian Hospitals in Gdynia, 10 Jagalskiego St, 84–200 Wejherowo, Poland
e-mail: szymanskam@gazeta.pl

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in 1999 [3]. An increasing trend of foetal macrosomia has been observed regardless the geographical area. In Queens, Australia a 17-year observation revealed an increase of foetal macrosomia from 12.2% to 12.8% [4].

Contrary to that, in some countries rising trends in foetal macrosomia has been reversed over the last 2 decades. Current studies reveal the decline in prevalence of macrosomia in United States of America, China and Brazil [1, 6, 10]. These results have been supported by the improvement of obstetric care, especially management of gestation diabetes [1]. In China, a 20-year review revealed an increase of macrosomia from 6% to 8.49% between 1994–2000 and following subsequent decline in 2005 to 7.83% [6]. The longest study (47 years) from United States conducted between 1971–2017 revealed initial increase of macrosomia from 8.84% to 11.8% in 1985 followed by a subsequent drop to 8.07% by the end of the study [1].

Complications of foetal macrosomia includes numerous aspects of perinatology: traumatic delivery, maternal and neonatal complications such as birth injuries, cardiology and respiratory failure and metabolic abnormalities that may significantly affect further physical development [11]. Long-term consequences of foetal macrosomia include diabetes, metabolic syndrome, obesity and asthma [12–14]. The risk of significant complications correlates with macrosomia grade [15, 16]. Although the risk of mortality and morbidity in the first stage of macrosomia is comparable to the general population, in children born with weight of 4500 g and more the risk of neonatal mortality is significantly higher [16, 17].

So far there has been no long-term study including the incidence, trends and phenotype of Polish infants with foetal macrosomia. Despite the implementation of widely applied guidelines of Polish Obstetrics and Gynaecology Society including appropriate management of pregnant women with risk of foetal macrosomia, still there are no neonatal guidelines regarding clinical management of large infants [18]. Due to common phenomenon of acceleration in birthweight, it is essential to revaluate potential risks and complications depending on grades of macrosomia and assess in which infants' additional clinical management should be applied.

Objectives

The aim of the study was to determine clinical characteristics of infants with foetal macrosomia born in two diverse Polish neonatal centres between 2010–2019.

Authors attempted to assess the variability of incidence in macrosomic births in studied population over a 10-year observation. In addition, the study aimed to assess two various cohorts of neonates born in distinct geographic area, different referentiality centres and to evaluate clinical complications according to applied perinatal management and grade of foetal macrosomia.

MATERIAL AND METHODS

The study retrospectively reviewed a population of 43 156 term live births (gestation age of 37 and more) from 2010–2019 in 2 various neonatal centres. Pre-term infants of < 37 gestation weeks were excluded from the study.

First cohort of patients included 27 465 term births from second stage referentiality Neonatal Unit in Wejherowo Specialistic Hospital. The second cohort included 15 691 term births delivered in third stage referentiality Department of Neonatology in University Hospital No. 2 in Bydgoszcz.

Studied cohorts were assessed separately and combined. Trends in the incidence of macrosomia and variability of maternal age were analysed over a 10-year period.

Data collected from birth medical records included: maternal age, birth weight, gender, mode of delivery, Apgar score, maternal complications including gestational diabetes, neonatal complications including birth injuries, respiratory, cardiological complications and jaundice. Birth injuries were divided into clavicular fracture, brachial plexus palsy and head injuries (caput succedaneum, cephalohaematoma and subaponeurotic haematoma).

Based on the recommended classification in the literature macrosomia was defined as birth weight ≥ 4000 g. The analysis of macrosomia phenotype included 3 grades: 1st grade 4000–4499 g, 2nd grade 4500–4999 g, 3rd grade ≥ 5000 g.

Macrosomic births were compared to controlled group of all term births.

Statistical analyses were performed using Wizard 2.0 (Evan Miller Chicago, IL). Categorical variables were expressed as count (n) and percentages. Continuous variables were expressed as mean ± standard deviation or median (minimum–maximum) dependently on the distribution. Normality of distribution was tested using Shapiro-Wilk test. Student t-test or ANOVA and Mann-Whitney or Kruskal-Wallis tests were used as appropriate. Categorical data was compared with a chi-squared test. Statistical significance (p) less than 0.05 was considered significant.

Approval for the study was granted by Bioethical Committee of Medical University in Torun, *Collegium Medicum* in Bydgoszcz (KB 356/2020).

RESULTS

During the study period 48910 live births were analysed in two described medical centres. Preterm births of < 37 gestation age (5754, 11.8%) were excluded from the study. Remaining 43 165 term births were analysed.

Foetal macrosomia was observed in 7179 (16.63%) infants with following grade distribution: 1st grade

Table 1. Characteristics of studied cohorts according to referentiality centres

	Neonatal Unit with Intensive Care in Wejherowo, Pomeranian Hospitals (2nd stage of referentiality)				Department of Neonatology University Hospital No 2 in Bydgoszcz (3rd stage of referentiality)			
	All term births		Foetal macrosomia (≥ 4000 g)		All term births		Foetal macrosomia (≥ 4000 g)	
	27465	100%	5026	18.30%	15691	100%	2153	13.72%
Male	14017	51.04%	3178	63.23%	8137	51.86%	1412	65.58%
Female	13448	48.96%	1848	36.77%	7551	48.12%	741	34.42%

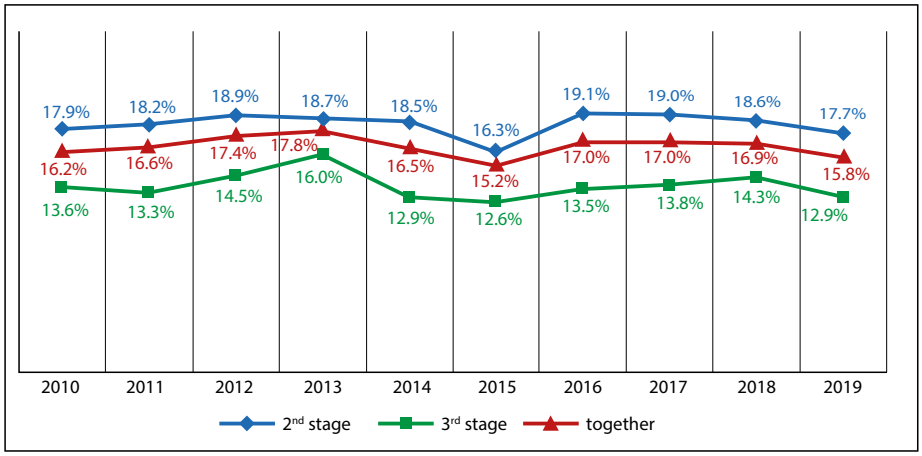

Figure 1. Incidence of macrosomia from 2010–2019 together (p = 0.092) and according to studied referentiality medical centre (2nd stage: p = 0.442, 3rd stage: p = 0.266)

5953 (13.79% of term births, 82.92% of macrosomic births), 2nd grade 1104 (2.56% of term births, 15.38% of macrosomic births), 3rd grade 122 (0.28% of term births, 1.7% of macrosomic births). The percentage of macrosomic infants was higher in 2nd stage referentiality unit (n = 5026, 18.3%) comparing to 3rd stage referentiality unit (n = 2153, 13.72%) (p < 0.001) In both cohorts, prevalence of macrosomia was higher in males (Tab. 1)

During a 10 year observation period no significant change in foetal macrosomia incidence was observed separate in each medical centre and all together (p = 0.092) (Fig. 1).

Maternal age

In both compared cohorts of mothers: mothers in total and mothers of macrosomic infants increase of maternal age was observed over a 10-year duration of the study (Tab. 2).

Although over a 10-year observation in total, mothers of macrosomic infants (n = 7196, mean age 29.55 ± 4.99 years) were older in comparison to mothers of all term infants (n = 43165, mean age 29.25 ± 5.25) (p < 0.001), at the end of the study, in year 2019 the age of macrosomic mothers and others was comparable (p = 0.95) (Fig. 2).

Table 2. Increase of maternal age (years) in studied cohorts between the years 2010–2019

Mean maternal age	2010	2019	p value
All infants > 37 hbd	28.62 ± 5.12	29.82 ± 5.31	< 0.0001
Macrosomic infants	28.81 ± 4.94	29.81 ± 4.94	< 0.001

Gestational diabetes mellitus

Analysed medical records revealed 4577 mothers with diagnosed gestational diabetes mellitus (GDM) (10.61%). The percentage of gestational diabetes in mothers of macrosomic infants was 10.25% (n = 7197) and was comparable to general population (p = 0.29). Figure 3 presents different GDM distribution according to referentiality centre. Regardless of analysed centre there was no significant difference of prevalence of GDM in mothers of macrosomic infants comparing to general population (2nd stage centre p = 0.05, 3rd stage centre p = 0.10).

Recognizability of gestational diabetes among pregnant women gradually increased over a study period from 9.61% in 2010 to 15.27% in 2019.

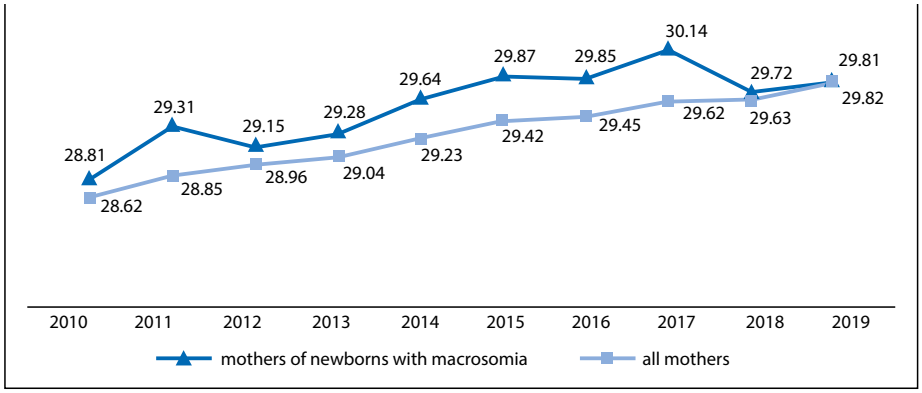

Figure 2. Distribution of mean maternal age (years) in 2010–2019 in macrosomic infants and all births

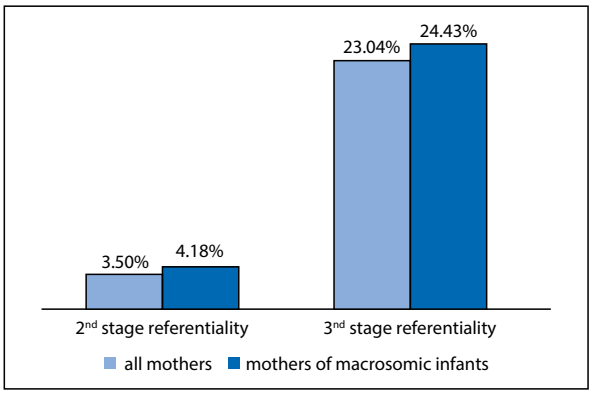

Figure 3. Percentage of gestational diabetes among pregnant women with distribution to referentiality centres

Due to limited data, it was not possible to analyse distribution of various types of gestational diabetes (Fig. 4).

Delivery mode

In studied cohort 32378 infants were born by vaginal delivery (VD) (75.03%) and 10 778 by caesarean section (CS) (24.97%). In 970 of infants delivered vaginaly (n = 970, 2.25%) vacuum or forceps were applied. In macrosomic infants increased number of caesarean sections (n = 2242, 31.23%, $p < 0.001$) and decreased number of vacuum/forceps delivery were observed (n = 143, 1.99%, $p < 0.001$) comparing to all infants.

Over 10-years the percentage of caesarean section deliveries significantly increased in total from 20.31% in 2010 to 29.26% in 2019 (Pearson correlation, $p < 0.001$, $r = 0.062$, $r^2 = 0.004$). Caesarean section deliveries of macrosomic infants also increased and ranged from 24.01% in 2010 to 38.25% in 2019 (Pearson correlation, $p < 0.001$, $r = 0.093$, $r^2 = 0.009$) (Fig. 5).

Figure 5 presents different rates of caesarean section deliveries according to referentiality centre.

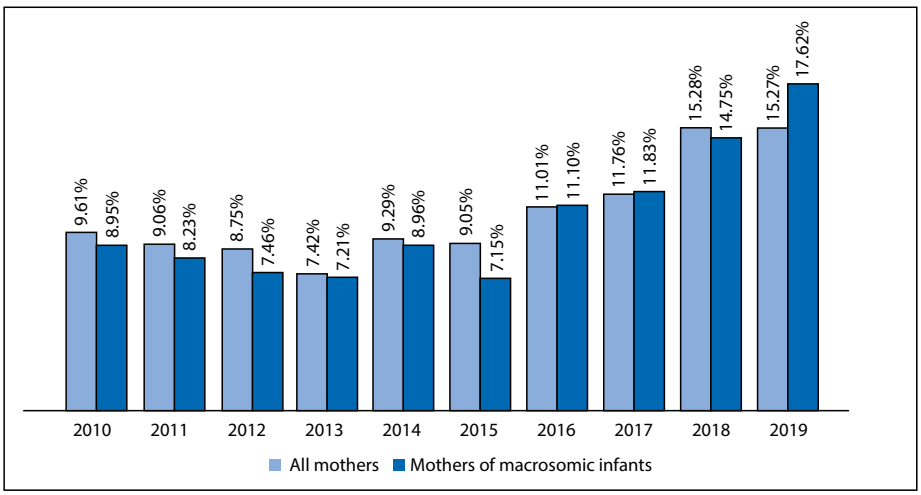

Figure 4. Recognizability of gestational diabetes among pregnant women in studied cohort during years 2010–2019

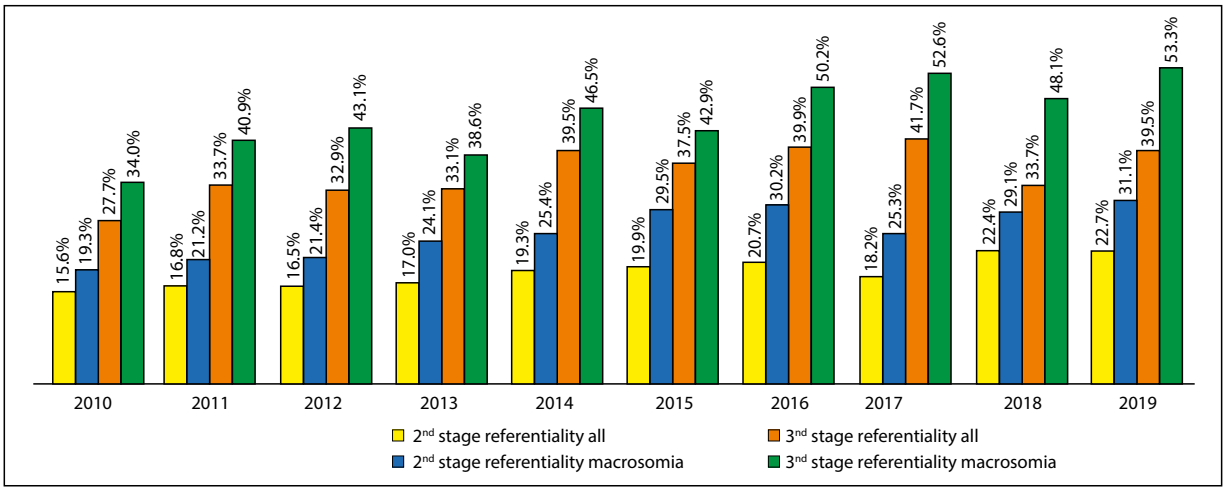

Figure 5. Rate of caesarean section delivery in studied cohorts from 2010–2019

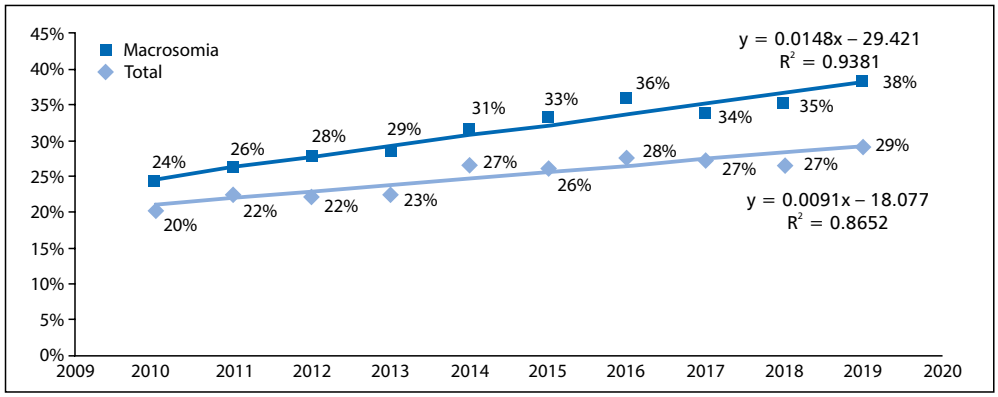

Figure 6. Rate of caesarean section deliveries in years 2010–2019 in total and in macrosomic deliveries

