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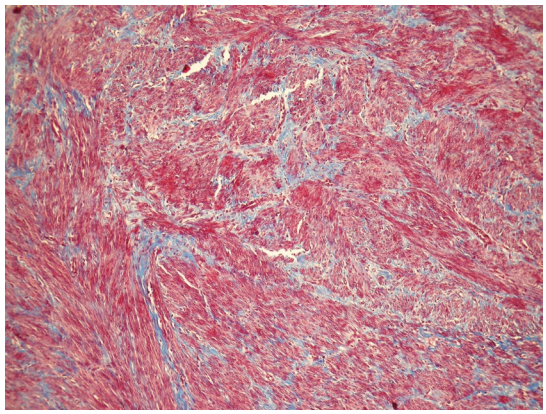

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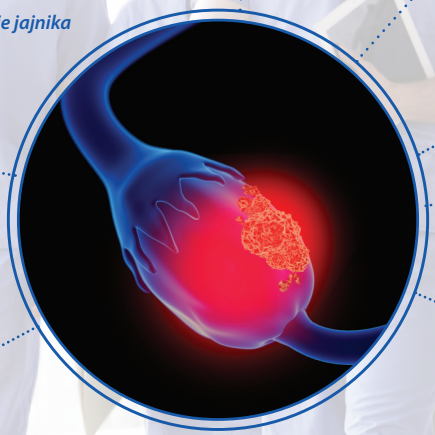

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Factors affecting puberty gingivitis in Polish girls with adolescent idiopathic scoliosis

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ABSTRACT

Objectives: Age at menarche and hormonal disturbances have been linked to the occurrence and severity of adolescent idiopathic scoliosis (AIS). Concomitantly, an increase in the production of sex hormones during puberty may result in steroid hormones-related gingivitis. Thus, the study aimed to assess the prevalence and factors affecting puberty gingivitis, including menarcheal status, in female patients with AIS and control subjects.

Material and methods: The study group was comprised of 59 girls aged 12–16 years with AIS and 50 healthy controls. Dental examination included the assessment of oral hygiene, gingivitis, and dental caries intensity. Data were statistically analyzed with a significance taken as $p < 0.05$.

Results: There wasn't any statistically significant difference in the age at menarche and menarcheal status of both groups. During regression analysis, three predictors significantly affected gingival status of girls: oral hygiene, orthopedic condition, and laterality of the curve. Scoliosis and left convex of the curve significantly increased the index of gingival inflammation.

Conclusions: The results indicate that gingivitis is frequent among female adolescents with AIS, due to poor oral hygiene and higher susceptibility to inflammation. It emphasizes a need for a development of preventive strategy for scoliotic patients, since incipient periodontal problems in children may turn into irreversible advanced periodontal diseases in adults.

Key words: adolescent idiopathic scoliosis; puberty gingivitis; menarche

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INTRODUCTION

Idiopathic scoliosis is a three-dimensional structural deformity of the spinal column that occurs in up to 3% of children globally [1]. Adolescent idiopathic scoliosis (AIS) is the most common form and in 80% of cases occurs in girls. The etiopathogensis of this disorder appears to be multifactorial with a genetic tendency to the deformity, which is triggered by biomechanical, neuromuscular, genetic, hormonal and environmental factors [1, 2].

AIS can be considered a disorder of growth, with a close association between patient's maturity and a risk of spinal curve progression [3]. An informative marker of female physical maturity and remaining growth potential during adolescence is the age of menarche [4]. Research studies revealed that the progression of the spinal deformity was related to growth velocity and thus significantly greater before menarche than after menarche [3]. Age at menarche was also linked to the occurrence of scoliosis. Delayed puberty and late age at menarche were associated with a higher prevalence of AIS and an increased risk of curve progression [3, 5], although the opposite tendency towards an early onset of menarche in scoliotic patients was also reported [6, 7]. The observed differences of menarcheal age of AIS patients as compared to healthy population have been

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attributed to hormonal disturbances involving estrogen, melatonin, and leptin [5, 8]. Several studies have linked high body mass index (BMI) with earlier puberty [4, 9]. Interestingly, low BMI has also been found to be associated with AIS [10, 16], although literature data regarding nutritional status of scoliotic patients are inconclusive [11, 12].

Sex hormones play an important role in the growth, maturation, and maintenance of bone [13–15]. Warren et al. [16] suggested that delayed menarche and prolonged intervals of amenorrhea that reflect prolonged hypoestrogenism may predispose young ballet dancers to scoliosis and stress fractures. In Esposito's study, the blood content of testosterone, 17 β-estradiol, and progesterone in adolescent females with AIS was lower than in their healthy age-mates [17], while Raczkowski observed increased testosterone and normal estrogen levels in girls with AIS [18]. Additionally, estrogen receptors polymorphisms have been suggested to be possible molecular markers for AIS prognosis [17, 19].

As far as oral tissues are concerned, sex hormones have been shown to exert influence on differentiation, proliferation, and growth of fibroblasts, and keratinocytes of periodontium. Estrogens reduce keratinization and effectiveness of epithelial barrier, stimulating proliferation of gingival fibroblasts and synthesis of periodontal connective tissue. Progesterone enhances blood circulation in capillary vessels, increases vascular permeability. and stimulate the production of prostaglandins. An increase in the production of sex hormones during puberty results in steroid hormones-related gingivitis characterized by gingival enlargement, increased inflammation, gingival bleeding, and microbial changes. The highest prevalence of puberty gingivitis falls at the age of 12 years, 10 months in girls and 13 years, 7 months in boys, which is coherent with the onset of puberty [20, 21].

Although it is widely accepted that patients with AIS should be screened for orthodontic problems [22], there are scarce data on their general oral health condition [23].

Thus, the aim of the study was to assess the prevalence and factors affecting puberty gingivitis, including menarcheal status, in female patients with AIS and control subjects.

MATERIAL AND METHODS

The research project was approved by the Bioethics Committee of the Poznan University of Medical Sciences (resolution no. 1307/18) and written informed consent was obtained from the parents and 16-year-old patients.

The study group was comprised of 59 female patients aged 12–16 years, who visited the pediatric orthopedic outpatient office (Poznan, Wielkopolska Province) for the conservative treatment of AIS with a Cheneau brace and had no previous orthodontic or periodontal treatment. Anterior/posterior spine x-rays were used to assess curve direction, and the severity of scoliosis expressed by the Cobb angle, according to the methodology by Harms Study Group [24]. The inclusion criteria were as follows: female gender, age 12–16 years old, a Cobb angle of 20–40°, absence of any diagnosed systemic disease (including obesity and moderate to severe acne according to Investigator's Global Assessment scale) or any medications of continuous use. Only patients with fully erupted permanent dentition (excluding wisdom teeth) were included in the study. Twenty-four patients had thoracic scoliosis, 22 patients had thoracolumbar scoliosis, and the remaining 13 patients had lumbar scoliosis. In 30 patients, scoliosis was convex to the right and in 29 patients to the left.

The control group of 50 orthopedically healthy females aged 12–16 with no history of systemic disease (including obesity and moderate to severe acne) and medications of continuous use, without previous orthodontic or periodontal treatment was recruited in two randomly selected schools in Wielkopolska Province, Poland. Their selection was carried out by an orthopedic surgeon and a dentist based on Adam`s forward bend test, the measurement of trunk rotation with the use of Bunnel scoliometer and the dental examination. Cases with a trunk rotation exceeding 4º were excluded from the study [25].

The patients from the study group were seen in the outpatient orthopedic clinic, while patients from the control group were seen at the school nurse's office. They were examined under the following conditions: the girl seated in a chair, an examiner stood in front of the chair with dental loupes with led light, a mouth mirror, and a WHO probe [26].

The dental caries was evaluated with the use of the number of teeth affected by caries (DT), teeth missing due to caries (MT) and restored due to caries (FT) calculated for all permanent teeth (DMFT). Dental caries diagnosis was based on visual and tactile examination in artificial light, with the use of a mouth mirror and a blunt probe. Active caries was recorded when the lesion showed a visible cavity, undermined enamel, or a softened area. Tooth restored due to caries (FT) was recorded when a tooth had at least one final restoration placed to treat caries. The missing (MT) component of DMFT was recorded when a tooth had been removed due to caries complications.

The gingival condition was assessed with the use of the Gingival Index (GI) by Löe and Silness on the six index teeth: upper right first molar, lower left first molar, upper right lateral incisor, lower left lateral incisor, upper left first premolar, and lower right first premolar). Marginal and interproximal tissues were scored separately. The criteria were: 0 = healthy gingiva; 1 = mild inflammation (slight change in color and edema without bleeding upon probing); 2 = moderate inflammation (edema, redness, and glazing, bleeding upon probing); 3 = severe inflammation (marked edema

and redness, ulceration with a tendency to spontaneous bleeding). The values of the four areas around the index tooth were summed and divided by four to calculate the GI for the tooth. The GI of the patient was obtained by adding the scores of each index tooth and dividing by the number of the teeth examined. The mean GI was used to assign categorical gingival status to the individual as follows: 0, healthy gingiva; 0.1–1.0, mild gingivitis; 1.1–2.0, moderate gingivitis; 2.1–3.0, severe gingivitis [27].

The evaluation of the oral hygiene by Silness-Löe plaque index (PLI) was carried out by recording plaque deposits on the same six index teeth. Each of the four surfaces of the teeth (lingual, buccal, distal, and mesial) was given a score from 0 to 3. The values from the four areas of the tooth were added and divided by four in order to calculate the PLI for the tooth with the following criteria: 0 = no plaque; 1 = a film of plaque adhering to the gingival margin and adjacent area of the tooth surface which can be detected by the probe; 2 = moderate accumulation of soft debris within the gingival pocket, or the tooth and gingival margin which can be seen with the naked eye; 3 = abundance of soft matter within the gingival pocket and/or on the tooth and gingival margin. The PLI of the patient was obtained by adding the scores of each index tooth and dividing by the number of the teeth examined. The subject's plaque status was assigned as follows: poor (2.0–3.0); fair (1.0–1.9); good (0.1–0.9); and excellent (< 0.1) [27].