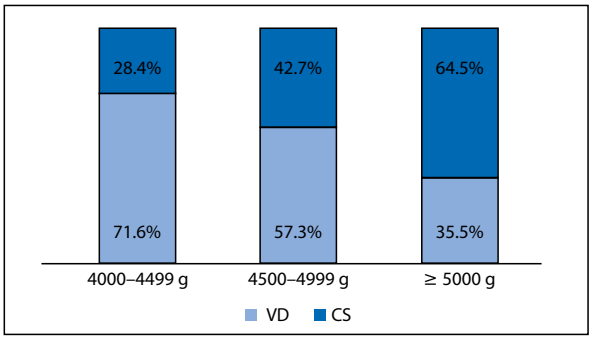

Figure 7. Increase of percentage of caesarean sections (CS) versus vaginal delivery (VD) according to macrosomia grade

The percentage of performed caesarean sections increased according to macrosomia grades with the highest percentage of 64.5% in infants with birthweight of 5000 g and more (Fig. 7).

Number of performed forceps or vacuum delivery decreased from 2.2% of infants with first grade macrosomia to 0.8% of infants with 3rd grade ($p < 0.0001$) (Fig. 6).

Perinatal complications

Cohort of macrosomic infants in both centres was characterised by increased number of birth injuries including head injury (caput succedaneum, cephalohaematoma and subaponeurotic haematoma), clavicular fracture and brachial plexus injury. Cardiovascular symptoms such as cyanosis, heart murmur or abnormal pulsoximetry test included 7.06% of macrosomic infants in comparison to 5.56% of all infants ($p < 0.001$). There was no difference in prevalence of respiratory symptoms in macrosomic infants comparing to other infants. Jaundice was observed significantly less frequently in macrosomia cohort ($p < 0.001$) (Tab. 3).

Distribution of perinatal complications was also analysed according to macrosomia grades. Birth injuries gradually de-

Table 3. Perinatal complications in studied cohorts

	All infants (n = 43165)	%	Macrosomia (n = 7196)	%	p value
Birth injuries					
Head injuries	750	1.74	102	1.42	0.024
Clavicular fracture	157	0.36	59	0.82	< 0.001
Brachial plexus injuries	23	0.05	12	0.17	< 0.001
Other complications					
Cardiovascular	2403	5.57	507	7.062	< 0.001
Respiratory	903	2.09	156	2.883	0.61
Jaundice	2264	5.25	316	4.402	< 0.001

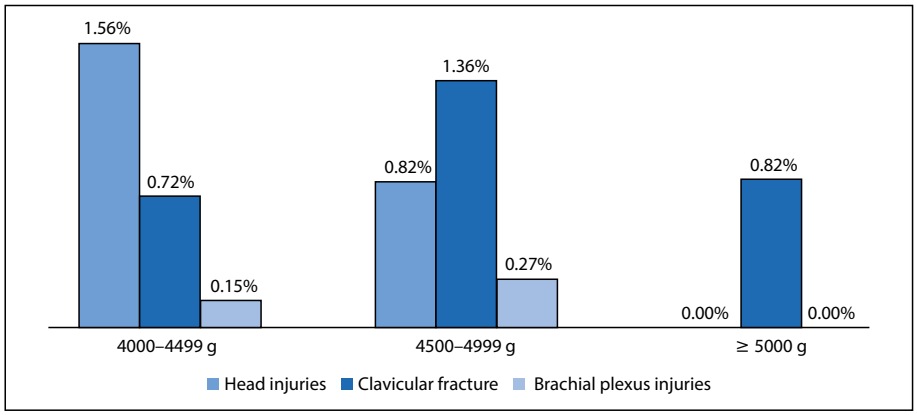

Figure 8. Percentage of birth injuries according to macrosomia grade

creased in subsequent macrosomia grades, what correlated with increasing percentage of caesarean sections and decreasing prevalence of vacuum and forceps deliveries. Number of head injuries significantly decreased in each macrosomia grade (1st grade: n = 93, 1.56%; 2nd grade: n = 9, 0.82%, p = 0.031; 3rd grade: n = 0, 0%, p = 0.017). Clavicular fractures were observed most frequently in 2nd grade of macrosomia (n = 15, 1.36% in 2nd grade vs n = 43, 0.72% in 1st grade, p = 0.031) and its percentage decreased in 3rd grade (n = 1, 0.82%, p = 0.013) (Fig. 8). Brachial plexus injuries were observed most frequently in 2nd grade macrosomia (n = 3, 0.27%), however there was no statistical difference between other grades of macrosomia (1st grade: n = 9, 0.15% vs 2nd grade: n = 3, 0.27%, p = 0.37; 2nd grade vs 3rd grade: n = 0, 0%, p = 0.25) (Fig. 9).

Increase of macrosomia grade was also related to decreased Apgar score in first minute after birth (p = 0.001) (Fig. 10).

All studied complications including cardiovascular symptoms, respiratory symptoms and jaundice were increasing in further macrosomia grades with highest percentage in 3rd grade macrosomia (p < 0.001, p = 0.006, p = 0.012) (Fig. 9).

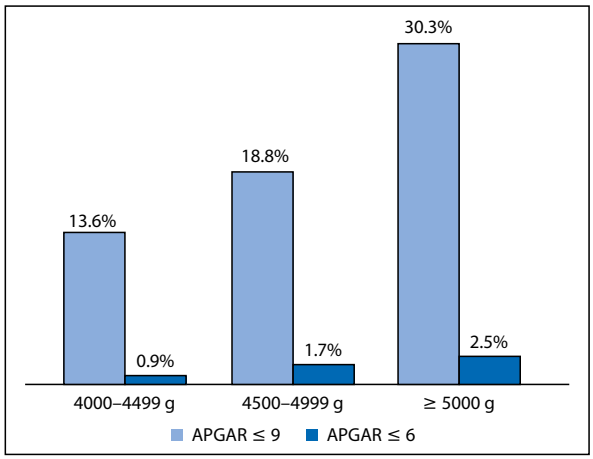

Figure 9. Percentage of cardiovascular, respiratory complications and jaundice according to macrosomia grades

DISCUSSION

Authors of the study analysed so far, the largest cohort of polish neonates regarding foetal macrosomia and managed to observe its prevalence over last decade.

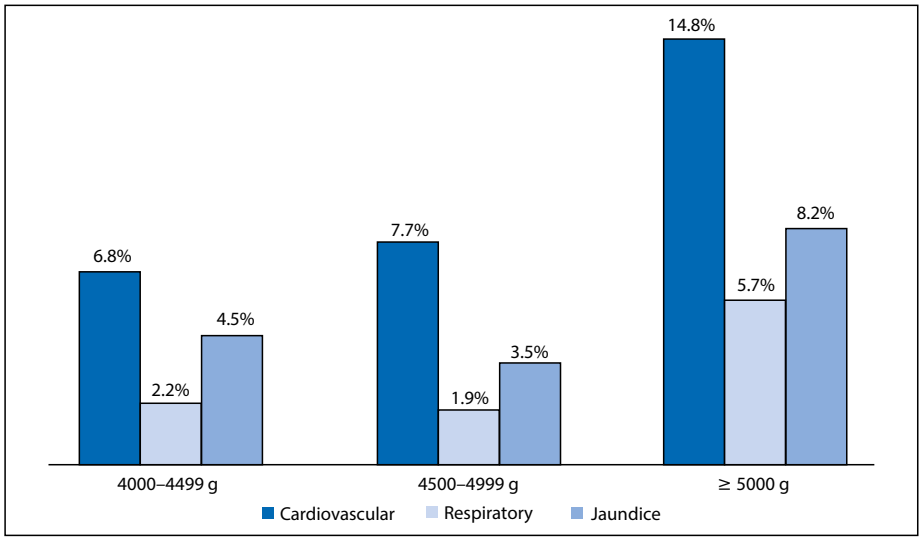

Figure 10. Percentage of decreased Apgar score in first minute of life according to macrosomia grade

Although large for gestational age (LGA) would be more adequate measure of excessive foetal growth, macrosomia grades (> 4000 g, > 4500 g, > 5000 g) more appropriately apply to perinatal standards and procedures [18]. Macrosomia with described weight compartments is also more frequently analysed in current international literature and it seems to be more consistent in view of more heterogeneous population.

The authors examined the trends in foetal macrosomia in 43 165 term neonates from 2 heterogenous medical centres. The centres were characterized of various geographical area and different referentiality stage, what applied to some of the results. 3rd stage referentiality centre in Bydgoszcz was dedicated to potentially high-risk pregnancies, what was related to higher rate of maternal morbidity such as gestational diabetes, increased rate of prematurity and higher rate of Casearean section deliveries.

Despite these differences in studied cohorts, authors manage to achieve consistent findings for both medical centres.

Overall incidence of macrosomia was 16.63% with higher incidence in 2nd stage Centre in Wejherowo comparing to 3rd stage Centre in Bydgoszcz. During the study period in both centres there was no significant change in its rate with baseline rate of 16.2% in 2010 and 15.8% at the end of the study. These results were inconsistent with decreasing trends in macrosomia observed in USA or China [1, 6]. Prevalence of macrosomia was more similar to described northern European cohorts [3]; however, the trend of macrosomia was stable in contrast to other countries [1, 3, 4, 6]. The longest and most current population-based study in USA revealed initial increase of macrosomia in first decade of the study with subsequent decrease in the following years [1]. In our cohort the macrosomia rate was stable, however long-term follow up in next decade would be crucial to analyse further trend.

Due to retrospective nature of the study and limited access to medical data authors managed to analyse only few risk factors of macrosomia including maternal age and gestation diabetes.

Increasing trend in maternal age of macrosomic mothers, as well as all mothers was observed over a 10-year study. Advanced maternal age is considered as an important risk factor for macrosomia what was confirmed by numerous publications [20]. In our study mothers of macrosomic infants were older in general. Increase of maternal age in macrosomic infants was subsequently observed from 2010–2017, however from 2018–2019 the mean age decreased and equalized with general population of mothers. Further observation of these trend needs to be performed.

Another risk factor related to foetal macrosomia is gestational diabetes. The incidence of GDM worldwide varies from 1 to 45% of pregnant women depending on studied population [21]. Among the Polish population, prevalence of GDM based on National Health found that in 2012 it was estimated as 7.45%, and the trend of its incidence was increasing [22]. In our study analysis of medical records in total revealed 10.61% of mothers diagnosed with gestational diabetes. Expected higher percentage of diabetic mothers in 3rd stage of referentiality was confirmed in the study. Prevalence of GDM in the study was higher than in general polish population, what can be explained by higher referentiality of our centres in comparison to general population. Regardless the stage of referentiality authors emphasise increasing trends in diagnosis of gestational diabetes over the last decade from 9.61% at the beginning of the study

to 15.27% in 2019 what is consistent with temporal trends in other countries [21, 22]. Although GDM is well known risk factor of foetal macrosomia in our cohort there was no significant difference of prevalence of GDM in mothers of macrosomic infants comparing to other infants, what is also consistent with some studies [23, 24].

Further study precisely assessing other risk factors including genetic factors such as parental birth weight, pre-gestational BMI, gestational weight gain and other is required.

Over the 10-year period the percentage of caesarean section deliveries significantly increased in studied cohort from 20.31% in year 2010 to 29.26% in 2019.

This trend of increase is observed overall in the Polish population [18], however the mean number of caesarean sections in analysed cohort was lower in comparison to general polish population with percentage of 43.85%.

The percentage of caesarean section deliveries of macrosomic infants was higher and ranged from 24.01% in 2010 to 38.25% in 2019. In 3rd stage referentiality centre the percentage of caesarean sections in macrosomic infants reached 53.3% in 2019 which is explained of increased number of high risks comparing to 2nd stage unit.

In addition, over the decade the number of vacuum/forceps deliveries gradually decreased with lower percentage of these procedures in macrosomia groups.

Grouping macrosomic infants into specific weight categories (macrosomia grades) has important implication in order to predict potential complications of foetal macrosomia [1, 13]. Authors noted that although the first grade of macrosomia (4000–4499 g) is the most common and less severe type of macrosomia is still related to increased incidence of birth trauma. These findings suggest that adequate perinatal care including caesarean section delivery should be considered in these group of patients with is consistent with current Polish and international recommendations [18, 19].

Authors also found 2nd and 3rd stage of macrosomia to be more severe types with increased perinatal complications regardless the mode of delivery. Higher macrosomia grades were related to increasing perinatal morbidity including lower Apgar score at birth and increased cardiovascular complications. The performed analysis showed no significant increase of respiratory symptoms and jaundice in macrosomia cohort; however, the number of these complications was significantly increasing with further macrosomia grades. These findings are consistent with international publications and impose the need of intensified medical attention in infants with macrosomia [1, 13, 15]. Higher perinatal morbidity of macrosomic infants should result in appropriate neonatal preparation in delivery room in order to perform effective NLS (Neonatal Life Support) procedures and intensified clinical attention in post-natal period.

CONCLUSIONS

The prevalence of macrosomia in studied cohort remained invariable over the last decade. Macrosomia is associated with increased rate of caesarean sections, increased maternal age and increased neonatal morbidity. Further studies on potential risk factors of macrosomia are needed.

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Conflict of interest

All authors declare no conflict of interest.

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The potential role of preoperative cystoscopy for determining the depth of invasion in the placenta accreta spectrum

Furkan Çetin[1, 2], Seyhun Sucu[2], Hüseyin Çağlayan Özcan[2], Özge Kömürcü Karuserci[2], Çağdaş Demiroğlu[3], Muhammed Hanifi Bademkiran[2], Emin Sevinçler[2]

[1]Department of Obstetrics and Gynecology, Dr Ersin Arslan Education and Research Hospital, Gaziantep, Turkey
[2]Department of Obstetrics and Gynecology, Faculty of Medicine, Gaziantep University, Gaziantep, Turkey
[3]Department of Obstetrics and Gynecology, Faculty of Medicine, SANKO University, Gaziantep, Turkey

ABSTRACT

Objectives: This study aims to determine the role of preoperative cystoscopy in specifying the degree of placental invasion to the bladder in the placenta accreta spectrum (PAS), especially in percreta.