Age at menarche was defined as age at the first menstrual bleeding, given in full years. Height and weight measures for the study group and for the control group were collected from the orthopedic patient's files and from school nurses' records, respectively. Diagnosis of overweight and obesity was based on body mass index (BMI). As proposed by World Health Organization, for children aged 5–19 years obesity and overweight correspond to BMI-for-age greater than 2 standard deviations and 1 standard deviation above the growth reference median, respectively [28].

Statistical analysis

The data was analyzed statistically by Statistica (version 12) for Windows 10 Home (version 10.0.15063) with significance taken as $p < 0.05$.

Three general linear regression analysis models were built with GI as the dependent variable. As a first step, a correlation analysis between GI and all the independent variables was performed using Spearman's rank correlation coefficient. Additionally, qualitative predictors were assessed with the use of Mann-Whitney's U Test and GI as the grouping variable. The aim of this step was to select the candidate independent variables for the regression analysis. Regression models included all covariates associated with GI with a p value < 0.20. PLI, patient's status (scoliosis vs control) and the presence of menarche were independent variables for the first two models explaining GI in all subjects. PLI, the presence of menarche, and laterality of the curve were independent variables for the last model explaining GI in the study group. Backward elimination procedure allowed for the construction of an optimal regression equation.

First model was based on data concerning all subjects. Since oral hygiene indices of scoliotic patients and controls differed significantly, the second model of regression was prepared after the selection of subjects with good/excellent oral hygiene (PLI < 1.0). The third model explained GI of scoliotic girls with good/excellent oral hygiene. The standardized regression coefficients (β), coefficients of determination (R^2), and statistical significance (p value) were reported.

RESULTS

Table 1 shows characteristics of the study subjects. Among the 109 patients analyzed, there were 7 scoliotic and 13 non-scoliotic premenarcheal girls, 2 scoliotic and 1 non-scoliotic girl reported late menarche (> 14 years of age). The difference between the number of patients with menarche in both groups was not statistically significant ($p = 0.0575$). The mean age at menarche in postmenarcheal girls in the study and the control group was similar (12.4 and 12.3 years, respectively). The number of patients with overweight was statistically significantly lower in the study group as compared to the control group (7 and 16, respectively, $p = 0.0103$), although mean BMI scores in both groups were similar (20.1 and 20.7, respectively).

There was a significant difference between PLI indices of scoliotic and non-scoliotic patients (1.01 vs 0.51, $p = 0.0008$, respectively). The number of patients with excellent/good oral hygiene was significantly lower in the study group, as compared to the control group (33 and 40, respectively, $p = 0.0078$). Poor oral hygiene (PLI ≥ 2) was significantly more common among AIS patients ($p = 0.0304$). Healthy gingiva (GI = 0) was significantly more common in the control group ($p < 0.0001$), while mild gingivitis (GI = 0.1-1.0) and moderate to severe gingivitis (GI = 1.1–2.0) were observed more frequently in the study group ($p = 0.0037$ and $p = 0.0184$, respectively). Scoliotic girls with good/excellent oral hygiene had significantly higher GI as compared to controls ($p = 0.0083$).

Table 2 presents correlation coefficients between GI and other quantitative variables. There was a strong correlation between GI and PLI scores with Spearman's rank correlation coefficient of 0.57 and 0.84 for the control group and the study group, respectively, and $p < 0.0001$ for both. No significant correlation was found between GI and any other variable, such as BMI score, DMF index and age in both groups, as well as Cobb in the study group ($p > 0.05$).

Table 1. Characteristics of the study subjects and statistical differences between the study and the control group

Variable		Control group n = 50	Study group n = 59	p (Mann-Whitney's U test, chi-square test)
Age [years]	Mean ± SD	14.2 ± 1.7	14.0 ± 1.3	0.4829
	Median	14.0	14.0	
	Range	12.0–16.0	12.0–16.0	
Cobb angle [°]	Mean ± SD	N.A.	27.76 ± 6.30	N.A.
	Median	N.A.	26.00	N.A.
	Range	N.A.	20.00–40.00	N.A.
Age at menarche [years] n = 89	Mean ± SD	12.3 ± 0.9	12.4 ± 1.0	0.5160
	Median	12.00	12.00	
	Range	11.00–16.00	10.00–15.00	
Absence of menstruation	n (%)	13 (26%)	7 (12%)	0.0575
Late menarche (> 14 years)	n (%)	1 (2%)	2 (3%)	0.6585
BMI	Mean ± SD	21.0 ± 2.4	20.7 ± 1.9	0.4417
	Median	20.7	20.1	
	Range	16.0–26.3	18.5–20.6	
Overweight	n (%)	16 (32%)	7 (13%)	0.0103*
PLI	Mean ± SD	0.51 ± 0.65	1.01 ± 0.91	0.0008*
	Median	0.30	0.80	
	Range	0.00–2.50	0.00–3.00	
PLI < 1.0 (excellent/good hygiene)	n (%)	40 (80%)	33 (56%)	0.0078*
PLI = 1.0–1.9 (fair hygiene)	n (%)	7 (14%)	14 (24%)	0.1994
PLI = 2.0–3.0 (poor hygiene)	n (%)	3 (6%)	12 (20%)	0.0304*
GI = 0 (healthy gingiva)	n (%)	38 (76%)	20 (34%)	0.0000*
GI = 0.1–1.0 (mild gingivitis)	n (%)	9 (18%)	26 (44%)	0.0037*
GI > 1.0 (moderate/severe gingivitis)	n (%)	3 (6%)	13 (22%)	0.0184*
GI of subjects with good/excellent oral hygiene n = 73	Mean ± SD	0.04 ± 0.12	0.22 ± 0.40	0.0083*
	Median	0.00	0.00	
	Range	0.00–0.50	0.00–2.00	
DMF	Mean ± SD	3.32 ± 3.69	3.13 ± 3.49	0.7971
	Median	2.00	2.00	
	Range	0.00–15.00	0.00–16.00	
Crowding of teeth	n (%)	22 (44%)	37 (63%)	0.0508

BMI — body mass index; DMF — the total number of teeth that are decayed, missing, or filled; GI — gingival index; PLI — Silness-Löe plaque index
*statistically significant difference (p < 0.05)

Table 2. Spearman's rank correlation coefficients between GI and other quantitative variables

Variables	Control group n = 50	Study group n = 59
Age [years]	–0.01	0.11
Cobb Angle	N.A.	0.04
PLI	0.57*	0.84*
DMF	0.25	0.03
BMI	0.12	–0.01

BMI — body mass index; DMF — the total number of teeth that are decayed, missing, or filled; PLI — Silness-Löe plaque index
*p < 0.0001, statistically significant

DMF numbers in the study group and the control group were similar (3.12 and 3.32, respectively). There wasn't any statistically significant difference between the prevalence of teeth crowding in the control group and the study group (37% and 44%, respectively) (p = 0.0505).

Table 3 shows descriptive statistics and Mann-Whitney's U test results for differences between GI of selected subgroups of subjects. There was a significant difference between GI indices of scoliotic and non-scoliotic patients (0.69 vs 0.18, p < 0.0001, respectively).

Postmenarcheal patients did not differ significantly from premenarcheal subjects in terms of GI (0.51 vs 0.23)

Table 3. Descriptive statistics and Mann-Whitney's U test results for differences between GI of selected subgroups of subjects

Grouping variable		GI	p (Mann-Whitney's U test)
Menarche	n	Mean ± SD	
Yes	89	0.51 ± 0.76	p = 0.1595
No	20	0.23 ± 0.40	
Scoliosis	n	Mean ± SD	
Yes	59	0.69 ± 0.82	p < 0.0001*
No	50	0.18 ± 0.44	
Curve direction	n	Mean ± SD	
Right	30	0.62 ± 0.85	p = 0.1705
Left	29	0.77 ± 0.80	
Crowding	n	Mean ± SD	
Yes	59	0.48 ± 0.71	p = 0.5524
No	50	0.43 ± 0.74	
Overweight	n	Mean ± SD	
Yes	23	0.44 ± 0.68	p = 0.7933
No	86	0.46 ± 0.73	

GI — gingival index; *p < 0.05, statistically significant

Table 4. Parameters of general regression models obtained after backward elimination of insignificant variables, predicting the value of GI based on PLI and orthopedic status (Model 1 and 2), PLI and curve direction (Model 3)

	Model 1	Model 2	Model 3
R	0.8545	0.4581	0.6138
R^2	0.7302	0.2099	0.3768
Adjusted R^2	0.7251	0.1873	0.3352
F	143.4736	9.2962	9.0681
p	< 0.0001	0.0003	0.0008

GI — gingival index; PLI — Silness-Löe plaque index

(p = 0.1595). Patients with crowding and these without crowding showed similar GI indices (0.48 vs 0.43, respectively). Patients with left convex did not differ significantly from patients with right convex regarding GI (0.77 and 0.62, p = 0.1705).

Our regression models allowed us to evaluate the joint effect of selected independent variables on the gingival status of our patients. First model was statistically significant (p < 0.0001) with adjusted coefficient of determination $R^2 = 0.7251$. The second and the third one also being statistically significant (p = 0.0003 and p = 0.0008) with adjusted coefficients of determination $R^2 = 0.1873$ and $R^2 = 0.3352$, respectively (Tab. 4). Bearing in mind that R^2 measures the percentage of the variation in the dependent variable that is explained by variation of the independent variables, we could see that first model explains 73% variation in the

Table 5. The regression coefficients (β) and statistical significance of the independent variables in four models of regression analysis

	Model 1, GI in all subjects from the study and the control group	
	β	p
PLI	0.8133	< 0.0001
Scoliosis	0.1151	0.0316
	Model 2, GI in subjects with good/excellent oral hygiene from the study and the control group	
PLI	0.3619	0.0013
Scoliosis	0.2194	0.0466
	Model 3, GI in scoliotic girls with good/excellent oral hygiene	
PLI	0.4495	0.0041
Left convex	0.3765	0.0143

GI — gingival index; PLI — Silness-Löe plaque index

outcome parameter (GI), while the second one and the third one (concerning patients with good/excellent oral hygiene) explain 19% and 33% of the variation of GI, respectively.