Material and methods: This prospective observational cohort study included 78 PAS patients. All included patients underwent the preoperative cystoscopy before the cesarean hysterectomy operation. The preoperative cystoscopy procedure identified markers of PAS as neovascularization, arterial pulsatility in neovascularized zones, and posterior bladder wall bulging. Then the patients were divided into subgroups according to the histopathological results of their cesarean hysterectomy specimens. Finally, the histopathological subgroups of PAS were estimated using preoperative cystoscopy signs in the designed logistic regression analysis model.

Results: The preoperative cystoscopic signs such as neovascularization, the posterior bladder wall bulging, and the arterial pulsatility in neovascularized zones were approximately associated with a 17-fold [OR = 16.9 (95% CI, 5.7–49.8)], 26-fold [OR = 26.1 (95% CI, 8.17–83.8)], and 9-fold [OR = 8.94 (95% CI, 2.94–27.1)] increase in the likelihood of placenta percreta, respectively.

Conclusions: Preoperative cystoscopy may significantly contributions to other standard imaging modalities to identify the degree of placental invasion, especially placenta percreta. Experienced obstetricians trained in hysteroscopic visualization may safely perform this preoperative cystoscopy procedure under the guidance of a specialist urologist. Accordingly, it may be possible to estimate the degree of invasion and the course of surgery in patients with PAS using the preoperative cystoscopy procedure.

Key words: cesarean hysterectomy; cystoscopy; placenta accreta; placenta accreta spectrum; placenta increta; placenta percreta

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INTRODUCTION

Placenta accreta spectrum (PAS) has emerged as one of the most important causes of massive obstetric hemorrhages in recent years [1, 2]. This spectrum is defined as a pathological placentation state in which villous tissue invades the uterine wall. There are three subtypes of PAS: (a) placenta accreta (chorionic villi in contact with myometrium), (b) placenta increta (chorionic villi invade the myometrium), and (c) placenta percreta (chorionic villi extend up to the uterine serosa, and sometimes invade the pelvic organs) [3, 4]. The PAS incidence increases in parallel with the increasing cesarean rates worldwide and varies between 1/533 and 1/2500 [5]. There may be potential challenges regarding estimating and diagnosing the degree

Corresponding author:
Furkan Çetin
Department of Obstetrics and Gynecology, Dr Ersin Arslan Education and Research Hospital, Gaziantep, Turkey
e-mail furkan.cetin01@gmail.com

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of placental invasion preoperatively. The most preferred method for evaluating placental invasion is transvaginal or abdominal ultrasonography (USG) [6]. Magnetic resonance imaging (MRI) for PAS diagnosis may be used as an additional component to increase the diagnostic accuracy of USG, especially for unclearly USG signs or the posteriorly located placenta. The disadvantages of MRI in PAS diagnosis are that it requires experience for accurate examination and is not cost-effective compared to USG [7]. On the other hand, placental invasion can usually be diagnosed preoperatively by USG or MRI [8], but the actual depth of placental invasion may be different compared to its preoperative diagnosis, especially by USG.

Considering the structures adjacent to the uterus, placental invasion most commonly affects the urinary organs, less frequently the rectum. The rate of urinary tract damage during surgery can reach up to 30%, and the most damaged urinary organ is the bladder [9]. Specifying the degree of placental invasion and taking appropriate precautions in the prenatal period is very crucial for the intraoperative management of PAS [10, 11]. Although the invasion depth of PAS may be predicted approximately by the preoperative USG, MRI, or cystoscopy [12, 13], the knowledge in terms of cystoscopy is particularly limited in previous studies.

Objectives

The present study aims to determine the role of cystoscopy in specifying the degree of placental invasion of the bladder in PAS, especially in percreta. Since the number of PAS patients is largest and the cystoscopy procedure is designed preoperatively, our study on this issue has a potentially new perspective.

MATERIAL AND METHODS

This prospective interventional cohort study was performed at the Department of Obstetrics and Gynecology of Sahinbey Research and Practice Hospital which belongs to the Faculty of Medicine of Gaziantep University, Gaziantep, Turkey. The study was approved by the Gaziantep University Ethics Committee (Date: 09 January 2019, Ethics committee number: 2018/259) and informed consent was obtained from patients. Informed consent included the information in detail regarding preoperative cystoscopy, cesarean hysterectomy method, and possible complications. This current study was carried out together with the ethical standards of the Declaration of Helsinki guidelines. Patient information has been stored in the hospital's highly secure digital data recording system. The patients' demographic characteristics, pre-and postoperative hemoglobin levels, data on blood loss, amount of blood transfusions, period of operation and hospitalization, complications, and cystoscopy signs were recorded and analyzed.

Patient selection criteria, Pre-operative diagnosis, and Patient classification

Exclusion criteria for the study were an unconfirmed diagnosis of PAS according to pathologic specimens, an emergent admission with massive vaginal or intraabdominal bleeding, and conservative surgery without hysterectomy. Hemodynamically stable patients who consented to the preoperative cystoscopy and had positive prepartum USG criteria for diagnosis of PAS were included in the study. We used the same high-resolution ultrasound device (GE Voluson® S10) in our department to diagnose all patients with PAS in the prenatal period. The sonographic criteria for the placental invasion were placental lacunae image, increased vascularity or the vascular bridge between the posterior bladder wall and lower uterine segment, turbulent flow in the doppler, and decreased myometrial thickness at the border of the vesicouterine fold [11].

A total of 123 PAS patients were operated at Gaziantep University Gynecology and Obstetrics Clinic between 2019–2021. Conservative surgical methods such as anterior uterine segment resection, bilateral hypogastric artery ligation, uterine balloon tamponade, and stepwise uterine devascularization were performed on 31 patients. Moreover, 92 patients underwent a cesarean hysterectomy. The ten patients who underwent an emergency cesarean hysterectomy and four who did not consent to preoperative cystoscopy were excluded from the study. Consequently, 78 patients who underwent planned cystoscopy before cesarean hysterectomy were included in the study. All cesarean hysterectomy specimens were histopathologically confirmed for PAS diagnosis and divided into three subgroups accreta, increta, and percreta.

Cystoscopy procedure

The same obstetrician team performed preoperative cystoscopy under the supervision of an expert consultant urologist. All cystoscopy procedures were performed in a low lithotomy position with the same device (Karl Storz®) before general anesthesia induction for patients. In addition, the diameter and angle of the cystoscopic telescope were the same, 22-French size and 30-degree, respectively. The present study was designed using current cystoscopic signs of placental invasion [13], such as neovascularization, arterial pulsatility, and posterior bladder wall bulging, illustrated in Figure 1. Consequently, the correlation between the preoperative cystoscopic signs and histopathological results of the PAS patients was examined in detail.

Statistical data analysis

Initiating the study, the sample size was computed by power analysis using Gpower3.1 software. The minimum possible number of patients found was 56 of the sample

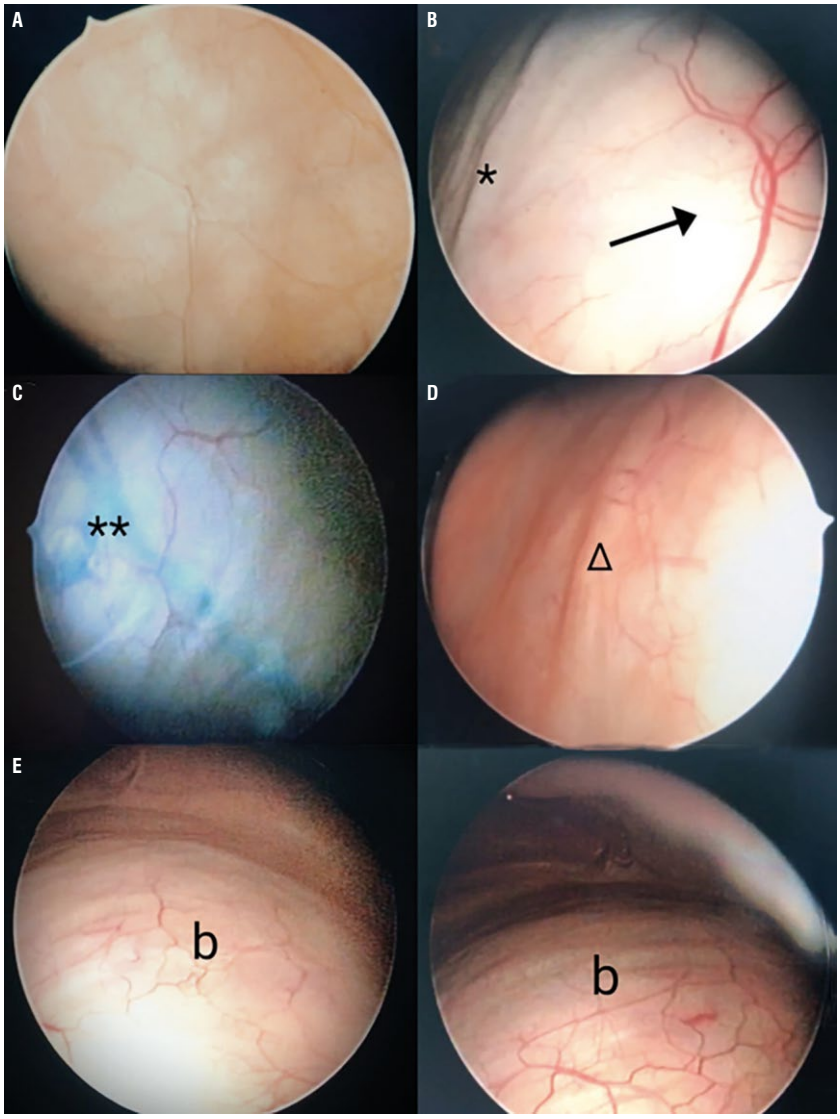

Figure 1. Cystoscopy images; **A.** A normal cystoscopic view of a posterior bladder wall [(*)]; **B.** The "asterisk" indicates an arterial blood vessel on the surface of the lower uterine segment through the bladder wall, "arrow" indicates the neovascularization area in the posterior bladder wall; **C**. The "double asterisk" in the neovascularization area at the posterior bladder wall indicates venous blood vessels of the placental invasion; **D.** The "triangle" indicates pulsatile arterial blood vessels on the surface of the lower uterine segment through the bladder wall; **E.** The "b" signs indicate bulging in the posterior bladder wall; *The image was obtained from a term-pregnant patient with informed consent

size analysis based on the data of the first 20 patients included in the study, considering a 95% confidence interval, medium effect size, and an 80% power. The compatibility of numerical variables to normal distribution was evaluated by the Shapiro Wilk test. ANOVA and LSD tests were used to compare normally distributed numerical measurements in three groups. Kruskal Wallis and All Pairwise tests were used to compare non-normally distributed numerical measurements in three groups. The comparison of categorical variables was done by using the Chi-square test. Logistic regression analysis was performed to the correlation and comparison of categorical variables (histopathologically confirmed subgroups of PAS, and cystoscopic signs). Receiver operating characteristic (ROC) curves and Bayesian decision theory graphs were drawn for neovascularization, bulging, and arterial pulsatility. Odds ratio, 95% confidence interval (CI), and p values were calculated by SPSS 22.0 Windows version and R version 3.5.1 (R Statistical Software, Institute for statistics and Mathematics, Vienna, Austria). The p value of less than 0.05 was considered statistically significant.

RESULTS

Table 1 shows the demographic, clinical, and perioperative characteristics of the included 78 patients in this study. According to histopathological results, 28% of the cases were accreta, 13% increta, and most of them, 59% percreta.

Table 1. Comparison of the demographic, clinical and perioperative features of the accreta, increta and percreta groups

Variables	Accreta group (n = 22)	Increta group (n = 10)	Percreta group (n = 46)	P
Age [years]†	31.09 ± 7.28	32.2 ± 6.7	32.72 ± 4.41	0.884
Gestational age [weeks]†	34.45 ± 3.94	35.8 ± 1.69	34.61 ± 2.37	0.303
BMI [kg/m^2]†	27.62 ± 3.41	26.09 ± 1.96	27.22 ± 2.79	0.512
Gravida [n]†	3.91 ± 2.99^A	4.7 ± 1.64	5.13 ± 1.42^B	**0.018***
Parity [n]†	1.86 ± 1.81^A	3 ± 1.15	3.57 ± 0.98^B	**0.001***
Number of previous cesarean sections [n]†	0.91 ± 1.15^A	2.5 ± 0.85^B	2.87 ± 0.96^B	**0.001***
Duration of operation [min]†	70.91 ± 15.71^A	102 ± 19.32^B	102.83 ± 20.83^B	**0.001***
Preoperative Hb [g/dL]†	11.58 ± 1.21	11.33 ± 0.82	11.21 ± 1.21	0.468
Postoperative Hb [g/dL]†	10.43 ± 1.08	10.34 ± 1.03	10.33 ± 1.14	0.713
Transfused pRBC [unit]†	0.5 ± 1.37^A	1.6 ± 1.96^B	1.63 ± 1.5^B	**0.001***
Estimated blood loss [mL]†	638.64 ± 463.15^A	1000 ± 848.2	866.3 ± 439.58^B	**0.002***
Duration of hospital stay [day]†	2.5 ± 1.47^A	2.9 ± 1.2	3.72 ± 1.71^B	**0.001***
Bladder injury‡	0 (0%)	1 (10%)	6 (13%)	0.083

BMI — body mass index; Hb — hemoglobin; pRBC — packed red blood cells,
†mean ± standard deviation; ‡ N (%); ^{B}is significantly higher than ^{A};* $p < 0.05$ value is significant

Table 2. Comparison of preoperative cystoscopic signs in accreta, increta and percreta groups

Groups	Accreta group (n = 22)	Increta group (n = 10)	Percreta group (n = 46)	P
Neovascularization †	3 (13.6%) ^{A}	7 (70%) ^{A}	39 (84.8%) ^{B}	0.001*
Posterior bladder wall bulging †	0 (0%)	6 (60%) ^{A}	37 (80.4%) ^{B}	0.001*
Arterial pulsatility †	0 (0%)	5 (50%) ^{A}	26 (56.5%) ^{B}	0.001*

†N (%); ^{B} is significantly higher than ^{A}; * $p < 0.05$ value is significant