Table 5 presents the regression coefficients (β) and statistical significance of the independent variables in three models of regression analysis.

PLI turned out to be the most important predictor of GI (β = 0.8133, p < 0.0001 in the first model, β = 0.3619, p = 0.0013 in the second model, and β = 0.4495, p = 0.0041). Patient's orthopedic status (scoliosis vs. control) was the second statistically significant predictor of GI (β = 0.1151, p = 0.0316 in the first model, β = 0.2194, p = 0.0466 in the second model).

Left convex of the curve was a significant predictor of GI in the third model prepared for scoliotic patients with good/excellent oral hygiene (β = 0.3765, p = 0.0143).

DISCUSSION

The prevalence and severity of gingival inflammation in adolescents are influenced by several factors, including oral hygiene, presence of rough and retentive areas on which plaque accumulates such as dental caries lesions, restorations or crowding of the teeth, and physiological teeth eruption [29]. Additionally, the sudden rise in steroid hormone levels during puberty affects the inflammatory status of the gingiva [29, 30]. Thus, although puberty-associated gingivitis is classified as a plaque-induced gingivitis, the predisposition to gingival inflammation in the presence of relatively small amounts of plaque is a key to distinguishing this condition. The response of gingiva to plaque is increased by circulating sex hormones through mechanisms such as increased fluid secretion, partial immune suppression, and stimulation of fibroblast synthetic activity [21]. Besides, the subgingival microflora (*i.e.*, Prevotella intermedia) can sub-

stitute progesterone and estrogen for vitamin K, which is an important bacterial growth factor [31]. The relationship between elevated levels of circulating sex hormones and prevalence of gingivitis in puberty is strengthened by the observation that puberty gingivitis peaks earlier in girls than in boys [32]. Gingiva condition of our subjects, who developed inflammation of gums even in the presence of small amounts of plaque (PLI < 1.0), match the criteria of steroid-hormone related gingivitis.

It is noteworthy that an increased BMI might be related to higher estrogen levels due to conversion of androgens to estrogens in adipose tissue. There is a growing scientific evidence supporting a link between increased childhood adiposity and early onset of puberty in girls [9]. At the same time, several studies demonstrate an association between obesity and periodontal problems in adults and adolescents [33–35]. Adipose tissue is not only a source of estrogens, but also pro-inflammatory cytokines (TNF-α, IL-1, IL-6), which play a fundamental role in the progression of periodontitis [33, 35]. Our results did not confirm the relation between gingival inflammation and BMI. However, most of our subjects had BMI within norm, and obese girls with extreme of BMI were excluded from the analysis.

Although the etiology of the AIS is not fully understood, it is also considered a sex-conditioned disease, in terms of sex hormones levels and their receptors activity. As suggested by Kulis, the multifactorial pathomechanism of AIS involves significant deficiency of estrogens, and especially estradiol [8]. Thus, our assumption was that the study group would present with a higher average age at menarche as compared to the controls and lower risk of steroid-hormone related gingivitis, due to lower levels of circulating sex hormones. Contrary to our expectations, there wasn't any statistically significant difference in the age of menarche and menarcheal status of both groups. Moreover, in the control group of patients the number of girls without menarche was almost twice as high as in the study group. Similarly, Grivas et al. did not observe later menarche in AIS patients, although they found a significant difference between postmenarcheal and premenarcheal scoliotic girls in relation to the laterality of scoliotic curves: the former showed predominantly right sided primary curves while the latter had mainly left sided primary curves [5]. It would suggest that girls with levoscoliosis differ in terms of auxology from the girls with dextroscoliosis. There is also some evidence in the literature, that left-leaning curves are more likely to be accompanied by other health conditions such as neuromuscular disorders, spina bifida, spinal tumors, chromosomal anomalies and rare syndromes [36]. Interestingly, our results suggest that left convex increased a risk of gingival inflammation, although, contrary to Grivas et al. [5] we did not observe any relation between menarcheal status of the girls or the age of menarche and laterality of the scoliotic curve. The question arises whether gingivitis could be a sign of some undiagnosed subclinical health conditions in scoliotic subjects with left convex.

In regression analysis models prepared for all subjects, two predictors significantly affected the gingival status: oral hygiene (PLI) and orthopedic condition (scoliosis vs. control). The first one is nothing unusual since bacterial plaque is considered the main risk factor of puberty gingivitis [31]. As reminded by Laskowska, the patients with AIS and their families tend to focus all their attention and resources on their primary health problem, often neglecting oral health [23]. The second predictor needs further investigation, because, contrary to our initial hypothesis, scoliosis significantly increased the index of gingival inflammation. The effect of orthopedic status on gingiva remained significant after elimination of subjects with poor/fair oral hygiene. To the best of our knowledge, it is the first study which indicates that scoliotic girls may present with an increased risk of puberty gingivitis as compared to their age-mates.

Trying to find the possible explanation of this phenomenon, we must remember that apart from sex hormones levels, expression of steroids receptors, especially estrogen receptor α (ERα) and estrogen receptor β (ERβ) in human periodontal tissues may modify their inflammatory response to dental plaque. Interestingly, polymorphisms in genes encoding estrogen receptors have been associated both with chronic periodontitis and idiopathic scoliosis, although the results of different studies are ambiguous [37, 38]. The effects of estrogen on gingival tissues are mediated by ERβ, which is the most predominant ER in human healthy and inflamed gingivae, while ERα gene polymorphisms are linked to alveolar bone loss in patients with periodontitis [39, 40]. The rs1256120 polymorphism in the gene for ERβ was reported to be associated with AIS predisposition and curve severity in Chinese [19], as well as with an increased risk of chronic periodontitis in Polish adults [41]. Whether estrogens receptors polymorphisms might be responsible for gingival inflammation in female patients suffering from AIS remains to be investigated.

Our study has several limitations that should be considered in the interpretation of the results. We investigated a relatively small number of female patients with low-grade scoliosis, which may limit the generalizability of the findings. Besides, we didn't assess hormonal profiles of the girls which would add valuable information to our analysis. On the other hand, the group was homogenous and inclusion criteria eliminated possible confounding factors related to changes in periodontium: during primary teeth exfoliation and permanent teeth eruption, after invasive orthopedic surgery, after orthodontic and periodontal treatment, due to obesity or potential excess of androgens (manifested as

moderate to severe acne), as well as due to gender-related hormonal differences.

CONCLUSIONS

The results indicate that gingivitis is frequent among female adolescents with AIS, due to poor oral hygiene and susceptibility to inflammation increased by additional systemic factor. The nature of this factor is currently unknown and needs further elucidation.

It emphasizes a need for collaboration between orthopedists, pediatric gynecologists, and dentists in the management of AIS, as well as development of preventive strategy for scoliotic patients, since incipient periodontal problems in children may turn into irreversible advanced periodontal diseases in adults.

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Intrauterine ectopic pregnancy — ultrasound typing and treatment

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ABSTRACT

Objectives: To analyze the correlation between ultrasound typing and treatment modality of patients with an intrauterine ectopic pregnancy (cervical and cesarean scar).

Material and methods: We retrospectively enrolled 65 patients diagnosed with cesarean scar pregnancy (CSP) or cervical pregnancy (CP) between February 2014 and May 2018. The cases were divided into two types according to the ultrasound presentation with a gestational sac (GS, type I) or a heterogeneous mass (HM, type II). Type I was further divided into type Ia (< 8 weeks) and type Ib (≥ 8 weeks); type II was defined as type IIa (with poor or no vascularity) and type IIb (with rich vascularity). Three treatment methods were applied in each group.

Results: Of included cases, there were 53 CSP and 12 CP. There was no significant difference between Type I and Type II groups in any variable. The beta human chorionic gonadotropin (β-hCG) level and gestational age of type IIb were significantly higher compared to type IIa ($p < 0.05$). There was a positive correlation between ultrasound categories and treatment methods ($rs = 0.723$, $p = 0.000$). Analysis of CSP cases of initial treatment failure indicated success rate of initial dilation and curettage (D&C) was dependent upon ultrasonic types, mean sac diameter, gestational age, hCG level, and number of cesarean sections.

Conclusions: The features of ultrasound imaging might provide an additional reference for the selection of clinical treatment methods.

Key words: cesarean scar pregnancy; cervical pregnancy; ultrasonography typing; treatment

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INTRODUCTION

Cesarean scar pregnancy (CSP) and cervical pregnancy (CP) are relatively rare and unusual types of ectopic implantations in the lower segment of the uterus. They are defined as pregnancies that implant within the uterus, but outside the uterine cavity [1, 2].

Cesarean scar pregnancy occurs when a gestational sac implants at the site of a previous cesarean section. With the recent change in China's One-Child Policy to a Two-Child Policy, the incidence and detection rate of CSP are rising. Cesarean scar pregnancy incidence has increased from 1 per 2,226 to 1 per 1,800 pregnancies [3], along with an increased rate of cesarean sections and increased knowledge and awareness of diagnostic ultrasound.

In the case of CP, the conceptus implants in the endocervical canal below the internal os. Cervical pregnancy occurs in less than 1% of all pregnancies, or 1 in 1,000 to 1 in 18,000 pregnancies [4]. The first case was reported in 1978 [5], and its risk factors have not been clearly elucidated.

The clinical symptoms of CP and CSP are similar [6]. Initially, patients may have no distinctive clinical presentation and often have mild vaginal bleeding, with or without vague abdominal pain. As pregnancy progresses, the risk of unexpected life-threatening hemorrhage or uterine rupture escalates due to the erosion of cervical blood vessels and

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invasion of the myometrium early in the first trimester [7]. On that account, timely diagnosis and individualized management are critical for reducing morbidity and mortality.

However, differentiating between CSP, CP, and threatened miscarriage via diagnostic ultrasound in a low-lying gestation sac is particularly difficult [8–10]. Not all cases of CSP and CP present with typical ultrasonic imaging [8]. Ectopic pregnancies are often accompanied by a hypoechoic mass in the lower uterine segment [11–14]. Hypoechoic masses are atypical and are sometimes misdiagnosed as anterior myometrial fibroids or trophoblastic tumors [7, 8]. At present, previous studies have mainly focused only on the gestational sac, and there is very little data on the hypoechoic mass on ultrasound findings as well as its proper management [11, 15].