The mean age was 32.19 ± 5.61 (Mean ± SD) years, the mean BMI was 27.18 ± 2.89 kg/m^2 (Mean ± SD) and the number of previous cesarean sections was 2.26 ± 1.31 (Mean ± SD) for included patients. The number of gravida and parity were 4.73 ± 2.05 (Mean ± SD) and 3.01 ± 1.47 (Mean ± SD), respectively. The gestational age of the patients at the time of the cesarean hysterectomy was 34.71 ± 2.83 (Mean ± SD) weeks. The mean duration of the cesarean hysterectomy operation was 93.71 ± 23.91 minutes (Mean ± SD), plus the mean duration of the cystoscopy procedure ranged from 2 to 4 minutes was 2.5 ± 0.69 (Mean ± SD). In addition, the mean duration of postoperative hospitalization was 3.26 ± 1.66 days (Mean ± SD). Moreover, the pre- and postoperative hemoglobin levels were 11.32 ± 1.16 g/dL (Mean ± SD) and 10.35 ± 1.09 g/dL (Mean ± SD), respectively. Furthermore, the approximate measured intraoperative blood loss was 819.23 ± 520 mL (Mean ± SD) for each patient, plus the number of intraoperative transfused packed red blood cells (pRBC) was 1.30 ± 1.58 units (Mean ± SD). Although 52 of the 78 patients (66.7%) included had at least one cystoscopic sign of placental invasion, the remaining 26 patients (33.3%) had no identified signs. While the cystoscopic signs of an invasive placenta were high-rate figured in the percreta group (91.3%), there were the least in the accreta group (13.6%). The most common cystoscopic sign image of PAS was neovascularization (62.8%), while the least common was arterial pulsatility in the neovascularized areas (39.7%). The neovascularization image was positive in cystoscopy for all three histopathological subgroups. On the other hand, the signs of posterior bladder wall bulging and arterial pulsatility in cystoscopy were found positive only in the increta and percreta groups. The comparison of cystoscopic signs according to all histopathological subgroups is presented in Table 2. The preoperative cystoscopic signs such as neovascularization, the posterior bladder wall bulging, and the arterial pulsatility in neovascularized zones were approximately associated with a 17-fold [OR = 16.9 (95% CI, 5.7–49.8)], 26-fold [OR = 26.1 (95% CI, 8.17–83.8)], and 9-fold [OR = 8.94 (95% CI, 2.94–27.1)] increase in the likelihood of placenta percreta, respectively. The sensitivity-specificity-accuracy of preoperative cystoscopic signs regarding histopathologically diagnosed placenta percreta cases were 80–76–78% for the neovascularization, 86–74–81% for the posterior bladder wall bulging, and 57–84–68% for

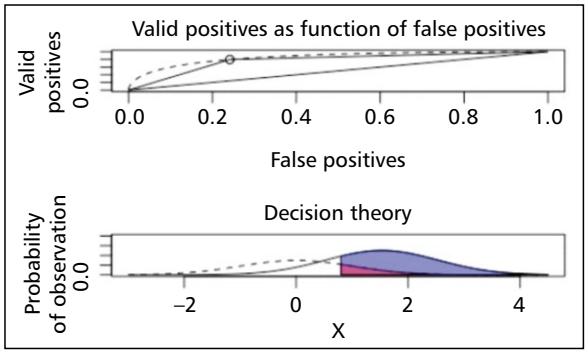

Figure 2. Valid positives receiver operating characteristic (ROC) curve and Bayesian decision theory graph for false positives regarding the sign of neovascularization

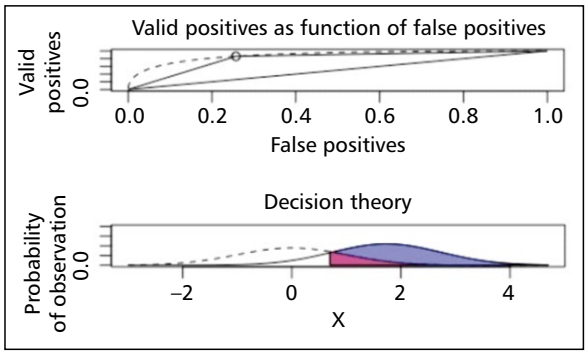

Figure 3. Valid positives receiver operating characteristic (ROC) curve and Bayesian decision theory graph for false positives regarding the sign of posterior bladder wall bulging

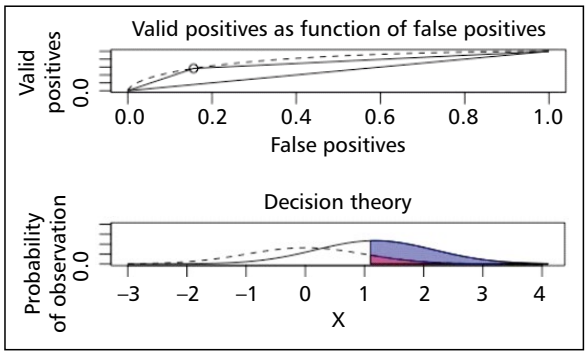

Figure 4. Valid positives receiver operating characteristic (ROC) curve and Bayesian decision theory graph for false positives regarding the sign of arterial pulsatility

the arterial pulsatility, respectively. In addition, their ROC curve and Bayesian decision theory graphs are presented in Figures 2, 3, and 4, in the same order.

Complications and management

A total of seven bladder injuries ranging in size from 2 to 8 cm were mainly repaired with continuous closure with 3/0 synthetic absorbable monofilament sutures for the mucosa plus interrupted closure with 2/0 polyglactin 910 sutures for the muscle and serosa. One of the patients operated on due to placenta percreta underwent re-laparotomy due to an 8 cm hematoma formation detected above the vaginal cuff by ultrasound on the postoperative sixth hour. Upon detection of bleeding at sites of previous placental invasion of the bladder in re-laparotomy of this patient, the bleeding was stopped using sutures plus bipolar coagulation. Two units of packed red blood cells (pRBC) and two units of fresh frozen plasma (FDP) were suitably given to the patient by an anesthesiologist during this re-laparotomy. Besides, the uninfected 5 cm wound dehiscence in the incision line on the seventh postoperative day was detected in a patient with placenta accreta. The un-infected wound opening was closed by interrupted 0 polypropylene sutures under sterile conditions with local anesthesia. In another patient with placenta percreta, a bride ileus complication developed at the end of the first week after surgery. The patient underwent re-laparotomy due to an acute abdomen, and a specialist general surgeon performed a bridectomy. None of the patients included in the study developed complications related to cystoscopy.

DISCUSSION

The current study was designed to determine the potential role of preoperative cystoscopy in indicating placental invasion depth for PAS patients and thus predict the possible surgical outcomes. The results regarding sensitivity, specificity, and accuracy of the three admitted preoperative cystoscopic signs reveal that preoperative cystoscopy may be helpful in the diagnosis of PAS and may have a crucial role in specifying the severity of placental invasion depth. In addition, the results signified that the diagnostic value and power of preoperative cystoscopy increased significantly in parallel with the severity of the depth of placental invasion.

Management of PAS patients is one of the most challenging procedures in obstetrics [14], and it is known that urinary organ injuries and severe hemorrhages are common intraoperatively. For this reason, it is recommended that the surgical procedures planned to be applied to the patients should be evaluated carefully and on a case-by-case basis preoperatively [14]. In recent years, the number of studies involving crucial surgical techniques such as internal iliac artery ligation or embolization [15, 16] on reducing the amount of perioperative bleeding in PAS patients with severe placental invasion has remarkably increased due to

the issue's vital importance. Severe placental invasion in PAS patients is one of the most important causes of intraoperative hemorrhages [17, 18]. Intraoperative hemorrhages are associated with many complications as hysterectomy, disseminated intravascular coagulation, multisystem organ failure, acute respiratory distress syndrome, and even death in these patients [19, 20]. Therefore, it is crucial to determine the severity of the placental invasion in the prenatal period to prevent possible complications [10, 11, 21]. Tikkanen et al. [22] reported that the PAS patients diagnosed in prepartum had less blood loss and required lower blood transfusions than those diagnosed during delivery. Another study presented a decrease in intraoperative hemorrhage risk, adjacent organ damage, and operative complications for PAS patients diagnosed in the prenatal period [18]. Although USG is the first method recommended for antenatal PAS diagnosis, MRI can also be used in selected patients to confirm the diagnosis [23–25]. A recent meta-analysis calculated 83% sensitivity and 95% specificity for USG versus 82% sensitivity and 88% specificity for MRI in PAS patients [26]. Although the rates of antenatal diagnosis of PAS have increased with improved imaging techniques, recent studies have reported that up to two-thirds of PAS patients may not be diagnosed in the prenatal period [27–29]. Increasing prevalence and diagnostic challenges for PAS have led obstetricians to search for new diagnostic techniques to identify PAS subgroups [30]. In addition, there have been significant advances in the prenatal diagnosis of PAS in recent years [22]. USG is still the most commonly used diagnostic method for detecting and sub-grouping PAS patients in the prenatal period; on the other hand, the preoperative cystoscopy procedure may be used innovatively as a primary or supplementary method for identifying the depth of placental invasion as closely as reality. Moreover, preoperative cystoscopy may be a promising, and novel minimally invasive method to specify the severity of placental invasion. As known, prenatal cystoscopy has the beneficial efficacy of assisting the primary diagnosis of PAS in the ultrasound examination of unclear or suspicious [12, 13, 31]. Al-Kahn et al. [13] declared that preoperative cystoscopic signs such as neovascularization and posterior bladder wall bulging could determine the severity of placenta accreta spectrum disorders. They reported that cystoscopic signs such as neovascularization and the posterior bladder wall bulging increased the likelihood of placenta percreta by 17-fold and 12-fold, respectively. In line with the previous study and with a higher association, our calculated ratios regarding cystoscopic signs such as neovascularization and posterior bladder wall bulging were 17-fold and 26-fold in the likelihood of placenta percreta increasing, respectively. Furthermore, we found a 9-fold increase likelihood of placenta percreta in the presence of arterial pulsation signs in the preoperative cystoscopy.

Yan Lui et al. [12] compared USG and cystoscopy in the prenatal diagnosis of PAS subgroups. Researchers noted that the diagnostic power of both methods increases in parallel with the depth of placental invasion and has similar diagnostic values. In addition, they reported that the sensitivity of cystoscopy was highest (100%) in the placenta percreta group, while the specificity was similar (86.4%) for all subgroups. Similarly, our study revealed that abnormal cystoscopic signs increase the depth of invasion. Neovascularization, posterior bladder wall bulging, and arterial pulsatility signs' sensitivity and specificity for placenta percreta prediction were 80–76%, 86–74%, and 57–84%, respectively.

Our study may contribute to the literature on this crucial and current topic. Furthermore, this study was differently designed from the previous studies. The cystoscopic procedure was performed in the preoperative period for PAS patients diagnosed with USG, and surgical specimens were configurated histopathological. As far as we know, our prospectively designed study on preoperative cystoscopy has the most extensive number of PAS patients and the subgroup of placenta percreta. This excess in the number of operated PAS patients may be related to our tertiary hospital, which serves the potential approximately 5 million people in the hinterlands in the southeast region of Turkey. The principal limitation of our study may be including patients who underwent only cesarean hysterectomy rather than different surgical techniques such as anterior segmental uterine wall resection in PAS management.

CONCLUSIONS

Our study shows that preoperative cystoscopy may provide helpful and complementary contributions to other imaging methods in specifying the depth of placental invasion. Experienced obstetricians familiar with hysteroscopy operations may perform the preoperative cystoscopic procedure safely under the guidance of a specialist urologist. Abnormal cystoscopic signs may identify high-risk PAS patients who need to be probably transferred to a multidisciplinary and experienced tertiary center. In addition, preoperative cystoscopy can provide beneficial preoperative knowledge to avoid urological complications in patients with severe signs of placental invasion. Further studies are needed to evaluate the success rates of preoperative cystoscopy in determining the degree of placental invasion in patients with PAS.

Authorship contributions

FC designed and carried out the study, performed the surgical procedures, followed up with the patients, contributed to the first draft of the paper, and revised the manuscript critically for important intellectual content. SS contributed to the design of the study and the first draft of the paper, edited the language, and revised the ma-

nuscript critically for important intellectual content. HCO designed the study, performed the surgical procedures, wrote the manuscript, and finalized the paper. OKK performed the surgical procedures, followed up with the patients, and contributed to the first draft of the study. ES and CD revised the manuscript critically for important intellectual content. HB analyzed and interpreted the data. All authors read and approved the final article.

Statement of ethics

The design of the study was approved by the local ethics committee (The Clinical Research Ethics Committee of Gaziantep University by its decision dated 09 January 2019 and numbered 2018/259) and performed by following the ethical standards described in the current version of the Helsinki Declaration guideline. In addition, informed consent forms were obtained from all participants.

Conflict of interest

The authors declared no conflict of interest.

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Is it possible to predict the success of single dose methotrexate in the treatment of tubal ectopic pregnancies?

Eren Pek[1], Fatma Beyazıt[1], Duygu Sıddıkoglu[2]

[1]*Department of Obstetrics and Gynecology, Faculty of Medicine, Canakkale Onsekiz Mart University, Turkey*
[2]*Department of Biostatistics, Faculty of Medicine, Canakkale Onsekiz Mart University, Turkey*

ABSTRACT

Objectives: In this study, the aim was to determine whether the use of endometrial thickness or neutrophil/lymphocyte and platelet/lymphocyte ratio would be useful in predicting the success of methotrexate in the treatment of ectopic pregnancies located in the fallopian tubes.

Materal and methods: This study was carried out by retrospectively examining 68 study group cases with an ultrasonographically detectable gestational sac in the fallopian tubes and 189 control group cases with an unruptured ectopic pregnancy diagnosis at any location. The cut-off value of endometrial thickness was calculated as a new marker between the cases in which single-dose methotrexate treatment was successful and the cases with treatment failure. Treatment success was evaluated with different models including endometrial thickness, fetal cardiac activity status, measurable crown-rump length, and β-hCG.

Result: The cut-off value of β-hCG for treatment success was determined as 2960.5 ng/mL, and the cut-off value for endometrial thickness was determined as 10.5 mm. Although NLR seems to be a marker with a cut-off value of 2.49, it does not provide an extra benefit in combined use as it is not a specific predictor. The highest success in predicting treatment success was achieved in the modeling in which crown-rump length + fetal cardiac activity + β-hCG + endometrial thickness were used together.

Conclusions: The use of endometrial thickness as a marker seems to be quite reliable in predicting treatment success. And we think it would be beneficial to thin the endometrium before using methotrexate.

Key words: ectopic pregnancy; endometrial thickness; prognostic endometrial knownledge; human chorionic gonadotropin- β; single-dose methotrexate; neutrophil-lymphocyte ratio; platelet-lymphocyte ratio

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INTRODUCTION

Ectopic pregnancy may constitute two percent of all pregnancies, and is often located in the fallopian tubes [1]. The management of ectopic pregnancies includes expectant management, pharmacological treatment with methotrexate, or surgery. However, methotrexate is relatively contraindicated in patients with initial human chorionic gonadotropin-β (β-hCG) levels of > 5000 mIU/mL, a gestational sac size of > 4 cm, presence of fetal cardiac activity and hemoperitoneum, which indicate a high treatment failure rate. Nevertheless, the use of methotrexate in the treatment of ectopic pregnancies is still the most commonly preferred treatment method in unruptured ectopic pregnancies [2]. The two most common methods of using methotrexate in ectopic pregnancy are; it is a single dose administration of calculated by the equation 50 mg/m^2 based on body surface area (without need for leucovorin rescue), or multiple dose regimen of 1 mg/kg (alternating with 0.1 mg/kg leucovorin rescue) [3]. Any ectopic and/or existing embryo with a pretreatment mass greater than 3.5 cm and a human chorionic gonadotropin level greater than 5000 mIU/mL is more likely to fail medical therapy and may be more suc-

Corresponding author:
Eren Pek
Department of Obstetrics and Gynecology, Faculty of Medicine, Canakkale Onsekiz Mart University, Turkey
e-mail: drerenpek@hotmail.com

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cessfully treated surgically [4]. But, these human chorionic gonadotropin-β levels and gestational sac sizes are admirably high, and they carry a risk of rupture. When a pregnant sac becomes larger in the tube and the tubal lumen cannot accommodate, tubal rupture may occur. Some previous studies have suggested that higher human chorionic β-hCG levels and gestational age seem to be significant risk factors for developing a ruptured ectopic pregnancy [5, 6]. So, paying special attention to pregnancies at risk of failure with a single dose of methotrexate [4].