In this report, we present an analysis of ultrasound findings and treatment strategy for patients diagnosed with CSP or CP at our institution during a 4-year period and to discuss the relationship between ultrasonography typing and treatment modality.

MATERIAL AND METHODS

This study was approved by our Institutional Review Board of Research Ethics Committee. Informed consent was obtained from all patients before they were enrolled in the study. We retrospectively included cases of CSP and CP at the Affiliated Ethnic Hospital of Guangxi Medical University from May 2014 to November 2018. Transvaginal and transabdominal ultrasound examinations were performed with an iU22 (Philips Electronics NV, Netherlands) or Hitachi EUB 6000 (Tokyo, Japan) ultrasound. The inclusion criterion for the study was the diagnosis of CP or CSP who were initially treated at our hospital. The exclusion criteria comprised the cases of CP or CSP who were initially taken an attempted curettage with failure in local clinics or community hospitals and subsequently transferred to our hospital, as well as abortion, heterotopic pregnancy and cornual pregnancies. The final diagnoses were established by histopathology or operative findings and were confirmed by clinical follow-up. A clinical database was compiled from information in electronic medical records including patient age, gestational age, β-hCG level at the time of primary diagnosis, initial and additional treatment.

Sonographic classification of CSP and CP

In this study, the diagnosis of CSP and CP were based on ultrasound criteria reported on the literature [1, 7–9, 12]. All cases were divided into two types according to the ultrasound presentation with a gestational sac (type I) or a heterogeneous mass (type II). Then, each group was further divided into two subtypes based on gestational age or vascularity within the mass. As previously reported [16–18], the gestational age of 8 weeks is regarded as the dividing line. The

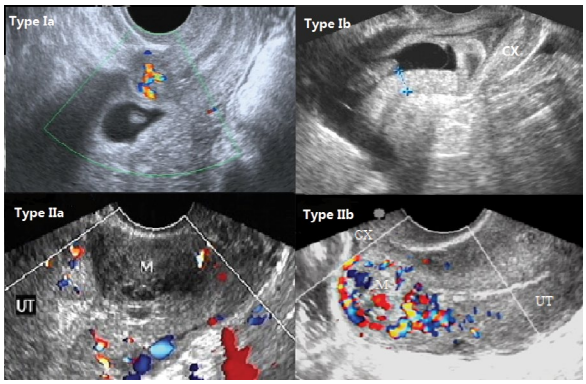

Figure 1. The description of our new ultrasound types for CSP and CP; **Type Ia** was defined as an early gestational sac (< 8 weeks); **Type Ib** represented a GS shape at ≥ 8 weeks gestation; **Type IIa** indicated a heterogeneous mass without vascular pattern; **Type IIb** implied a heterogeneous mass with rich trophoblastic circulation, partly generating an arteriovenous fistula

treatment of gestational sac ≥ 8 weeks is different from the ones less than 8 weeks. Consequently, type Ia could be defined as a GS at > 8 weeks and type Ib represented a GS shape at ≥ 8 weeks gestation. Similarly, type IIa indicated a heterogeneous mass was highly suspected to be an ectopic pregnancy in the lower uterine segment present with poor or no vascularity on color Doppler ultrasound imaging, and type IIb implied the heterogeneous mass in a high index of suspicion had rich vascularity by color Doppler ultrasound (Fig. 1). Two experienced radiologists (F.Y.J. and H.Q.S.) were blinded to study variables and independently categorized cases; inter-rater agreement was 100%.

Treatment modalities for CSP and CP

Although many management options have been proposed, there is no consensus on the preferred mode of treatment for CSP or CP. The treatment strategies remain highly varied [19]. Three therapeutic methods were applied as initial treatment in this study. The first method, D&C, was suitable for hemodynamically stable (minimal blood loss) cases of endogenous CSP and asymptomatic CP at < 8 weeks of gestation. This method was combined with adjuvant therapy such as oral mifepristone or injection of methotrexate (MTX) and often performed under ultrasound guidance. The second method, hysteroscopic resection (HR), was often combined with additional hemostatic measures, for instance, cervical cerclage, balloon tamponade, and local injection of MTX. This treatment method was most regularly used in CP cases. Also, it was adapted for endogenous CSP patients who declined D&C treatment. The third method, surgical resection (SR), was performed by laparoscopy, hysterotomy, or hysterectomy to cut out gestational tissues. Surgical resection was suitable for all the cases of CSP or CP with severe symptoms like hemodynamic instability,

uterine rupture, or placental implantation abnormalities, as well as the cases of exogenous CSP. Surgical resection was occasionally combined with hysteroscopy and local injection of MTX. As previously mentioned, strict treatment guidelines did not exist for clinical management.

Statistical analysis

Statistical analysis was performed using SPSS version 22.0 (Chicago, IL, USA). Quantitative data was presented as mean ± standard deviation or frequency (%). The correlation between ultrasound types and treatment methods were calculated by Spearman correlation. One-way analysis of variance (ANOVA), Student t test and Fisher's exact test were used to compare group characteristics and treatment methods. Statistical significance was defined as $p < 0.05$.

RESULTS

During the 4-year period, a total of 74 patients with CSP and CP were hospitalized at our hospital. Nine patients were (eight patients with CSP, one patient with CP) excluded from this study on account of their initial treatment failed at other hospitals. Ultimately, in the ectopic pregnancies enrolled, there were 53 CSP and 12 CP. The mean patient age of CSP cases was 33.30 ± 4.05 years and the gestational age was 4–10 weeks. The mean age of CP patients was 31.00 ± 5.75 years and the gestational age was 4–9 weeks.

Ultrasound findings

The ultrasound examination revealed that 45 patients presented with a gestational sac (69.2%, 45/65) and 20 patients presented with a heterogeneous mass (30.8%, 20/65). The numbers of patients categorized as type Ia, Ib, IIa, and IIb were 32, 13, 7, and 13, respectively. The detailed distribution is shown in Figure 2 and Figure 3.

No statistical difference was found between type I and type II groups with respect to patient age, β-hCG level, mean sac diameter, and gestational age at diagnosis. When ultrasonography both manifested a heterogeneous mass (type II), the average β-hCG level and gestational age of type IIb patients were significantly higher compared to type IIa cases (Tab. 1).

Comparison of treatment modalities between CSP and CP

In general, the initial treatment methods utilized in this study were D&C (n = 31, 47.7%), hysteroscopic resection

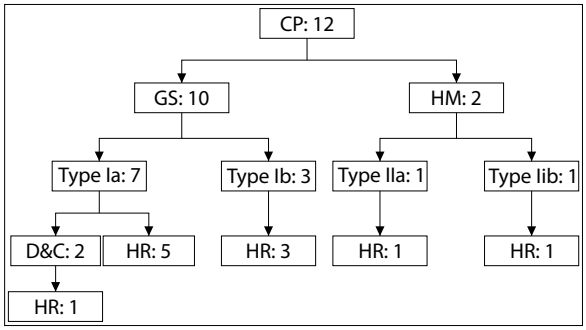

Figure 2. Ultrasound classification and treatment options for cervical pregnancy (CP); GS — gestational sac; HM — heterogeneous mass; D&C — dilation and curettage; HR — hysteroscopic resection; Only one patient performed additional treatment

Table 1. Comparison of preoperative conditions between two ultrasound subtypes

	Type IIa	Type IIb	p
Patient age [y]	30.60 ± 4.775	33.89 ± 3.333	0.154
Gestational weeks	5.50 ± 1.456	8.033 ± 0.893	0.002
Initial hCG level [milliunits/mL]	6841.20 ± 3259.18	31577.4 ± 21902.77	0.030
Gestational sac size [mm]	31.60 ± 9.127	41.16 ± 11.89	0.154

Data are mean ± SD; hCG, — human chorionic gonadotropin;
Type IIa — a heterogeneous mass present with poor or no vascularity;
Type IIb — a heterogeneous mass present with rich vascularity

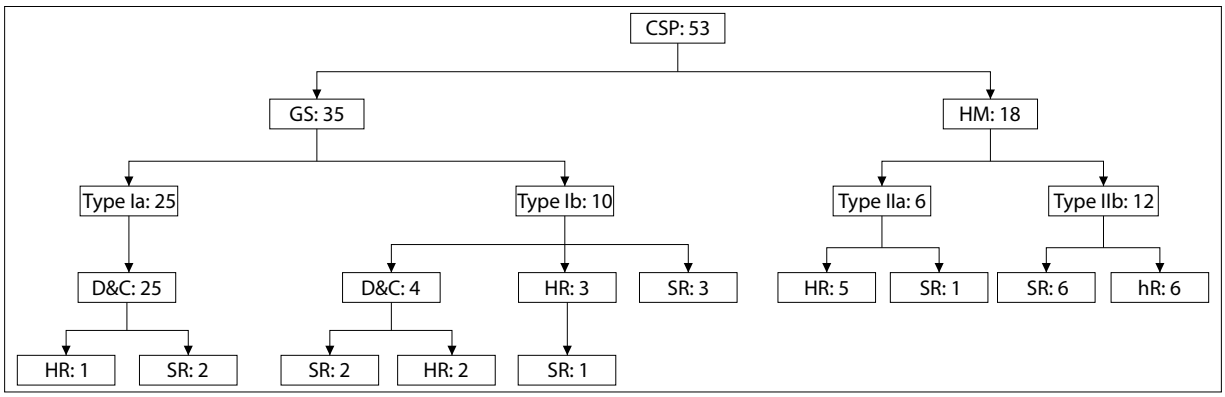

Figure 3. Ultrasound classification and treatment options for cesarean scar pregnancy (CSP); GS — gestational sac; HM — heterogeneous mass; D&C — dilation and curettage; HR — hysteroscopic resection; SR — surgical resection; There were 8 patients performed additional treatment

(n = 24, 36.9%), and surgical resection (n = 10, 15.4%). Cervical pregnancies were mainly treated by hysteroscopic resection (n = 10, 83.3%), D&C (n = 2, 16.7%) (Fig. 2). Cesarean scar pregnancies were primarily treated by D&C (n = 29, 54.7%), hysteroscopic resection (n = 14, 26.4%) and surgical resection (n = 10, 18.9%) (Fig. 3). The success rate of initial treatment was 91.7% for CP patients and 84.9% for CSP patients. The total number of cases after initial treatment failed was 9, including 1 CP and 8 CSP. Among of these failed cases, 8 patients were originally performed by D&C treatment, which were 1 CP and 7 CSP respectively. A closer analysis of CSP failed cases revealed that successful treatment by D&C was dependent upon the ultrasound types, mean sac diameter, gestational age, β-hCG level, and number of cesarean sections (Tab. 2).

Comparing the three different treatment modalities of the ectopic pregnancy located in the lower segment of the uterus, the gestational age, mean sac diameter, and β-hCG level of patients undergoing surgical resection were significantly higher than those of patients undergoing D&C and hysteroscopic resection (Tab. 3). By contrast, the cases of D&C were all patients present with a gestational sac on ultrasonic imaging, along with smaller gestational age, mean sac diameter and lower β-hCG levels than the others. Spearman correlation showed that ultrasound classification was highly correlated with treatment method (rs = 0.723, p = 0.000). The average patient age did not have significant differences among treatment modalities (Tab. 3).

DISCUSSION

It is well known that ultrasonography plays a central role in the diagnosis of ectopic pregnancies [20, 21]. In this study, there was a notable characteristics of ultrasound findings. A proportion of enrolled cases (30.8%) were shown heterogeneous masses upon ultrasound examination, which had less been previously reported in the literature.

Generally, the presence of an echogenic mass may indicate a different status of conception compared to a GS. It may or may not show vascularity at color Doppler US corresponding to its state, which may be related to the level of β-hCG [13]. Our data indicated the amount of vascularity (type IIa: poor vascularity, type IIb: rich vascularity) was correlated with β-hCG level and gestational age (p = 0.030 and p = 0.002, respectively). Type IIb cases presented rich vascularity surrounding a gestational trophoblastic mass. Three of these patients (1 CP, 2 CSP) were found arteriovenous malformations within the mass, which were easily misinterpreted as trophoblastic tumors. These observations implied that this type of mass may be an active trophoblastic tissue [13]. Conversely, our study revealed that ultrasound evidence of an avascular hypoechoic mass indicated that it was be either a degeneration of the conceptus whose serum β-hCG levels had reduced, or an subchorionic hematoma. These were consistent with surgical results.

Moreover, our data indicated a high association between ultrasound findings and treatment modalities in the first

Table 2. Comparison of preoperative conditions between successful and failed treatments of CSP by dilation and curettage

	Success	Failure	p
Patient age [y]	33.0 ± 3.57	32.67 ± 5.28	0.875
Gestational weeks	6.33 ± 0.741	7.767 ± 1.041	0.004
Initial hCG level [milliunits/mL]	15379.17 ± 9920.198	56322.33 ± 26271.802	0.000
Gestational sac size [mm]	13.633 ± 3.671	28.717 ± 9.567	0.000
Number of CS	1.083 ± 0.289	1.667 ± 0.516	0.007
Type Ia	22	3	0.001*
Type Ib	0	4	

CSP — cesarean scar pregnancy; hCG — human chorionic gonadotropin; CS — cesarean sections; Data are mean ± SD, n; * — Fisher's exact test

Table 3. Comparison of preoperative conditions in three different treatment methods

	Dilation and curettage	Hysteroscopic resection	Surgical resection
Patient age [y]	33.33 ± 4.304 (A1)	31.63 ± 5.679 (A2)	34.80 ± 1.924 (A3)
Gestational weeks	6.69 ± 1.149 (B1)	7.01 ± 1.695 (B2)	8.53 ± 0.612 (B3)
Initial hCG level [milliunits/mL]	28418.45 ± 24481.593 (C1)	18073.79 ± 15377.408 (C2)	46589.17 ± 23771.756 (C3)
Gestational sac size [mm]	18.705 ± 9.109 (D1)	29.484 ± 10.175 (D2)	46.883 ± 9.156 (D3)

Data are mean ± SD; Comparisons of patient age have no statistical difference: A1 vs A2, p = 0.319; A1 vs A3, p = 0.564; A2 vs A3, p = 0.204; The gestational weeks indicates a significant difference among the three groups: B1 vs B2, p = 0.469; B1 vs B3, p = 0.006; B2 vs B3, p = 0.022; Initial β-hCG level indicates a significant difference among the three groups: C1 vs C2, p = 0.131; C1 vs C3, p = 0.070; C2 vs C3, p = 0.006; Sac size indicates a significant difference among the three groups: D1 vs D2, p = 0.001; D1 vs D3, p = 0.000; D2 vs D3, p = 0.000

trimester. All of the cases firstly treated by D&C were shown a gestational sac on ultrasound findings while the patients' presence of a heterogeneous mass suggested to better initially treat with a more complex surgical procedure. This was different from the pervious studies [2, 12, 22]. In majority of reported cases, the selection of treatment modality was based on severity of symptoms, preoperative β-hCG levels, and the individual physician's preference and expertise in order to minimize possible effect on future fertile capability of the patient [18]. There was scant data on the correlation between ultrasound findings and treatment methods in the available literature.

At present, there were no consensual protocols for the treatment of CP and CSP. The management strategies of CP and CSP were somewhat different. Most patients with CP were performed by hysteroscopic resection in combination with adjuvant hemostatic techniques including balloon tamponade, cervical cerclage, and local injection of MTX. The primary management of CSP cases was D&C and the second was hysteroscopic resection. Surgical approach was performed in only 10 patients with CSP. No patient with CP required a surgical resection.

In the present study, D&C was the primary treatment. Although it was performed in many cases (n = 31, CSP: 54.7%, CP: 16.7%) due to its shorter operation time, shorter hospital stay, and lower hospital cost compared to other therapeutic approaches [23], the initially unsuccessful treatment was most commonly managed with D&C [24]. Our data showed that 88.9% (8/9) of failed cases were performed by D&C. Particularly among them, 87.5% (7/8) of cases were CSP. This might be a factor that the success rate of initial treatment of CP was superior to CSP (91.7% vs 84.9%). It was well-known that there were 2 types of CSP, with type 1 growing toward the uterine cavity and type 2 progressing toward the bladder and abdominal cavity [23]. D&C treatment was ideal for type 1 CSP (endogenous CSP) to completely remove the abnormally adherent trophoblastic implantation. Unfortunately, type 2 CSP (exogenous CSP) with growth toward the bladder and abdominal cavity cannot be easily treated by D&C [24]. It may be difficult to scrape the gestational tissue products completely because of the invasion of the myometrium and erosion of bladder early in the first trimester, which would result in the high risk of a hemorrhagic event and uterine rupture. Furthermore, we found that the patients with type Ia (< 8 weeks) were more suitable for initial D&C treatment than type Ib (≥ 8 weeks). All of type Ib cases were applied additional treatment after performed D&C. In addition, the current study revealed that larger gestational sac, higher β-hCG level, and more numbers of previous cesarean sections may increase the risk of D&C treatment failure. An earlier gestational age would likely improve D&C success rate.

This study had some limitations. Firstly, one notable limitation was retrospective nature. This influences the way in which medical data was collected and have consequently included biases as unrecognized or unmeasured factors. Secondly, 9 patients with diagnosis of CP or CSP failed by D&C treatment at other hospitals were excluded from our analysis as an attempted curettage often alters the typical ultrasound findings, which may have an effected our results. Thirdly, this study mainly summarizes the ultimate therapeutic outcomes of these patients, without detailed comparison of some relevant clinical data, such as operation time, hospital stay, and hospital cost, and hospitalization cost. Finally, this was a small-sized, single center study.

In summary, the features of ultrasound imaging may provide an additional reference for the selection of clinical treatment methods. In a high degree of suspicion of intrauterine ectopic pregnancy in the lower segment of the uterus, the patients with a gestational sac less than 8 weeks on ultrasound imaging could be initially treated by D&C treatment while women with a heterogeneous mass in a high degree of suspicion may be better treated with a more complex surgical procedure. Future prospective and large-scale studies are warranted to validate this finding.

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Rudimentary horn pregnancy — ten years of experience

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ABSTRACT

Objectives: This study aimed to evaluate data on early diagnosis and therapeutic management of rudimentary horn pregnancy (RHP).

Material and methods: Patients diagnosed with RHP at a tertiary center between for two periods of 2008–2012 and 2013–2018 were analysed retrospectively. We obtained information of patients from hospital electronic archive registration system. Data on demographic characteristics, clinical presentation, gestational age at presentation, presenting symptoms, diagnostic methods, and therapeutic management were noted and analysed by descriptive statistical method. Demographic datas, the complaint of patient's admission to hospital, history of cesarean section, preliminary diagnosis and intraoperative diagnosis were compared between periods of 2008–2012 and 2013–2018.

Results: A total of 14 RHP patients were included. Eight (57.1%) of these patients were diagnosed between 2008–2012 (Group 1), whereas six patients (42.9%) were diagnosed between 2013–2018 (Group 2). Rudimentary horn was non-communicating in 13 patients (92.8%). Communicated form was observed in 1 patient in group 1. RHP was diagnosed on the left side in nine patients (64.2%). Six of these patients were observed in group 1 and 3 were in group 2. The pre-rupture diagnosis was made in 10 (71.4%) patients. Six (100%) of 10 patients were in group 2. In addition, in group 1, four patients (50%) experienced intraoperative RHP rupture. RHP was diagnosed before rupture in 2 (33.3%) patients in group 2.

Conclusions: It is an indication of advanced ultrasonographic technology as well as increased carefulness on the physician side and raised alertness on the patient side that today both RHP and preoperative rupture of RHP are less frequent. Still, further awareness is required among physicians of the necessity of excision of a rudimentary horn that is detected at the time of C-section.