Methotrexate is a folinic acid antagonist (folic acid analogue) that shows its effectiveness by inhibiting dihydrofolate reductase. By binding to dihydrofolate reductase, it reduces thymidylate, purine synthesis and cell proliferation. As can be seen, it is a pharmaceutical agent that interferes with almost all cellular activities such as nucleic acid synthesis, DNA-RNA repair, cellular replication [7]. Therefore, besides malignant cells or tissues; normal cells with rapid cellular turnover, such as trophoblast, bone marrow, endometrium, keratinocytes, and reproductive cells, are also highly sensitive to these effects of methotrexate [8]. Erdil et al. [8], in their study with methotrexate in ectopic pregnant and non-pregnant uterus, showed that the expression of some superficial receptors was also significantly affected at the endometrium level. This result suggests that the endometrium is also a factor in the success of methotrexate, which we use in the treatment of ectopic pregnancy [8]. However, in another study, Tas et al. [9] reported that the endometrial thickness did not affect the results in their study evaluating the success of single--dose methotrexate administration.

On the other hand, there are also studies in the literature reporting that hematological parameters can be an effective marker in predicting the success of methotrexate due to inflammatory processes [10, 11]. Akkaya et al. [12] reported that MPV and RDW could be used as independent markers to predict the success of treatment.

Today, research on the factors affecting the success of single dose methotrexate is still ongoing. The vast majority of them are concentrated on human chorionic β-hCG. In our study, we aimed to evaluate whether the endometrial thickness (ET), neutrophil/lymphocyte (NLR) and thrombocyte/ /lymphocyte ratios (PLR) measured at the time of diagnosis can also be used as a marker to predict the efficacy of methotrexate. Based on these results in the literature, we aimed to reveal whether there are other markers that are stronger in predicting the success of single-dose methotrexate use in ectopic pregnancies located in an unruptured fallopian tube.

Impact statement

What is already known on this subject?

Precise information that can predict the success of a single dose of methotrexate is still not available in the literature. Many modalities have been developed and proposed. Often, gestational sac size, fetal cardiac activity status, β-hCG value and similar markers are used.

What the results of this study add?

Endometrial thickness provides us with information about the success in predicting the prognosis with a very high accuracy. This finding made us think that it may be very useful in clinical management.

What the implications are of these findings for clinical practice and/or further research?

Our study concluded that endometrial thickness affects treatment success. In this case, curettage the endometrium before methotrexate administration may increase the success rate of a single dose of methotrexate. However, it also revealed that NLR and PRL are not specific markers for the medical treatment of ectopic pregnancy.

MATERIAL AND METHODS

Ethics

All ethical approvals required for the study were obtained from the Çanakkale Onsekiz Mart University Clinical Research Board. (2022-YÖNP-0013/ 06.04.2022:06-13).

Selection and creation of the sample of the study

Women who were diagnosed with ectopic pregnancy and treated in our clinic between 2011 and 2021 were retrospectively analyzed. All the data obtained were provided by scanning the hospital electronic patient record system. As a result of this preliminary research, full data of 189 cases of ectopic pregnancy whose initial treatment was methotrexate were reached. Due to the changes in the electronic patient registration system over the years, the inability to access all the data of all the cases has created a limitation. Since it was aimed to evaluate the factors that may affect the success of a single dose of methotrexate, the cases that were ruptured at the time of diagnosis and required acute abdominal surgery were not included in the study. Apart from this, cases with rheumatic, inflammatory or similar chronic diseases for any reason were not included in the sample to avoid drug interactions. None of the women included in the study were heterotopic pregnancy. After all these exclusion criteria were applied, the number of ectopic pregnancy cases with fallopian tube localization to be included in our study was determined as 68 without bias. All of these 68 cases had a gestational sac that could be observed and measured ultrasonographically in the fallopian tubes. Cases that were evaluated as ectopic pregnancy with their biochemical and sonographic findings at the start of treatment, but who did not have a gestational sac that could be visualized in the fallopian tubes ultrasonographi-

cally due to the level of serum β-hCG hormone at the time of decision were not included in this group. This elimination was necessary and important for the validity and reliability of the results of the study. Of course, an exception to this was the cases in which surgical treatment was applied as a result of treatment failure and tubal rupture was detected. These have already been reported separately as treatment failure. And, all of the cases without observable gestational sac located in the fallopian tube were considered as other locations (cervical, cesarean scar, cornual, ovarian, unknown location etc.) to avoid any bias. Therefore, in our study, we did not specify any rate about the frequency of ectopic pregnancy locations. It was confirmed that all cases included in the sample received the standardized dose of methotrexate accepted in the literature (50mg of methotrexate per square meter of body surface area).

Modelling

First of all, ectopic pregnancy locations were divided into study-case group and control group. The first group consisted of only those located in the fallopian tubes (group 1), which constituted the study group, and the second group consisted of the control group with all ectopic pregnancies (group 2). The reason for creating two groups was to measure whether the results we obtained in our study, which we carried out to predict the success of single-dose methotrexate in the treatment of ectopic pregnancies localized in the fallopian tubes which was the aim of our study, to evaluate whether it was generalizable for the treatment of all ectopic pregnancies and to measure its internal consistency. This is very important for the validity and reliability of our study. First, the mean values and standard deviations of some parameters, which we think may have an effect on the success of methotrexate, were analyzed separately for both groups. And it was evaluated whether the results differed statistically. These included the following parameters; mean age (year), success rate of single dose methotrexate, presence or absence of crown-rump length (CRL), presence or absence of fetal cardiac activity (FCA), neutrophil-lymphocyte ratio, platelet-lymphocyte ratio, endometrial thickness (mm). Neutrophil/lymphocyte ratio value was calculated by dividing the number of neutrophil by the number of lymphocyte. Similarly, the PLR value was calculated by dividing the platelet count by the lymphocyte count.

Subsequently, the median values were calculated separately in group 1 and group 2 for the success and failure of single-dose methotrexate administration by including the serum β-hCG level measured at the time of treatment to the same parameters. It was evaluated whether the medians found were statistically significant in case of ectopic pregnancy located in the fallopian tube or in the case of treatment success and failure in all ectopic pregnancies.

As a result of this statistical analysis, the cut-off values of the parameters that gave a significant value on the treatment success in any group were determined separately for both groups. And their sensitivities, specificities, positive predictive values and negarite predictive values were calculated in these cut-off values. On the other hand, no further evaluation was made at this stage for CRL and FCA, which are accepted in the literature and whose presence adversely affects the success of methotrexate.

Finally, we evaluated the effect of endometrial thickness on treatment success and failure for ectopic pregnancies with fallopian tube location, at the cut-off value that we determined for serum β-hCG, whose increase and height is also considered to have a negative effect on treatment success in the literature. We then reassessed the same analysis by adding the presence of crown-rump length to the β-hCG level and then adding the presence of fetal cardiac activity to these. Then, we also performed the same evaluation and comparison for another parameter, NLR, which we evaluated for the first time in terms of literature. This modeling is important and original in that it is the first in the literature.

Statistical evaluation

Nominal variables were expressed as frequencies and percentages (%) whereas continuous variables were expressed as mean ± standard deviation (SD) or median and interquartile range (IQR) for the non-normally distributed variables. The Kolmogorov-Smirnov test was used to assess the normality assumption for the continuous variables. The significance of the difference between the tubal group and the control group was analyzed using paired samples t- test. Categorical variables were evaluated using Pearson's chi-square test or Fisher's exact test. Receiver-operating characteristic (ROC) analysis was performed to identify a threshold value for endometrial thickness, β-hCG (level at the time of treatment), NLR. ROC analysis was used to calculate the areas under the receiving operator curves (AUROC) with 95% confidence intervals for study parameters to predict methotrexate success. The DeLong test was then used for a pairwise comparison of AUROCs. All statistical analyses were conducted using SPSS for Windows (IBM Corp. Armonk, NY, USA). All p values of less than 0.05 were considered to indicate statistical significance.

RESULTS

Our study, in which we evaluated the endometrial thickness and hematological parameters in predicting the success of methotrexate, was performed on 68 cases with an ectopic pregnancy focus located in the definitive fallopian tube, ultrasonographically or surgically detected. Initial treatment of all cases included in the study group and control group was standardized dose methotrexate.

Table 1. Shows the mean values and statistical difference of the parameters evaluated between tubal localized ectopic pregnancies and all ectopic pregnancies in the control group

Evaluated parameter	Mean ± SD		p value
	Group 1	Group 2	
Age [year]	30.47 ± 5.18	30.72 ± 5.24	0.731
Endometrial thickness [mm]	9.70 ± 3	8.95 ± 2.88	0.039
NLR	3.05 ± 2.15	2.76 ± 2.02	0.311
PLR	141.25 ± 100	122.94 ± 69.55	0.101
Measurables CRL	15 (22.1%)	24 (12.7%)	0.065
Measurables FCA	9 (13.2%)	14 (7.4%)	0.149
Success of single-dose	42 (61.8%)	138 (73.0%)	0.082
β-hCG [mIU/mL]	3862.63 ± 2428.90	2527 ± 2962.85	< 0.001

SD — standard deviation; NLR — neutrophil /lymphocyte ratio; PLR — thrombocyte /lymphocyte ratios; CRL — crown-rump length; FCA — fetal cardiac activity ($p < 0.05$); β-hCG — human chorionic gonadotropin-β

As a result of our first statistical analysis, we determined that the age of the woman, the neutrophil-lymphocyte ratio, platelet-lymphocyte ratio, presence of fetal cardiac activity and measurable crown-rump length did not difference between ectopic pregnancies located in the fallopian tube and all ectopic pregnancies. These findings are important in terms of showing us that the parameters we evaluated are distributed in a homogeneous and coincidental similarity between the fallopian tube or other ectopic locations. But, there was a statistically significant difference between tubal localized ectopic pregnancies and all ectopic pregnancies in terms of the mean endometrial thickness and serum β-hCG. This difference regarding β-hCG was due to low titer plateauing ectopic pregnancies in the control group and ectopic pregnancies of unknown location, which did not increase regularly and did not have an ultrasonographically detectable gestational sac. Comparison of fallopian tube parameters in the study group and all ectopic pregnancies in the control group are presented in Table 1.

Then, the statistical significance and differences of these parameters between treatment successful cases and treatment unsuccessful cases in ectopic pregnancies which were located in the fallopian tube were tested. Except for the endometrial thickness, there was no statistically significant difference between the treatment -successful cases and the unsuccessful cases which were located in the fallopian tube. In other words, the patient's age, serum β-hCG level, presence or absence of CRL, presence or absence of FCA and others were not meaningful on their own in determining the success of treatment, in group 1. However, in our control group (group 2), which included all ectopic pregnancies (cases that did not have any observable gestational sac in the fallopian tube; cases whose serum β-hCG level did not make it possible to visualize the gestational sac sonographically or those who did not show a steady increase by drawing a plateau; cases where the gestational sac is observed to be located outside the fallopian tube), except of PLR in all parameters were statistically significant on cases where the treatment was successful or failure. All data of this analysis are presented in detail in Table 2. In both the case and control groups, found that the mean endometrial thickness of 7 mm (6–9 mm) in cases which a single dose of methotrexate was successful; on the other hand, in cases which a single dose of methotrexate was not successful, this thickness was 13 mm (12–14 mm) on average. When the effect of endometrial thickness on the success rate was examined, we found that it was statistically significant ($p < 0.05$).

After this stage, we did not perform any further evaluation with PLR, which was neither selective nor statistically different between the two groups. And we calculated the cut-off values for β-hCG, NLR and endometrial thickness in both groups separately. These values were surprisingly similar in both groups, measuring 2960.5 mIU/mL for β-hCG, 10.5 mm for endometrial thickness, and 2.49 for NLR. The value of endometrial thickness (prognostic endometrial knownledge) in predicting the success of a single dose of methotrexate in tubal ectopic pregnancies and all other ectopic pregnancies is presented as the ROC curve in Figure 1. Sensitivity, specificity, positive predictive value and negative predictive value on treatment success in the fallopian tube and control group are presented in tables regarding these cut-off values. It was determined that the thickness of the endometrium differed from others in terms of sensitivity and specificity in predicting the success of treatment and gave stronger information in terms of prognosis. All results are presented in detail in Table 3.

Finally, we developed a model, and tested the strongest combination that could allow us to predict the success of single-dose methotrexate in the fallopian tubes

Table 2. The relationship of single dose methotrexate administration with ectopic pregnancies located in the fallopian tubes and the control group to variable parameters is shown

Evaluated parameter		Result of treatment	Group 1		Group 2	
			Median (q1–q3)	p value	Median (q1–q3)	p value
Endometrial thickness [mm]		**Successful**	7.00 (7.00–9.00)	< 0.001	7.00 (6.00–9.00)	< 0.001
		Failure	13 (12.00–14.00)		13.00 (12.00–13.25)	
β-hCG [mIU/mL]		**Successful**	2863 (1961.50–5031.50)	0.579	1415.00 (456.25–2813.50)	< 0.001
		Failure	3364 (2035.00–6061.50)		2976.00 (826.00–6019.00)	
NLR		**Successful**	2.52 (1.69–3.23)	0.468	2.11 (1.57–2.95)	0.038
		Failure	2.65 (1.98–3.66)		2.59 (1.93–3.65)	
PLR		**Successful**	125.83 (94.61–163.1)	0.791	107.84 (88.14–142.95)	0.055
		Failure	136.00 (98.36–154.03)		125.00 (96.77–151.74)	
CRL	**Present**	**Successful**	9 (21.42%)	0.873	12 (8.4%)	0.007
	None		33 (78.57%)		126 (91.6%)	
	Present	**Failure**	6 (23.1%)		12 (23.4%)	
	None		20 (76.9%)		39 (76.6%)	
FCA	**Present**	**Successful**	5 (11.9%)	0.681	7 (5.7%)	0.044
	None		37 (88.1%)		131 (94.3%)	
	Present	**Failure**	5 (15.4%)		7 (13.7%)	
	None		22(84.6%)		44 (86.3%)	

β-hCG — human chorionic gonadotropin-β; NLR — neutrophil /lymphocyte ratio; PLR — thrombocyte /lymphocyte ratios; CRL — crown-rump length; FCA — fetal cardiac activity ($p < 0.05$)