Key words: Mullerian anomalies; obstetrics complications; prenatal care

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INTRODUCTION

Unicornuate uterus with a rudimentary horn is an unusual Mullerian anomaly that brings about a high incidence of obstetrical complications, including ectopic pregnancy in the rudimentary horn. The actual prevalence of Mullerian duct anomalies remains unclear because of the asymptomatic state that prevails among patients; however, it is estimated to be 1:200–1:600 infertile women. Rudimentary horn pregnancy (RHP) appears in approximately 1/76.000 pregnancies and usually manifests itself with first- or second-trimester uterine rupture [1]. The most frequent form of uterine anomalies is uterine septum whereas the least form is unicornuate uterus with a rudimentary horn [2]. American Society for Reproductive Medicine (ASRM) classifies Mullerian anomalies into seven groups and further classifies unicornuate uterus into four sub-groups as follows: A1a) Unicornuate uterus with a communicating rudimentary horn (endometrial cavity present); A1b) Unicornuate uterus with a non-communicating rudimentary horn (endometrial cavity present); A2) Non-cavitated unicornuate uterus with rudimentary horn; B) Isolated unicornuate uterus [3]. Almost in 90% of the cases, the rudimentary horn is cavitated and non-communicating [4]. Of all RHP cases, 45–50% are asymptomatic, and only 8% of them get a clear diagnosis before symptoms become visible [5].

The purpose of this study was to evaluate data on demographic characteristics, presenting symptoms, diagnostic methods and therapeutic management of RHP for the

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periods of 2008–2012 and 2013–2018. There are several case reports and reviews in the literature on rudimentary horns. However, this is the first study in the literature to investigate and detect improvements in early diagnosis and therapeutic management of RHP, which are attributable to advanced ultrasonographic technology and increased alertness among patients.

MATERIAL AND METHODS

Study Design

The hospital records of women who diagnosed with RHP between 2008 and 2018 at the Obstetrics and Gynecology Clinic of Dicle University Hospital, which is a tertiary center public hospital were examined retrospectively. Before the study, approval was obtained from the local ethics committee of Dicle University (Approval no. 125). We searched electronic medical records from January 01, 2008 to January 01, 2018. Hospital record search regarding the keywords as the index "ectopic pregnancy", "rudimentary horn pregnancy", "horn pregnancy", "uterine horn excision ", and " rudimentary horn excision" was conducted.

Ultimately, we identified 14 cases conforming to RHP (ASRM Type 2 A1a, A1b) in this study. All patients or their parents were informed that the patients' clinical data might be used for research and scientific publications and signed an informed consent before surgery. The study period was divided into two 5-year periods. Patients diagnosed Group 1 were assigned to the pre-2013 group, whereas those diagnosed after 2012 were assigned to the Group 2. Data on demographic characteristics (age, gravidity, parity, previous history of pelvic surgery), clinical presentation (abdominal pain, missed abortus, pregnancy follow up, shock symptoms), gestational age at presentation, presenting symptoms, diagnostic method and management were analysed. The complaint of patient's admission to hospital, history of cesarean section, preliminary diagnosis and intraoperative diagnosis were compared between the two groups.

Rudimentary horns without endometrium (Type 2 A2), rudimentary horns excised and identified during surgery and unicornuate uterus without rudimentary horn (Type 2 B) were excluded from the study. Also, ectopic pregnancy without rudimentary horns were excluded. Pregnancies which were determined in rudimentary horns communicant or non-communicant were included in the study. Patients were diagnosed either preoperatively with the guidance of ultrasonography (transabdominal and transvaginal) or at laparotomy. The diagnosis was established using the ultrasonographic criteria suggested by Tsafrir et al. [6]. These criteria included the following:

a) A pseudo pattern of asymmetrical bicornuate uterus,
b) Absent visual continuity tissue surrounding the gestation sac and the uterine cervix,
c) Presence of myometrial tissue surrounding the gestation sac.

We used a single ultrasound device in our clinic for the pre-2013 period. We could not reach the ultrasound in the post-work. After 2012, a new technology ultrasound device was purchased in our clinic. Accessibility to ultrasonography increased.

In patients with intraoperative diagnosis, which side of the rudimentary horn is, whether the rudimentary horns with endometrium were communicated with the uterus were recorded. Patients with RHP were recorded as communicant and non-communicant according to the ASRM classification. Patients with RHP were managed by excision of the rudimentary horn combined with ipsilateral salpingectomy. All of our patients underwent laparotomy by experienced surgeons.

Statistical Analysis

Data were analysed with IBM SPSS Statistics version 21 using descriptive statistics to demographic characteristics of participants. Mean ± standard deviation and frequency were evaluated as descriptive statistics. Chi-square test was used to evaluate categorical data. $p < 0.05$ was considered significant.

RESULTS

We evaluated all of the gynecologic and obstetric patients during the study period and five patients excluded from the study because of having Type 2A2 and Type 2B rudimentary horn. When we excluded these patients, a total of 843 ectopic pregnancies were managed in our clinic during the 10-year-period covered by this study, and RHP accounted for 14 (1.7%) of these 843 pregnancies. Eight hundred twenty-nine cases of ectopic pregnancies other than communicated and non-communicated rudimentary uterine horn pregnancies were excluded from the study. Of the 14 patients, 8 (57.1%) got a diagnosis between 2008 and 2012 (Group 1), whereas six (42.9%) got a diagnosis between 2013 and 2018 (Group 2). Demographic data and clinical findings of each patient are shown in Table 1. The mean gestational week was 17.7 ± 3.0 among all of the patients. Rudimentary horn was noncommunicating in 13 patients (92.8%) and 1 (7.2) patients communicant nature. Communicant rudimentary horn pregnancy was admitted to hospital with rupture in shock (100%). Rudimentary horn was on the left side in 9 patients (64.2%). All of the patients had a singleton pregnancy (Tab. 1).

There were no significant differences between groups 1 and 2 in terms of demographic data. As a preliminary diagnosis, RHP was diagnosed in 2 (33.3%) patients in Group 2. Group 1, 6 (75%) patients were diagnosed with EUP (p: 0.02). No patients presented with shock complaints in

Table 1. Demographic and clinical characteristics of the cases

Cases (no) and diagnosis date	Age [year]	Gravidity	Parity	History of cesarean section	Gestational age [week]	Presentation	Presumptive diagnosis	Intraoperative observation
Before 2013	18	2	1	Caesarean section	16	Abdominal pain	Rupture of Ex-u	Left ruptured comminicating RHP
Before 2013	23	2	1	none	19	Abdominal pain-Shock	Rupture of Ex-u	Left ruptured non-communicating RHP
Before 2013	19	4	0	none	14	Missed abortus	Missed abortus	Left unruptured non-communicating RHP
Before 2013	25	1	0	none	17	Abdominal pain	Rupture of Ex-u	Right ruptured non-communicating RHP
Before 2013	26	1	0	none	8	Pregnancy follow up	Ex-u?	Left unruptured non-communicating RHP
Before 2013	21	2	1	Caesarean section	22	Abdominal pain-Shock	Uterin rupture	Left ruptured non-communicating RHP
Before 2013	30	3	1	none	13	Pregnancy follow up	Ex-u?	Right unruptured non-communicating RHP
Before 2013	22	1	0	none	9	Pregnancy follow up	Ex-u?	Left unruptured non-communicating RHP
After 2012	27	3	2	none	9	Pregnancy follow up	Ex-u?	Right unruptured non-communicating RHP
After 2012	28	5	3	none	16	Pregnancy follow up	RHP?	Left unruptured non-communicating RHP
After 2012	19	1	0	none	9	Pregnancy follow up	RHP?	Left unruptured non-communicating RHP
After 2012	24	3	2	Caesarean section	38	Pregnancy follow up	Placenta percreata	Left unruptured non-communicating RHP
After 2012	32	2	1	None	30	Pregnancy follow up	Placenta percreata + IUMF	Right unruptured non-communicating RHP
After 2012	27	2	1	Caesarean section	25	Pregnancy follow up	Impaired Fetal Doppler	Right unruptured non-communicating RHP

Ex-u — extrauterine pregnancy; RHP — rudimentary horn pregnancy

Group 2. However, there were no significant differences between the groups in terms of complaints in between two groups (p: 0.525). All patients in group 2 were diagnosed during routine pregnancy follow-up. Two patients (33.3%) had a history of cesarean section in Group 2 (Tab. 2). Four patients (50%) were diagnosed with intraoperative rupture Group 1 (p: 0.04). In addition, 4 patients (50%) with a mean gestational week of 18.5 ± 2.6 (ranging from 16 to 22) experienced preoperative RHP rupture. No intraoperative rupture was diagnosed in Group 2 (Fig. 1). All of the patients underwent laparotomy for excision of the rudimentary horn.

DISCUSSION

This study provided a period-wise evaluation of data on RHP, a rare but life-threatening condition. It demonstrated decreased frequency of both RHP and preoperative RHP rupture, increased early diagnosis of RHP with the use of preoperative ultrasonography screening, and an increased number of cases taken into surgery in a stabile state instead of a shock state in the post-2012 period compared to earlier times.

Unicornuate uterus with a non-communicating rudimentary horn stems from incomplete development of one of the Mullerian ducts with failure to fuse completely with the contralateral side [7]. Pregnancy in the rudimentary horn is an absolute emergency since pregnant rudimentary horn can rupture imminently, especially between 10th and 15th weeks of gestation [8]. In the present study, the mean gestational week was 17.7 ± 3.0 among the patients. In addition, 4 patients (50%) with a mean gestational week of 18.5 ± 2.6 (ranging from 16 to 22) experienced preoperative RHP rupture. These patients were from the pre-2013 group, and there was no case of preoperative RHP rupture in the post-2012 group, which is attributable to advancements in ultrasonographic technology as well as an increased number of informed and careful patients who regularly attend their follow-up visits.

In a vast majority (83%) of the patients, the rudimentary horn is non-communicating [9]. In the present study, 13 patients (92.8%) had a non-communicating rudimentary horn.

Despite the increased use of early ultrasonography screening, it is still challenging to establish a pre-rupture diagnosis of RHP. Reports show that preoperative diagnosis is established in only 22% of gynecologic cases and 29% of obstetrical cases, which indicates that a majority of diagnoses can be confirmed only after laparotomy. Routinely performed ultrasonography, especially in the first trimester of pregnancy, assumes great importance for a clear diagnosis as well as for protection of maternal health [10]. In the present study, preliminary diagnoses made in the rest of the patients were mainly as follows: the rupture of ectopic pregnancy, uterine rupture, missed abortion and

Table 2. Comparisons of clinical findings between Group 1 and Group 2

		Group 1, n: 8 [%]	Group 2, n: 6 [%]	p
Age		23.0 ± 3.9	26.1 ± 4.3	0.935
Gravidity		2.0 ± 1.0	2.6 ± 1.3	0.551
Parity		0.5 ± 0.5	1.5 ± 1.0	0.089
Gestational week		14.7 ± 4.7	21.1 ± 11.8	0.010
History of cesarean section		2(25%)	2(33.3%)	0.733
Complaint of patient's admission to hospital	Abdominal pain	2 (25%)	1 (16.7%)	0.525
	Missed Abortus	1 (12.5%)	1 (16.7%)	
	Shock	2 (25%)	0	
	Pregnancy	3 (37.5%)	4 (66.6%)	
Preliminary Diagnosis	RHP	0	2 (33.3%)	0.020
	EUP	6 (75%)	1 (16.7%)	
	Uterin Ruptured	1 (12.5%)	0	
	Missed Abortus	1 (12.5%)	0	
	Placenta Previa	0	2 (33.3%)	
	Determined Doppler	0	1 (16.7%)	
Intraoperative Diagnosis	Rupture	4 (50%)	0	0.040
	Non- rupture	4 (50%)	6 (100%)	

Independent Student T test, χ -test $p < 0.05$; RHP — Rudimentary Horn Pregnancy; EUP — extrauterine pregnancy

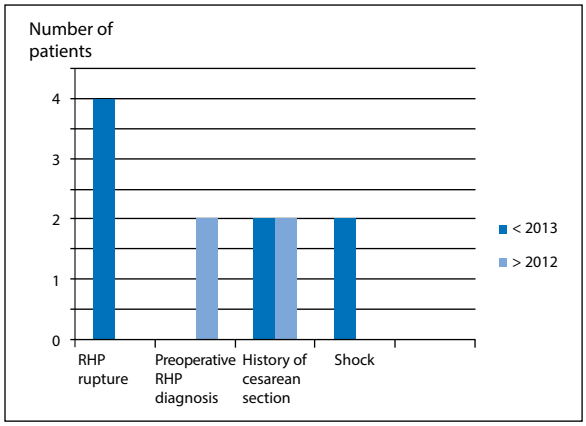

Figure 1. Clinical outcomes pre-2013 and post 2012

placenta previa. Prenatal diagnosis of RHP could be made in 2 patients (14.3%). Those two patients that were taken into surgery with the prenatal diagnosis of RHP were both from the post-2012 group (33.3%), which is also attributable to advancements in ultrasonographic technology.

Rudimentary horn pregnancy usually manifests itself in the form of vaginal bleeding and lower abdominal pain as seen in ectopic pregnancy. In case of rupture, patients might also experience dizziness, feebleness and collapse [11, 12]. In the present study, among of patients; 7 patients (50%) presented with no symptoms to regular pregnancy follow-up visit whereas 3 patients (21.4%) presented with abdominal pain, 2 patients (14.3%) presented in a shock state and 2 patients (14.3 %) presented with vaginal bleeding. Two patients in a shock state presented in Group 1. In Group 2, all of 6 patients were diagnosed by asymptomatically during routine pregnancy follow-up. There were no significant differences between the pre-2013 and post-2012 period.

Another cause of abdominal pain in RHP is endometriosis. Previous studies reported cases of the non-communicating rudimentary horn of unicornuate uterus with concomitant stage III pelvic and extra-pelvic endometriosis. Endometriosis reported in these cases provides support for the retrograde menstruation theory. Retrograde menstruation from ipsilateral tuba results in the development of endometriosis, which is usually severe and may cause dysmenorrhea, chronic pelvic pain, and dyspareunia [13]. None of the patients included in the present study was found to have endometriosis intraoperatively. However, three patients had complaints of abdominal pain, which might be associated with RHP rupture. Therefore, abdominal pain should be considered in pregnant women and further investigations should be performed.

Preoperative rupture, which is one of the most serious complications in rudimentary horn pregnancies, can shock the patient and endanger his life [14]. Two of our patients (14.3%) were admitted to the hospital with shock. These patients were admitted before 2013, and although one patient had a previous cesarean section, horn excision was not performed. In this study, one of our aims is to inform the specialist physicians about the necessity of excising rudimentary horns detected during cesarean section.

Studies in the literature showed that rupture was significantly higher in communicant rudimentary horn pregnancies. Rupture was observed in communicant 60% and non-communicants 17.6% [15]. In our study, one patient with communicating rudimentary horn pregnancy was admitted to our clinic with rupture (100%). Rupture was observed in three of the 13 cases in non-communicant rudimentary horn pregnancy (23.1%). We should be more careful in terms of rupture, especially in communicant rudimentary horn pregnancies.

Given the fact that myometrial tissue is thin in rudimentary horn, cases of pregnant rudimentary horn have a high frequency of uterine rupture. Therefore, its excision is recommended in the case of prophylactic purposes once it is detected intraoperatively during search for some other potential problems [16]. In the present study, 4 patients (28.5%) had a history of cesarean section with no simultaneous excision of the rudimentary horn. Two of these four patients (25%) were from the pre-2013 group whereas the remaining patient was from the post-2012 group, with no significant numeric differences between the two groups. In respect, we came to the understanding that physicians must be fully aware of the necessity of excision of a rudimentary horn detected at the time of cesarean section.

Pregnancy in a non-communicating rudimentary horn is believed to develop from transperitoneal sperm migration. This is a rare condition but may result in life-threating complications such as rupture, intra-abdominal bleeding and hemorrhagic shock [17]. In the present study, 2 patients (14.3%) presented to our clinic in a shock state. Both of these patients belonged to the pre-2013 group. In the post-2012 group, there were no cases of rupture or shock, which points out to the increased alertness of the importance of routine pregnancy follow-up on the patient side as well as increased use of detailed ultrasonography especially in the first trimester on the physician side after 2012. In a case report submitted in 2019, it was misdiagnosed as missed abortion and induction was tried with misoprostol that was unsuccessful. When no response to misoprostol was obtained, the diagnosis was made by ultrasonography repeat before rupture [18]. In the present study, preliminarily diagnosed as RHP were diagnosed in 2 (25%) of 8 RHP patients from 2008 to 2012 and 2 (33.3%) of 6 RHP patients after 2012, with no significant numeric differences between the two groups. In this respect, it might be advanced technology and increased carefulness and precision among physicians that led to a decreased number of cases after 2012.

Following the confirmation of RHP and excision of the horn, termination of pregnancy must be considered and performed, if necessary [15]. In the present study, 2 (33.3%) of 6 patients got a diagnosis of RHP during routine pregnancy follow-up visits after 2012. Once the RHP was confirmed, horn excision was performed in these patients despite the fact that they had no complaints. However, this study had the limitation that small sample size. When we look at the literature, studies about rudimentary horn pregnancies are generally presented as case reports. However, we think the strength of our study is one of the largest series of studies about rudimentary horn pregnancies in the literature. Besides, multi-centre studies are needed for statistical comparisons in this area.

The present study provided a period-wise evaluation of data on RHP, a rare but life-threatening condition. It resulted in the following finding: both RHP and preoperative RHP rupture were less frequent, more cases got an early diagnosis of RHP with the use of preoperative ultrasonography screening, and more cases were taken into surgery in a stabile state instead of a shock state in the period covering 2013–2018, which mainly points out to advanced ultrasonographic technology as well as increased carefulness and precision on the physician side and raised alertness on the patient side after 2012. However, further awareness is required among physicians of the necessity of excision of a rudimentary horn that is detected at the time of C-section.

CONCLUSIONS

Rudimentary horn pregnancy is a rare condition that may be misdiagnosed before surgery, have a higher risk of potential complications. Ultrasound in the first trimester may provide a means of an early diagnosis. However, the gynaecologist can be challenged for rudimentary horn diagnosis despite ultrasound. Still, further awareness is required among physicians of the necessity of excision of a rudimentary horn that is detected at the time of C-section.

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Open fetal surgery for myelomeningocele — is there the learning curve at reduction mother and fetal morbidity?

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ABSTRACT

Objectives: We aimed to show how increased experience of a surgery team in fMMC repair influences maternal and fetal/neonatal outcomes.

Material and methods: We compare perinatal results of fMMC repair in our Fetal Surgery Center (FSC) in cohort groups for the early period (2005–2011 year; previous — PFSC, n = 46) and current period (2012–2015 year; current — CFSC, n = 74) to results of the randomized Management of Myelomeningocele Study (MOMS, 78 patients).

Results: The maternal morbidity due to fMMC repair was low and there was no difference comparing CFSC to PFSC and MOMS. The frequency of iatrogenic preterm labor (iPTL) ≤ 30 weeks of gestation decreased from 34.1% in PFSC to 23.9% in CFSC. Iatrogenic preterm premature rupture of membranes (iPPROM) was a common complication after fMMC repair in all cohorts. The total reduction rate of hindbrain hernation (HH) was similar in CFSC — 90.3% and PFSC — 82.1%.

Conclusions: The increasing experience of our surgery team in fMMC repair majorly decreased the risk of iPTL.

Key words: myelomeningocele; fetal surgery; spina bifida; Chiari malformation

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INTRODUCTION

Myelomeningocele (MMC) is a serious congenital defect of the central nervous system (CNS). It occurs if neurulation is not completed, which physiologically should happen between the 15th and 30th day after conception. MMC prevalence depends on race, sex, and geographical region. It affects about 3–4 per 10 000 live births. In Poland the numbers reach 4–6 cases per 10 000 live births [1].

The risk factors for MMC occurrence are: folic acid deficiency (seasonal or permanent), presence of 677C > T polymorphism in the methylenetetrahydrofolate *reductase gene, hyperthermia,* low economic status, antispasmodic (especially valproic acid and carbamazepinum), antihistamine, and sulfonamides drug intake, increased BMI [2].