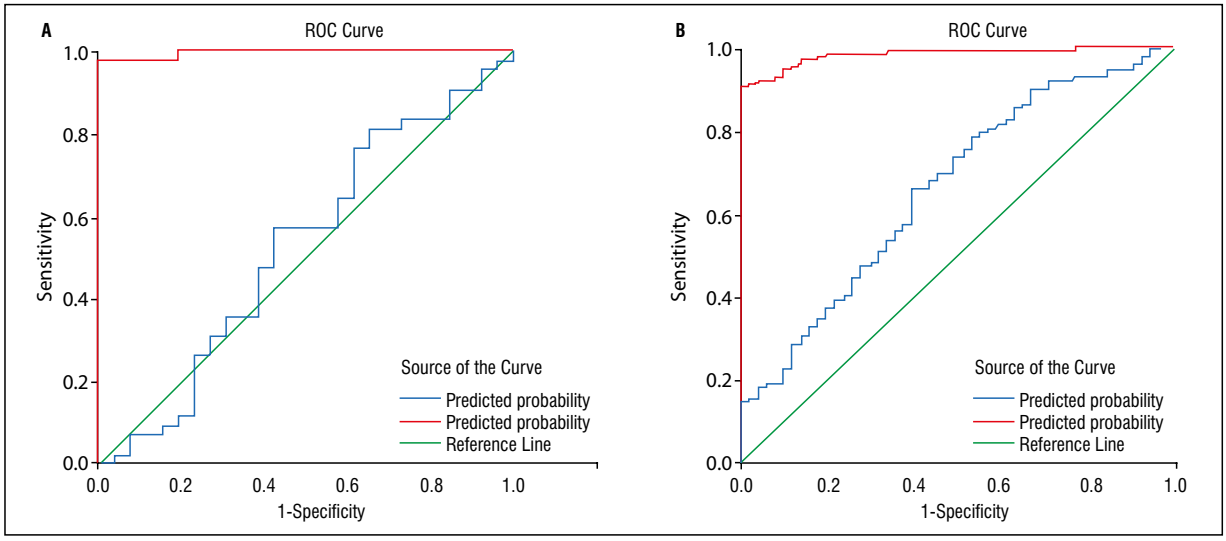

Figure 1. A. Shows the effectiveness of endometrial thickness in predicting the success of a single dose of methotrexate in tubal ectopic pregnancies, while **B** shows the effect of endometrial thickness on the success of a single dose of methotrexate in all ectopic locations; ROC — receiver operating characteristic

Table 3. Cut-off values predicting the success of single-dose methotrexate use and their confidence intervals, sensitivity, specificity, positive predictive value, and negative predictive values are presented ($p < 0.05$)

	Cut-off	AUC	SD	p value	Lower B.	Upper B.	Sens.	Spec.	PPV	NPV	Acc.
Endometrial thickness [mm]											
Group 1	10.5	0.994	0.006	< 0.001	0.982	1.000	0.929	0.990	0.990	0.897	0.956
Group 2	10.5	0.968	0.012	< 0.001	0.943	0.992	0.941	0.935	0.977	0.841	0.936
β-hCG [mIU/mL]											
Group 1	2960.5	0.540	0.074	0.579	0.394	0.686	0.542	0.656	0.718	0.471	0.588
Group 2	2960.5	0.666	0.045	< 0.001	0.578	0.754	0.511	0.775	0.811	0.456	0.704
NLR											
Group 1	2.49	0.553	0.072	0.468	0.412	0.693	0.552	0.701	0.711	0.551	0.617
Group 2	2.49	0.589	0.046	0.038	0.507	0.588	0.638	0.588	0.807	0.375	0.624

AUC — area under the curve; SD — standard deviation; B. — bounds; PPV — positive predictive value; NPV — negative predictive value; Acc. — accuracy; β-hCG — human chorionic gonadotropin-β; NLR — neutrophil /lymphocyte ratio

from this model. In this modeling, it was determined that in the presence of ectopic gestational sac located in the fallopian tubes, when added to the combination of endometrial thickness, serum β-hCG level + CRL status + FCA status, it made a very high contribution to predicting the prognosis. On the other hand, we also found that NLR did not make any prognostic significance or contribution. Simultaneously, we performed the same analyzes for the control group as a proof of modeling. And modeling has been shown to yield similar results. Table 4 contains the results for all models.

DISCUSSION

Studies on estimating the effectiveness of methotrexate used in the treatment of ectopic pregnancy are still ongoing. In the management of ectopic pregnancies, markers such as β-hCG level, presence of fetal cardiac activity, size of ectopic mass focus, presence of free fluid in douglas' dead end play a decisive role. Of course, when evaluating these markers, the status of vital signs is also taken into account [13]. As a matter of fact, these were the criteria that shaped the treatments we applied in our retrospective study as well. Patients with acute abdominal emergency surgery findings and no stabilization of vital signs were not included in the sample of our study because they were taken directly to surgical treatment. Our aim was to investigate whether endometrial thickness, NLR and PLR could be used as markers to predict treatment outcomes, apart from the criteria discussed in the literature, in the management of tubal localized ectopic pregnancies.

In our study, the cut-off value of β-hCG, which predicts the success of a single dose of methotrexate, was found to be 2960.5 mIU/mL. Recently, Sindiani et al. reported that they found this cut-off value as 3924 mIU/mL in their study with 110 patients [14]. On the other hand, Mashiach et al. reported this value as 2002.5 mIU/mL in their study on 111 patients [15]. Erdil et al. [8] calculated this value as 2678 mIU/mL in their study. Of course, this variability in hCG value can be affected by many factors. For example, the location of the ectopic pregnancy, the week of diagnosis of the ectopic pregnancy, the week of pregnancy made by the treatment decision and similar conditions will affect the measured serum β-hCG value. However, it has been reported in the literature that the success rate of methotrexate decreases and even the risk of rupture increases at when the serum β-hCG values above 5000 mIU/mL [2, 4]. But, the resistance of all tissues is unfortunately not the same. And variability can be seen between rupture times. In our study, we found the mean β-hCG value to be 3862.63 ± 2428.90 mIU/mL in cases with ultrasonographically visible ectopic pregnancy mass located in the fallopian tube. In cases where a single dose of methotrexate was successful, this mean value was 2863 mIU/mL. However, when we evaluated all ectopic pregnancies, the mean β-hCG value was measured as 2527 ± 2962.85 mIU/mL, and this value was 1415 mIU/mL in the group in which a single dose of methotrexate was successful. It is quite normal and to be expected that the results are so different. Because our most important criterion was the presence of a gestational sac that could be demonstrated ultrasonographically in the tubal location. In the control group, there were ectopic pregnancies with unknown locations, those with low β-hCG levels but drawing plateau, and others, and these constituted a very large majority. Therefore, it was necessary to determine a cut-off value at the maximum height at which effective treatment was achieved, especially in tubal localized ectopic pregnancies, and we did. We determined this cut-off value as 2960.5 mIU/mL and below in the population in which we conducted our study. This cut-off value was the most optimal result obtained both in the medical treatment of ectopic pregnancies located in the fallopian tubes and in all ectopic pregnan-

Table 4. Impact of the endometrial thickness and neutrophil /lymphocyte ratio score on the discrimination accuracy of MTX success

Prognostic model	AUROC (95% CI) without Endometrial thickness	AUROC (95% CI) with Endometrial thickness	DBA	SE	95% CI	Z statistic	p value
Group 1							
β-hCG	0.540 (0.394; 0.686)	0.968 (0.930; 1.000)	–0.428	0.307	–0.285; –0.570	–5.876	< 0.001
β-hCG + **CRL**	0.527 (0.375; 0.678)	0.968 (0.918; 1.000)	–0.441	0.311	–0.293; –0.590	–5.823	< 0.001
β-hCG + **CRL + FCA**	0.553 (0.408; 0.698)	0.995 (0.942; 1.000)	–0.469	0.284	–0.321; –0.616	–6.218	< 0.001
Group 2							
β-hCG	0.666 (0.578; 0.754)	0.977 (0.959; 0.994)	–0.311	0.232	–0.400; –0.222	–6.832	< 0.001
β-hCG + **CRL**	0.664 (0.576; 0.751)	0.977 (0.960; 0.994)	–0.313	0.232	–0.402; –0.224	–6.893	< 0.001
β-hCG + **CRL + FCA**	0.661 (0.573; 0.749)	0.981 (0.966; 0.996)	–0.320	0.229	–0.407; –0.232	–7.163	< 0.001
	AUROC (95% CI) without NLR	**AUROC (95% CI) with NLR**					
Group 1							
β-hCG	0.540 (0.394; 0.686)	0.596 (0.450; 0.742)	–0.056	0.378	–0.175; 0.064	–0.916	0.360
β-hCG + **CRL**	0.527 (0.375; 0.678)	0.591 (0.447; 0.734)	–0.064	0.380	0.064; 0.192	0.981	0.327
β-hCG + **CRL + FCA**	0.553 (0.408; 0.698)	0.586 (0.446; 0.727)	–0.033	0.375	–0.157; 0.091	–0.521	0.603
Group 2							
β-hCG	0.666 (0.578; 0.754)	0.667(0.576; 0.757)	–0.001	0.296	–0.045; 0.044	–0.025	0.980
β-hCG + **CRL**	0.664 (0.576; 0.751)	0.666 (0.576; 0.756)	–0.002	0.295	–0.045; 0.041	–0.098	0.922
β-hCG + **CRL + FCA**	0.661 (0.573; 0.749)	0.663 (0.573; 0.753)	–0.002	0.296	–0.046; 0.042	–0.076	0.939

AUROC — area under the receiver operating characteristic curve; CI — confidence interval; DBA — difference between areas; SE — standart error; β-hCG — human chorionic gonadotropin-β; CRL — crown-rump length; FCA — fetal cardiac activity; NLR — neutrophil /lymphocyte ratio

cies in our control group. Although different results were reported, the β-hCG cut-off value which we obtained was generally compatible with the literature.

As a new marker, we tested, for the first time in the literature, the prognostic contribution of endometrial thickness in the medical treatment of ectopic pregnancies located in the fallopian tubes. As a result of our statistical analyzes, we determined the upper limit of the endometrial thickness as 10.5 mm, where the maximum benefit from medical treatment can be seen in the presence of an ectopic pregnancy mass located in the fallopian tubes. In addition, we tested the contribution of the cut-off value we determined for endometrial thickness in the management of all other ectopic pregnancies in our control group. The results we found were reproducible and identical. This result is very important in terms of its contribution to the literature. As a chemotherapeutic agent methotrexate affects rapidly dividing cells, which also include ovarian or endometrial cell populations [16]. Erdil et al. [8] have recently demonstrated the cytotoxic effects of methotrexate on the endometrium and its receptors. In-vitro studies of the rat uterus have demonstrated a possible effect of methotrexate on the inhibition of estrogen receptor protein synthesis [17, 18]. In one case, Kroft et al. [19] reported that secondary amenorrhea developed in a woman using methotrexate for rheumatoid arthritis. Da Costa Soares et al. [20] reported a mean value of 6.4 mm and 1,936.2 mIU/mL β-hCG for endometrial thickness in cases of success with a single dose of methotrexate. In their study,

the mean values of endometrial thickness were 11.7 mm and β-hCG was 6.831.3 mIU/mL in case of failure [20]. Takacs et al. [21] reported that the success rate of methotrexate showed significant variability at values below and above 12 mm of the endometrium. In fact, Nikolic et al. [22] reported that low-dose methotrexate can be used together with raloxifene in the treatment of endometrial hyperplasia. As a opposing view, Taş et al. [9] investigated the efficacy of a single dose of methotrexate, but reported that endometrial thickness was not a determining factor in their study. Cecchino et al. [23], in their review, reported that endometrial thickness reflects hormonal levels and that the higher the β-hCG level, the higher the endometrial thickness and the worse the prognosis of methotrexate treatment. Cecchino et al. [23] were right in their results. The rising β-hCG level increases the secretion of the hormone progesterone, which plays the most important role in the continuation of pregnancy. Increasing progesterone, on the other hand, has an anabolic effect on the endometrium, thickening and softening it, making it ready for pregnancy [24–26]. This explains the excellent agreement between β-hCG and endometrial thickness in predicting treatment success. As a note, endometrial thickness has also been tried in the evacuation of early pregnancy losses and reported to be an effective factor for the effectiveness of misoprostol [25]. The sensitivity and specificity of the cut-off value determined in our study regarding the endometrial thickness in predicting the success of methotrexate is acceptable. For this reason, we used the name 'prognostic endometrial knownledge (PEK)' for this value due to its contribution.

Akkaya et al. [12] evaluated the contribution of inflammatory markers in the prediction of ectopic pregnancy in their study, but reported that NLR and PLR did not provide any benefit. Kanmaz et al. [11], on the other hand, reported that NLR may contribute to predicting the success of a single dose of methotrexate. In our study, we found that NLR and PLR values did not make a statistical difference in the success of methotrexate in tubal ectopic pregnancies. On the other hand, NLR value showed a statistical difference in all cases diagnosed with ectopic pregnancy in our control group. The possible cause of this situation may be ectopic pregnancies of unknown location, which were treated at lower β-hCG levels in the early period. However, as a final result, NLR was far from being an accurate predictor of making any contribution to prognosis. In our study, CRL and FCA did not seem to differ statistically for single-dose methotrexate success in tubal localized ectopic pregnancies. However, the reason for this was that the cases in which only the presence of gestational sac in the fallopian tubes could be observed ultrasonographically were included in this group with great care. Because the results we obtained in our control group were statistically significant in accordance with the literature.

CONCLUSIONS

We think that endometrial thickness is a parameter that should be considered in predicting the success of methotrexate. In this case, curetting the endometrium before methotrexate administration may increase the success rate of a single dose of methotrexate. And we believe that inflammatory markers do not make any contribution to the prediction of treatment success. Although our sample is large enough to allow us to comment on this subject, the importance of the subject will increase with the presentation of other studies to the literature.

Ethics

All ethical approvals required for the study were obtained from the Çanakkale Onsekiz Mart University Clinical Research Board. (2022-YÖNP-0013/ 06.04.2022:06-13)

Authorship contributions

Concept: EP, FB; Design: EP, FB; Data Collection or Processing: EP, FB; Analysis or Interpretation: EP, DS; Literature Search: EP; Writing: EP.

Conflict of interest

The authors declared no conflict of interest.

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VIA MEDICA

RECCOMENDATIONS

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The Polish Society of Gynecologists and Obstetricians' Expert Group Recommendations regarding adolescent pregnancy

Agnieszka Drosdzol-Cop[1], Jakub Staniczek[1], Dominika Orszulak[1], Karolina Kowalczyk[2], Anna Fuchs[3], Piotr Sieroszewski[4], Miroslaw Wielgos[5], Jaroslaw Kalinka[6], Hubert Huras[7], Piotr Wegrzyn[8], Sebastian Kwiatkowski[9], Mariusz Zimmer[10], Rafal Stojko[1]

[1]Chair and Department of Gynecology, Obstetrics and Gynecological Oncology, Medical University of Silesia, Katowice, Poland
[2]Department of Endocrinological Gynecology, Medical University of Silesia, Katowice, Poland
[3]Clinical Department of Obstetrics and Gynecology, Medical University of Silesia, Katowice, Poland
[4]Department of Fetal Medicine and Gynecology, Medical University of Lodz, Poland
[5]Lazarski University, Warsaw, Poland
[6]Department of Perinatology, Medical University of Lodz, Poland
[7]Department of Obstetrics and Perinatology Jagiellonian University, Cracow, Poland
[8]Department of Obstetrics, Perinatology and Gynecology, Medical University of Warsaw, Poland
[9]Department of Obstetrics and Gynecology, Pomeranian Medical University in Szczecin, Poland
[10]2nd Department and Clinic of Gynecology and Obstetrics, Wroclaw Medical University, Wroclaw, Poland

The recommendations present current methods of treatment that may be subject to modification and change in justified cases, after careful analysis of the given clinical situation. In the future, this may be the basis for their modification and updating.

INTRODUCTION

Recent decades have seen an improvement in the quality of life in both social and economic terms. This translates into a reduction in the incidence of problems which in previous years were due to poorer access to sexual education. We are currently seeing a significant shift in the average age of patients who have their first pregnancy. However, the problem of teenage pregnancy has not disappeared and, with the shift in the age limit for first pregnancy, has often become more stigmatized by society than in previous decades. Early sexual initiation is associated with high risk of pregnancy and sexually transmitted diseases (STD). Teenage pregnancy is very often an unwanted and unaccepted pregnancy, with mothers reporting too late to the doctor due to fear or ignorance, and lack of accessibility to a gynecologist. This requires a more empathetic and supportive approach on the part of us doctors, to guide often very young girls through this special time.

The purpose of these recommendations is to present the current state of knowledge based on the authors' experience and sound scientific data. It also aims to identify the social background and potential complications of adolescent pregnancy and the management of their outcome. The management of pregnancy with particular reference to ultrasound diagnosis is also included, as well as its termination. In addition, guidelines on contraception and prevention of unwanted underage pregnancies are included.

Definition

Adolescent pregnancy is defined when a pregnant woman is between 10 and 19 years of age. This paper uses data from the Central Statistical Office, whose index includes pregnancies '19 years and under' [1].

EPIDEMIOLOGY

Most teenage pregnancies are related to unprotected intercourse and early sexual initiation. It is a global problem,

Corresponding author:
Jakub Staniczek
Chair and Department of Gynecology, Obstetrics and Gynecological Oncology, Medical University of Silesia, Katowice, Poland
e-mail: jstaniczek@sum.edu.pl

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with nearly 16 million teenage girls aged 15–19 and two million girls under 15 becoming pregnant each year. According to the United Nations Children's Fund (UNICEF) data for highly developed countries, the country with the lowest percentage of births per 1,000 pregnant women under 20 is South Korea — 2.9, and the highest in the USA — 52.1. For Poland the indicator is 18.7 [2–4]. It should be remembered that adolescent pregnancy is associated with more complications and risk of maternal and child death. Based on the available data, it is the leading cause of death for adolescents aged 15–19 years in the world [5–7]. Increased mortality is also associated with poorly performed abortions that led to permanent damage to health, complications or outright death, it is reported that 5.6 million abortions are performed annually on girls aged 15–19, of which 3.9 million are improperly performed [1–3, 7].

The young age of the mother leads to an increased risk of systemic infection, eclampsia, puerperal endometritis, premature birth and is also associated with low birth weight and severe neonatal morbidity [5].

It is worth noticing that according to a World Health Organization (WHO) report, in Scandinavian countries where access to contraception and abortion is very easy, it is reflected in the rate of underage pregnancies, which is much lower compared to other countries [1].

General Statistics of Poland (GUS, *Główny Urząd Statystyczny*) data for 2020, state that in Poland mothers aged 19 and under gave birth to 7118 children. This compares to 11,230 in 2016 for the same age group. Year on year, we are seeing a downward trend in our country [6].

SOCIAL BACKGROUND

Adolescent pregnancy is a challenge not only from the medical side but also from the social point of view. There is now a reduced age of first menstruation, which is associated with better nutrition and increased standards of living and health care [1, 2]. The problem of unwanted pregnancy is often associated with low socioeconomic status, although it affects all levels. This is related to poorer access to education, lack of money for contraception or family patterns [1]. Table 1 summarizes the causes of adolescent pregnancy.

In many countries around the world, adolescent pregnancy is primarily related to the cultural pattern of the age of marriage. It is concluded earlier in developing countries. In developed nations, the scale of the phenomenon is decreasing [1, 7]. Based on the GUS data, in Poland in 2020, 1367 women aged 19 and less were married. This compares to 29,345 for those aged 20–24. Interestingly, only 245 men aged 19 and below got married, while for those aged 20–24 it was 13,444. In 2015, the numbers were as follows women married at age 19 and below — 3797, and aged 20–24 — 53359, men aged 19 and below 526, while for those aged 20–24 it was 26909. Therefore, we observe a decreasing trend in both age groups irrespective of gender, which is also reflected in the number of children born to women in these age groups [6–9].

Table 1. Biological, sociological and psychological factors that may predispose to teenage pregnancy [1]

Factors influencing the adolescent pregnancy	
Early puberty in girls	Early sexual initiation
Risky sexual behaviour	Sexual violence
Lack of proper education	Ineffective pro-family education
Social pressure — media	Low self-esteem
Lack of proper role models	Low socio-economic status
Lack of family care and support	Lack of affection and family warmth

In recent years, we have observed a significantly earlier sexual initiation. The results of analyses conducted by Woynarowska et al. [9] on a group of 15-year-old adolescents have shown that 9.2% of 15-year-old girls have had sexual initiation (mean age of initiation — 14.7 years), among all sexually active 15-year-olds 27% have declared that neither they, nor their partners have used any contraceptive methods during the last intercourse. Among sexually active 18-year-olds, one in four young people had three or more sexual partners. 49% use ineffective methods of contraception, such as intermittent intercourse or natural methods [10]. In comparison, in the USA 25% of adolescents report that they did not use protection during the first time, in the United Kingdom and Sweden 21–22%, and in France 11% [1]. These data are alarming because lack of knowledge or difficult access to contraception for adolescents is also associated with a higher risk of sexually transmitted diseases (STDs) including HIV. Therefore, young women are most vulnerable to STDs at the beginning of their reproductive period [1, 5, 11].

The sexual education is another aspect. It is most important during childhood and adolescence. It is a lifelong process and therefore should be adapted to the level of psychosexual development. A study conducted by Skonieczna et al. [12] for secondary school students and their parents found that 96.1% of parents and 94.3% of students consider sex education to be important. However, the most frequently indicated sources of students' knowledge were colleagues (61.7%, 208 persons) and Internet portals (60.5%, 204 persons). As we know, these are points of quite disputable quality and reliability of information. Only 43% of respondents declared the school as the place where they gain their knowledge. A study by the Institute of Educational Research (IBE) showed that the teacher is the second main source of knowledge in this area (38%), just after peers (56%) [13]. Adolescents in Poland often do not have access

at school to reliable, complete and world-view ambivalent knowledge on sexuality. The family also often does not fulfill its duty of sexual education of a young person, which is due to, among others, the common stereotypes that sex is a taboo subject. It occurs that parents shift the responsibility for this area of education to the teaching system [12]. Another important problem is the support of a young girl in the face of the vision of motherhood. The challenges of pregnancy overlap with the difficulties of adolescence, difficulties at school and the problem of social stigma. The support of the family, medical staff and a psychologist may be crucial not only for the proper course of pregnancy, but also for preparing a young girl to take up the challenge of parenthood.

LEGAL DIFFERENCES IN ADOLESCENCE PREGNANCY

According to art. 200 of the Polish Penal Code, a person who has sexual intercourse with a minor under the age of 15 or commits another sexual act towards such a person or causes him to submit to such acts or to perform them, shall be punishable by imprisonment from 2 to 12 years. The legislator has assumed that anyone who engages in sexual activities with a minor thereby violates his/her sexual freedom not because it violates his will in this respect (a minor may in fact allow or even inspire such acts), but because the victim of such an act is unable to express a legally valid decision to consent to the acts in question. If such a crime is suspected, it should be reported in person, by reporting such a fact to the Police station competent for the place of the crime, or in writing, by sending an appropriate letter to the appropriate Police unit or the District Prosecutor's Office competent for the place of the crime. If a suspected crime is not reported, in such a situation the person who had reliable information is exposed to criminal liability.

Situations in which a person before the age of 15 becomes pregnant are extremely difficult because they also involve the court, whose role is to verify the circumstances surrounding the sexual relationship of such young people and the correctness of the care that is given to them [11]. A woman under the age of 18 is not entitled to parental authority over a child. In such a situation, the child's legal guardian is the person indicated by the child's mother/father (usually these are the parents of the child's mother/father).

INFORMED CONSENT FROM A MINOR PATIENT

The general rule is that the consent to the provision of health services is given by the patient himself. However, this does not apply to the treatment of minors, *i.e.*, people under 18 years of age. In this case, we can deal with two types of consent:

Substitution consent — when consent for treatment of a child under 16 is generally expressed by the patient's parent (or other legal representative).

Cumulative consent — when consent for treatment of a child over 16 years of age expressed by the patient himself and his parent (or other legal representative). The doctor should remember that granting consent should be preceded by comprehensive and understandable information — provided to the parent and the minor patient who is over 16 years old.

As for patients under 16, they also have the right to obtain information, but in the scope and form necessary for the proper course of the treatment process. This aspect is of course subject to the assessment of the doctor who should consider not only the child's age, but also his emotional maturity and developmental level.

The decision regarding the medical procedures applied to the newborn is taken by his statutory representatives.

Recommendations

1. Who recognizes a pregnancy in a minor patient is obliged to inform the patient's parents/legal representatives.
2. If you suspect a crime involving a minor, report it to the nearest police station.
3. In the case of a minor, it is good practice to sign an informed consent with the child's parents for all possible medical procedures.
4. When consent for treatment of a child under 16 is generally expressed by the patient's parent (or other legal representative).
5. When consent for treatment of a child over 16 years of age expressed by the patient himself and his parent (or other legal representative).

MANAGEMENT OF PREGNANCY

Pregnancy in an adolescent should be treated as a high-risk pregnancy (especially for girls aged 11–14) [1]. Such a pregnancy requires from the doctor experience and knowledge of possible risks and complications that may complicate pregnancies in a adolescence. Conducting such a pregnancy requires periodic visits to the pregnancy pathology clinic under the 3rd degree of reference or to reference clinics specializing in pediatric and adolescent gynecology with appropriate obstetric/perinatological facilities.

It should be emphasized that for a young girl who becomes pregnant, this is a heavy burden, both financially, physically, and psychologically. It's later reflected during the pregnancy. Adolescent mothers are very often at risk of malnutrition, resulting from an inadequate diet. The mental pressure leads to the use of stimulants. As reported by Jessica Dalby et al, underage pregnant women are more likely to use tobacco products (36% vs 7%) and alcohol and recreational drugs (1.1% vs 0.2%). They also face housing problems, domestic violence and abandonment by their partner [14]. It is therefore important to diagnose preg-

nancies early to avoid increased perinatal risk. The family, especially the teenage mother's partner, should be involved as much as possible to ease her through this difficult time, and they should be educated about infant care and development. WHO recommends at least four gynecological visits in uncomplicated pregnancy — at 16 weeks, between 24 and 28 weeks, at 32 and 36 weeks [1]. In contrast, the Canadian Paediatric and Adolescent Gynaecology and Obstetricians (CANPAGO) recommends that visits especially in the second and third trimester be more frequent to regularly assess fetal well-being and prevent preterm birth [15]. In principle, the obstetric medical supervision of a pregnant adolescent is no different from the perinatal care of a pregnant adult [1].

Teenagers may present to the doctor's office with quite non-specific symptoms and, as clinicians, we must be very sensitive especially to irregular menstrual periods and other cycle disorders typical for their age. Strong denial of the possibility of pregnancy must be taken under consideration. The presence of a caregiver additionally influences the embarrassment and openness of adolescents about starting intercourse. The typical symptoms most reported by girls on suspicion of pregnancy are amenorrhea, nausea and vomiting, breast tenderness, weight change, abdominal pain, and dizziness [14].

Mukhopadhyay et al. [16] compared the perinatal differences between 350 adolescents (13 to 19 years) and 350 adults (20 to 29 years), their study found that the 13–19 age group was at higher risk of preterm birth (27.7%), low birth weight (38.95%) and stillbirth (5.1%) [16].

The main cause of the above-mentioned complications seems to be uterine immaturity. Brosens Ivo et al. [17] used the term "great obstetrical syndromes" to describe the clinical heterogeneity related to impaired vascular adaptation of the maternal spiral arteries in the process of intravascular trophoblast invasion. This term covers the range of pregnancy complications, preeclampsia, small for gestational age, preterm labor, premature rupture of the membranes, late spontaneous abortion and placental abruption. These pathologies are characterized by the presence of obstructive lesions in the myometrial segment of the uteroplacental spiral arteries and reduced vascular remodeling in the placenta [17, 18].

Attention should be paid to the structure and dimensions of the bony pelvis. It has been shown that in girls under 16 years of age, who are in addition measure less than 150 cm, a constricted pelvis is more frequently diagnosed. The bony skeleton is formed for up to 3–5 years after the onset of menarche, hence the pelvis often has a small volume, and this makes natural childbirth more difficult. In addition, the smaller pelvic diameter in adolescent mothers has been shown to have a direct effect on the weight of the baby, which was significantly lower in these mothers, often leading to intrauterine growth restriction. We must also bear in mind the increased calcium requirements of adolescent girls during pregnancy and lactation, both due to pregnancy and the ongoing skeletal ossification process. It has been proven that young mothers are more likely to lose bone mass during breastfeeding than adult women. It is therefore important to ensure that the pregnant woman has an adequate supply of not only vitamin D but also calcium [17–19].

Education on proper nutrition should be carried out at the first visit. Adolescents are increasingly suffering from eating disorders (ED), so during the medical interview, attention should be paid to the perception of body image. During pregnancy, the need for folic acid, iron or iodine increases [1, 15, 20, 21].

During the first visit, we should screen for sexually transmitted diseases (STDs), as teenagers are much more vulnerable to them than adult women. This is because teens are much more likely to exhibit unsafe sexual behavior, have sex without mechanical protection and with many casual partners. Re-examination should be carried out in the third trimester. Potential infection with HIV, *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, *Treponema pallidum*, HPV, HSV, bacterial vaginosis should be excluded. If a positive test is obtained, a follow-up swab should be done after treatment has been completed for up to 3–4 weeks. The young mother's partner should also be referred for a screening. Education should be introduced on the use of condoms to protect against STDs [1, 15, 22].

Another aspect to be addressed during the first visit is the plan of birth. It is important to establish it as soon as possible since minors are at risk of preterm delivery. The patient's age (especially if the underage girl is less than 14 years old), the referral level of the hospital, the patient's mental state, and the pelvic anatomy should be considered when selecting the facility and the method of delivery [1].

We should not forget about the stimulants used by minors. According to the National Survey on Drug Use and Health conducted by the Substance Abuse and Mental Health Administration and NSDUH, younger pregnant women were much more likely to use drugs than their peers who were not pregnant. They were most likely to use marijuana, cocaine, opioid and painkiller drugs [23].

Other studies report that the most frequent substance used by teenagers is alcohol, as much as 15.85% of those surveyed. The second most frequent is marijuana — 14.55%, while the third is other drugs — 5.30%. We observe a decrease in the consumption of drugs by half in the second trimester, compared to the first. The same pattern applies to the third trimester, compared to the second [24]. Young patients should be sensitized to the consequences of drug use during pregnancy, such as intrauterine growth restric-

tion (IUGR), preterm delivery, fetal malformations, placental pathology or increased perinatal mortality. We should also carry out screening for intoxicating substances and provide appropriate education [1, 15, 23, 25].

Recommendations

1. Pregnancy in an adolescent should be treated as a high-risk pregnancy (especially for girls aged 11–14).
2. Conducting such a pregnancy requires periodic visits to the pregnancy pathology clinic under the 3rd degree of reference or to reference clinics specializing in pediatric and adolescent gynecology with appropriate obstetric/perinatological facilities.
3. Education on proper nutrition should be carried out at the first visit. Dietary recommendations for pregnant teenagers include:
   - The caloric value of the diet depending on the nutritional status should be approx. 2200 to 2500 kcal.
   - Supplementation of 0.4 mg of folic acid and 30-60 mg of elementary iron for 3 months.
   - Iodine intake of 200 µg per day.
   - Taking 200 mg DHA daily.
   - Taking 2000 IU of vitamin D daily.
   - Taking 1.0 g of Calcium daily.
4. During the first visit, screening for STDs and TORCH should be performed.
5. Screening for intoxicating substances and provide appropriate education.

ANAEMIA

Anaemia is a decrease in hemoglobin (Hb), hematocrit (Ht) and the number of erythrocytes in the blood below normal values for age and sex. According to WHO, anemia can be diagnosed in pregnant women with hemoglobin levels < 11 g/dL, severe anemia with levels of 7 g/dL [20, 24]. The most frequent causes of anemia are poor nutritional habits, genetic factors or an infectious disease. The consequences of anemia can be prematurity, fetal growth restrictions (FGR) and low birth weight. Hemoglobin and ferritin levels should be monitored regularly. In case of severe anaemia, hospitalization of the patient should be recommended.

According to the guidelines of the Polish Society of Gynecologists and Obstetricians (PTGiP), women with an iron reserve of about 500 mg (ferritin 60–70 µg/L) have a low risk of anaemia during pregnancy, despite the lack of supplementation. Iron supplementation should be considered in women with ferritin levels below 60 µg/L, despite the absence of anemia. A ferritin level of less than 12 µg/L indicates depletion of iron stores. After the 16th week of pregnancy, iron supplementation of up to 30 mg/day should then be introduced. In case of normal test results PTGiP does not recommend iron supplementation during pregnancy [24]. In case of anemia due to folic acid deficiency, it is necessary to administer folic acid at a dose of 2.5 mg/day in girls up to 5 years of age and 5 mg/d in older girls. Treatment should be carried out from 1–4 months. The effectiveness of the treatment is demonstrated by the rapid increase in the number of reticulocytes in the 4th to 7th day after starting the treatment [1, 20, 26].

Recommendations

1. Iron supplementation is not recommended in the presence of normal blood results.
2. Iron supplementation at a dose of 30 mg/d is acceptable in non-anemic women with ferritin levels below 60 µg/L after the 16th week of pregnancy.
3. In case of anemia due to folic acid deficiency, it is necessary to administer folic acid at a dose of 2.5 mg/day in girls up to 5 years of age and 5 mg/d in older girls. Treatment should be carried out from 1–4 months.

PERINATAL CARE

The analysis of literature data shows differences in the number of vaginal deliveries and cesarean sections in the group of teenagers. The results of many retrospective studies in highly developed countries have shown a higher percentage of vaginal delivery and a lower rate of cesarean sections in the group of teenagers compared to the group of adult women. A shorter duration of the active stage of labour was also observed with a comparable time of the second stage of labour and a lower rate of the use of vacuum extractor and obstetrical forceps. Additionally, it is noteworthy that most cesarean sections are performed due to emergency indications. Literature data also show that in the group of adolescents during childbirth the epidural anesthesia is used less frequently [27–29].

Karataşli et al. [30] observed a higher rate of cesarean sections in adolescents < 15 years of age which may be due to their biological immaturity. The pelvis in juveniles is not fully developed which is reflected in its small capacity and anthropoid structure (transversely constricted pelvis). Malabarey et al. [31] conducted a large cohort study, the results of which confirm that a higher rate of cesarean sections correlates with a younger age of a pregnant adolescent (19.59% in the group of pregnant adolescents at the age of 12 vs 13.92% at the age of 15).

Data on attempted trial of labour after cesarean (TOLAC) in the group of adolescents are limited and inconsistent. The Israeli study showed that TOLAC was successful in 83% of the study group (117 women), while low birth weight is an independent risk factor of vaginal birth after cesarean (VBAC) failure [31, 32]. Damle et al. [33] observed a significantly lower VBAC rate among adolescents who attempted vaginal delivery after cesarean section — 48% of the study group [33].

Contentment and satisfaction related to perinatal care in adolescents is much lower. Juvenile patients more often perceive the birth experience as traumatic which is mainly influenced by the pain of labour and fear [28]. An extremely

important role in this age group of pregnant patients should be played by antenatal education, which according to the standard of perinatal care of the Ministry of Health, should start between 21st and 26th week of pregnancy. Antenatal education is not only a significant point in preparing a teenager for childbirth and childcare but is also associated with the increase of the sense of security and acceptance of pregnancy by the teenager, thus reducing, among others, the risk of postpartum depression [34].

Researchers emphasize the continued need to conduct large, multicenter studies in order to establish the most effective model of adolescent pregnant patients' perinatal care. In the opinion of experts, adolescent pregnancy is not an indication for caesarean section, unless there are clear indications for surgery. It is recommended that perinatal care in the group of adolescent patients < 19 years of age is based on the guidelines of the Polish Society of Gynecologists and Obstetricians and the Regulation of the Minister of Health on the organizational standard of perinatal care of 16th August 2018 [34–36].

Recommendations

1. Adolescent pregnancy is not an indication for caesarean section, unless there are clear indications for surgery.
2. TOLAC is not a contraindication in adolescent pregnancy.
3. Antenatal education is a significant point in preparing a teenager for childbirth and childcare.

ULTRASOUND FOR FETAL ANOMALIES AND COMPLICATIONS

Adolescent pregnancies are associated with a higher risk of complications such as preeclampsia, fetal growth restrictions, preterm labor, low birth weight, prematurity and stillbirth. Statistically, newborns of adolescent mothers are more likely to require admission to the intensive care units. Moreover, non-chromosomal anomalies (NCA) are common in adolescent pregnancies [37–40]. It is estimated that 26.5/1000 births of teenage mothers are associated with the occurrence of NCA. For comparison, the incidence of defects decreases with increasing maternal age (22.5/1000 births for mothers aged 25–29, 21.5/1000 for mothers 30–34 years old, 21.4/1000 for mothers aged 35–39 years old), until a slight increase in the number of defects at the age of 40-44 (22.6/1000 births) and a further increase in the incidence of NCA for mothers aged 45+ (25.3/1000 births). The non-chromosomal anomalies are in adolescent pregnancies include musculoskeletal anomalies, defects of the abdominal wall, anomalies of the gastrointestinal tract, central nervous system, and heart. Studies have reported that younger women have lower awareness of folic acid supplementation which causes more frequent occurrence of spina bifida/meningocele in this group. Statistically, non-immune hydrops associated with maternal infection is more common, especially related to rubella, toxoplasmosis, cytomegaly, herpes simplex and parvovirus. It should be emphasized that compared to the general population, teenage mothers are six times more likely to have a child with gastroschisis and almost five times more likely to suffer from malformations and non-immune hydrops associated with maternal infection. Adolescent pregnancies are associated with almost three times the risk of having a child with atresia or stenosis of the tricuspid valve, and almost twice as high the risk of anencephaly. An additional factor causing fetal defects in adolescence pregnancy is amniotic band syndrome (ABS) and/or limb body wall complex (LBWC), which is more common in this group [40–43]. The more frequent abuse of psychoactive substances contributes to the increase in the number of pregnancy defects and complications in this group of patients. Some data show that 33.4% of adolescents consume alcohol and 34.8% of adolescents are sexually active by the age of 15 without any form of contraception. This contributes to the higher incidence of Fetal Alcohol Syndrome (FAS) in newborns [44]. The most common abnormalities of young mothers' fetuses are presented in Table 2.

The risk of chromosomal abnormalities increases with the mother's age; therefore the incidence of these defects is low in the group of adolescent mothers. The estimated frequency of births of a child with Down's syndrome in patients under the age of 15 is 0.634/1000 births and remains at a similar level to around the age of 25. The estimated birth rate for a child with Edwards, and Patau Syndrome is even lower, less than 0.112/1000 and less than 0.0764/1000 births respectively. However, it should remember about diseases that do not show a correlation between the mother's age and the risk of its occurrence, such as X-chromosome monosomy (Turner syndrome) or 22q11.2 deletion syndrome (DiGeorge syndrome) [45].

The most common obstetric pathologies in young mothers, including preeclampsia, hypertension, fetal growth restriction and premature birth, are a consequence of severe pathology of the uteroplacental vessels, with origins in early pregnancy. Also, uterine immaturity in very young teenagers is likely a major cause of defective deep placentation and adverse reproductive outcome. Additionally infrequent menstruations may prolong uterine immaturity because of lack of "menstrual preconditioning". The pathogenesis of preeclampsia in adolescence is associated with abnormal deep placement in the immature uterus, impaired uterine decidualization, intrinsic decidual resistance and uterine maturation and spontaneous decidualization. There is also a link between cardiovascular risk factors in young women and early-onset preeclampsia associated with atherosclerosis of the uteroplacental arteries. The risk of preeclampsia

Table 2. The most common abnormalities of young mothers' fetuses

Central nervous system	
Anencephaly	Microcephaly
Spina bifida	Caniorachischisis
Holoprosencephaly	Hydrocephalus
Craniofacial	
Cleft face	Cleft lip
Ear defects	Cleft palate
Heart	
D-transposition of the great arteries	Right ventricular outflow tract obstruction
Tricuspid atresia/stenosis	Mitral valve atresia/stenosis
Total anomalous pulmonary venous return	Heterotaxia with Congenital heart
Double outlet right ventricle	Pulmonary valve anomalies
Digestive tract	
Omphalocele	Gastroschisis
Duodenal atresia	Anorectal atresia/stenosis
Urinary tract	
Kidney agenesis	Genital defects
Limbs	
Polydactyly	Syndactyly
Genu varum	Clubfoot

among those younger than 20 is 1.25 times higher than that among 20- to 24-year-old women, and the risk of eclampsia is 2.3 times higher. Preeclampsia/eclampsia may affect up to 15 % of adolescent pregnancies [46–47]. The above changes in the placenta may be related to the fact that studies suggest that young maternal age is also more significantly associated with placental abruption than the advanced maternal age [48].

Premature delivery is an important indicator of newborn welfare and is associated with severe morbidity and mortality. In the group of adolescent women, preterm labor occurs with a frequency of about 15%. Additionally, young mothers have a significantly increased risk of having extremely premature babies and newborns with extremely low birth weight. Low birth weight (LBW) is a complication that occurs much more frequently in pregnant teenagers (about 33%) than in adult women. It mainly affects girls aged 10–14 years. LBW is one of the main causes of neonatal mortality. In adolescents it is a consequence of lack of proper prenatal care, malnutrition, smoking and the use of other stimulants. Low birth weight and very low birth weight (VLBW, < 1500 g) predispose to preterm delivery [1, 27, 49].

According to the standards and protocols of the Polish Society of Gynecologists and Obstetricians, the ultrasound assessment should be performed on the 11th–14th, 18th–22th, 28th–32nd and 40th (with CTG) weeks of pregnancy additionally the risk of growth restrictions should be assessed in each adolescent patient at the beginning of pregnancy and at each visit. [50–52].

Recommendations

1. In the 11th–14th week of pregnancy, the assessment of the anatomical structures of the fetus, the search for early structural defects, the assessment of the size of the fetus and the determination of the duration of pregnancy. Risk assessment of the most common chromosomal aberrations based on the combined test (assessment of fetal nuchal translucency and maternal serum free beta-hCG and PAPP-A).
   a. In the case of diagnosis of fetal malformation, amniocentesis and array comparative genomic hybridization (aCGH) and genetic consultation is recommended.
   b. We recommend that each pregnant woman use screening to assess the risk of developing FGR with early onset, with maternal factors, uterine artery pulsatility index (UtA PI), mean arterial pressure (MAP), and gestational placental growth factor (PlGF). When PlGF cannot be used, pregnancy-associated plasma protein A (PAPP-A) values below 0.4 multiple of the median (MoM) suggest an increased risk of developing preeclampsia. When PAPP-A cannot be used, maternal factors, UtA PI, mean arterial pressure (MAP) should be used to calculate risk. In high-risk situations (> 1:100), it is justified to start the administration of 150 mg of acetylsalicylic acid before 16 weeks of gestation and continue it until the 36th week.
   c. In a group at high risk of FGR and/or preeclampsia identified on the basis of the first trimester screening, a screening between 19th–24th weeks of gestation should be considered using the patient's history and UtA PI, mean arterial pressure (MAP) and if it possible with PlGF and soluble fms-like tyrosine kinase-1 (sFlt-1) evaluation.
   d. In a group of low risk of FGR and/or preeclampsia, the assessment of UtA PI should be considered. In the case of normal biometry and PI UtA above the 95th percentile, we recommend an additional control of growth dynamics between 34th–38th week of pregnancy.
   e. In a high-risk pregnancy, fetal growth should be assessed additionally at week 26th–28th and at 34th–38th week of pregnancy.
   f. If FGR is diagnosed, further proceeding should be based on the Recommendations of PTGIP [53, 54].
7. In the 18th–22th week of pregnancy, a detailed assessment of the fetus in terms of the presence of congenital abnormalities, taking into account typical abnormalities for an adolescent pregnancy. In the case of fetal malformation, amniocentesis and aCGH and genetic consultation is recommended. Transvaginal assessment of cervical length is recommended as prevention of preterm labor.
8. In the 28th–32th and in the 40th week of pregnancy, an assessment of the fetus in terms of the presence of congenital abnormalities, taking into account typical abnormalities for an adolescent pregnancy and an assessment for fetal well-being and growth.

POSTPARTUM CARE

Both WHO/UNICEF and Polish Society for Pediatric Gastroenterology, Hepatology and Nutrition recommend exclusive breastfeeding during the first 6 months. Young breastfeeding mothers may additionally benefit from increased intervals between pregnancies and stronger

mother-infant bonding. Unfortunately, teenage mothers are less likely to start breastfeeding compared to older mothers (44% mothers ≤ 19 years vs 65% mother > 19 years) [55–57]. Factors diminishing breastfeeding rate include poor socioeconomic status, limited social support, the lack of prenatal intervention, obesity, cesarean delivery, and preterm birth [58].

Adolescent mothers are twice more likely to suffer from postpartum depression (PPD) compared to adult mothers. Most investigators estimate the prevalence of adolescent postpartum depression on approximately 25%. The most important risk factors are limited social support, low socioeconomic status, and depression prior to pregnancy. There are specific psychosocial challenges making teenage mothers more vulnerable to PPD, such as isolation from peers, family and partner conflict, single motherhood, low self-esteem, and body dissatisfaction. Adolescent mothers in postpartum depression are at high risk for near future pregnancy. The peak onset of depression in adolescent mothers shifts to four months after birth. This justifies starting screening in pregnancy and continuing during the first year after birth. According to Polish Perinatal Standard of Care, screening for depression is recommended in the first and third trimester of pregnancy, as well as in the postpartum period [58]. Edinburgh Postnatal Depression Scale questionnaire serves as a first-line diagnostic tool. Creating a support network for adolescent mother is one of the most important preventive strategies, as it reduces five times the risk of PPD [59–61].

In a well effective contraceptive method for young women, we must consider the following factors age, education, economic situation, obstetric history and dosage. Patients should also be asked about issues of accessibility to health care, in order to regularly check the prescribed pharmaceutical [1]. Adolescent mothers are at significant risk for repeat pregnancy, with 25% becoming pregnant again within two years of delivery [62].

Recommendations

1. Breastfeeding should be recommended and sufficient support for those in high risk for discontinuation.
2. It is recommended that pregnant adolescent women are monitored for depression in the first and third trimesters of pregnancy, and adolescent mothers are monitored for up to a year after delivery.
3. Effective contraception should be offered.

SUMMARY

The issue of teenage pregnancy has major social implications. Teenage mothers are more likely to drop out of school, which results in worse living conditions for her and her child. Therefore, the priority of adolescent sexual health should be sound sexual education about puberty, contraception, family planning and, above all, sexually transmitted diseases.

Conflict of interests

All authors declare no conflict of interest.

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