The pathogenesis of clinical signs of MMC is unclear. Two theories attempt to explain how abnormal cerebrospinal fluid (CSF) circulation influences this distinct anomaly of CNS. In the 'unified theory' of McLone and Knepper the CSF leakage results in posterior fossa compression and finally in development of hydrocephaly (HC) [3]. Regarding Heffez et al. neural defects in children with MMC are associated with a 'two hit theory' [4]. The disturbance of neurulation in the embryo is the first hit. The second one involves the inflammatory effect of amniotic fluid compounds and mechanical destruction of the protruding spinal cord that hits the uterine wall [4].

Clinical presentation of MMC in approximately 90% of the cases overlaps with the Arnold-Chiari syndrome [5]. The main consequences in later life include lower extremity paresis, urinary and bowel incontinence, sexual dysfunction and impaired psychomotor development [6, 7]. Sense and motor deficiency depend on the MMC location level [6, 7].

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Published data concerning prenatal evolution of Chiari Malformation type II (CM II) show that as the pregnancy progresses, hindbrain hernation (HH) degree increases and the fourth ventricle and the venous sinuses are gradually being compressed [6, 7]. This leads to inappropriate CSF circulation and progression of HC [2]. In more than 80% of children with CM II, the presence of HC in the postnatal period may entail the necessity of ventriculo-peritoneal shunt (VPS) implantation or endoscopic third ventriculostomy (ETV) [8]. In almost 50% of patients, the drainage system must be replaced in their first year of life due to its frequent obstruction and infection [9].

In further development of children with CM II, in the event brain stem dysfunction is present; the mortality reaches 35% during their first year of life [5].

The idea of in utero MMC repair that arises from the two 'hit theory' proposed by Heffez is confirmed in early pathomorphological studies as well as in experimental animal research [10]. The fMMC repair aims to protect the nerve fibres from the neurotoxic reaction caused by amniotic fluid compounds and to restore normal CSF circulation [11]. The fMMC repair procedure counteracts the serious consequences of natural in utero evolution of CM II. The results of a randomized trial of prenatal versus postnatal repair of myelomeningocele publised in 2011 clearly showed that prenatal surgery for myelomeningocele reduced the need for shunting and improved motor outcomes at 30 months [5].

Objectives

We aimed to show how the increasing experience of our surgery team in fMMC repair majorly decreased the risk of iatrogenic preterm labor.

MATERIAL AND METHODS

Perinatal results of fMMC repair in the following cohort groups were compared:

— Previous study in our Fetal Surgery Center (FSC), from January 2005 to December 2011 (PFSC, n = 46), [12] vs
— Current study in our FSC, from January 2012 to December 2015 (CFSC, n = 74), vs
— Management of Myelomeningocele Study (MOMS), from February 2003 through December 2010 (n = 78), [5].

Patients qualification in Polish FSC, Bytom

The procedure of fMMC repair has been performed in the FSC of the Clinical Department of Obstetrics, Gynecology, and Oncological Gynecology in Bytom, Poland since 2005 [13]. Seventy-four (74) of 183 patients with CM II referred to our FSC were qualified for fMMC repair, based on the protocol of the randomized MOMS criteria [5].

Major inclusion criteria were: maternal age ≥ 18 years, single pregnancy, gestational age between 19 weeks, 0 days and 25 weeks, 6 days, location of fMMC at the S1 level or above with presence of Chiari II malformation in prenatal US and MRI, lateral ventricular size of fMMC less than 17 mm, maintain lower extremities motor function, no other major anomalies, normal karyotype, normal feto-placental function and consent of the parents [5].

Major exclusion criteria were kyphosis > 30°, oligohydramnion, placenta previa, high risk of preterm labor (short cervix ≤ 20 mm, previous preterm labours), previous hysterotomies, contraindication for epidural analgesia, maternal diseases like diabetes mellitus type 1, hypertension, obesity (BMI > 35), thrombophilia, and infectious diseases (TORCH, abnormal bacterial flora in the cervical canal, respiratory tract infection, urinary tract infection, chronical infectious diseases of urinary tract) [13–15].

Like in other medical centers for maternal and fetal surgery, the decision of fMMC repair taken by the prospective parents was autonomous. The information about the fMMC repair procedure, the influence of CM II on child's further development and quality of life was presented by the perinatal team.

The primary end points were maternal morbidity, preterm labor (iPTL) ≤ 30 weeks of gestation, iatrogenic preterm premature rupture of membranes (iPPROM), reduction of hindbrain herniation, severe infections < 7 days of life. In order to objectively evaluate the posterior fossa, abnormality, based on MRI, grading was assigned as follows: grade 0, normal; grade 1, visible fourth ventricle and cisterna magna without cerebellar displacement below the foramen magnum, tentorium could be vertically oriented, and tectal breaking could be present; grade 2, visible cisterna magna without displacement of the cerebellum below the tentorium, no visible fourth ventricle; and grade 3, displacement of cerebellum below the foramen magnum and obliteration of all posterior fossa CSF spaces.

Grading was assigned by the attending neuroradiologist (L.T.B.). It was not possible to do this in a blinded manner, since the approximate age of the fetus and the preoperative or postoperative status was apparent from the MRI studies.

The evaluation of postoperative evolution of cerebral changes of HH and ventriculomegaly (VM) was based on MRI, performed in 30^{+4}–33^{+0} gestational weeks in the group PFSC — 28/44 and CFSC — 31/71 (Fig. 1).

In addition, serial US examinations every 7–10 days after fMMC repair were performed to verify CM II evolution, with measurement of the anterior diameter (AD) of VM, HH degree, and fetal well-being.

Diagnosed HH degree was defined based on the Sutton et al. [16] scale.

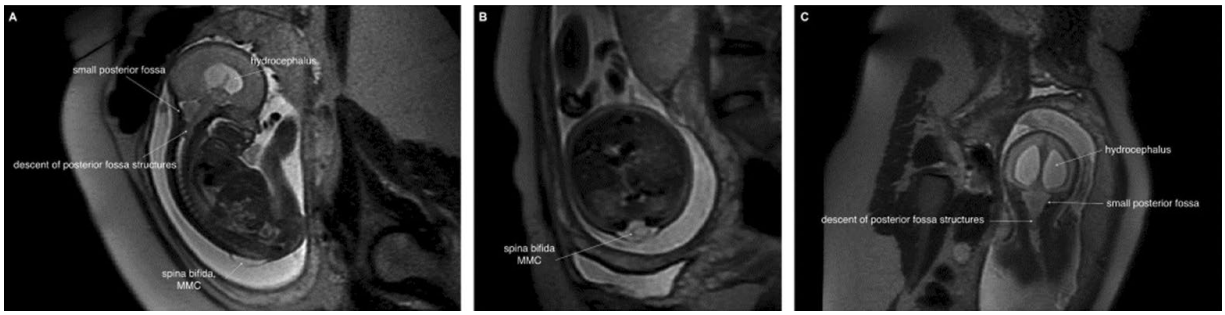

Figure 1. A. Fetal MRI, SSFSET2 sequence, sagittal plane: Chiari II — descent of the posterior fossa structures into cervical vertebral canal, small posterior fossa, supratentorial hydrocephalus, spin bifida cum myelomeningocele (arrows); **B.** Fetal MRI, SSFSET2 sequence, axial plane: Chiari II — spina bifida, myelomeningocele (arrows); **C.** Fetal MRI, SSFSET2 sequence, coronal plane: Chiari II — descent of the posterior fossa structures into cervical vertebral canal, small posterior fossa, supratentorial hydrocephalus (arrows)

VM was diagnosed when the atria of the lateral cerebral ventricles measure > 10 mm in diameter on an axial view of the fetal head, obtained at the level of the thalami [17]. The severity of VM was classified as: **mild** (lateral ventricular diameter between **10–12** mm), **moderate** (lateral ventricular diameter between **12.1–15** mm), and **severe** (fetal VM > 15 mm), sometimes also classified as fetal hydrocephaly (lateral ventricular diameter **> 95 pc**) [18].

Statistical analysis

The analysis was performed using MedCalc 14.12.0 (MedCalc Software bvba, Ostend, Belgium). Values were presented as percentages and mean values ± SD and ranges. The comparison of qualitative variables with data in published cohorts was done with χ^2 or χ^2 for trend tests. The difference was considered statistically significant when, the 'p' value was below 0.05.

fMMC repair — surgical protocol

Twenty-four hours before the fMMC repair procedure, Betamethasone 24 mg (as RDS prevention) Ceftazidime 2.0 g *i.v* (antibiotic prophylaxis), Indomethacin 150 mg/24 h, and Nifedipine 40 mg/24 h (tocolytic treatment) were administered.

The surgery was conducted under simultaneous general anesthesia and subdural analgesia. The abdomen was opened with the Pfannenstiel incision or in the scar after previous laparotomy. The incision of the uterine muscle was made in the mid sagittal line above the MMC, ≥ 5 cm from the placenta margin. The amniotic fluid was then extracted and the incision was enlarged using Auto Suture Poly CS™ stapler (Covidien Mansfield, MA, US). The fMMC was manually placed into the hysterotomy site. For fetal anesthesia, opioids (fentanyl 10–20 mcg/kg) and muscle a relaxant drug (Pancuronium 0.1–0.3 mg/kg) were administered.

There are essentially no differences between prenatal and postnatal procedures performed by the pediatric surgeons during MMC repair. Waterproof closing of the dura is usually very difficult due to the tissue fragility. In our opinion the most important part of MMC closing is placode and cauda equine release. The next step is mobilization of the fascio-muscular layers from the both sides (erector spinalis muscles) to the median line applying single sutures. Suturing of the skin caused minor difficulties but, when it is necessary, relaxing incisions, or slight cutaneous flap movements, were performed. The fetal part of the surgery on average takes 30–40 min but up to 60 min in very difficult cases.

The amniotic fluid was supplemented with warm crystalloid fluids. The closure of the uterine muscle with two layers of monofilament continuous suture was preceded by intra-amniotic infusion of 1.0 g Ceftazidime. Figure 2 presents the fMMC repair steps.

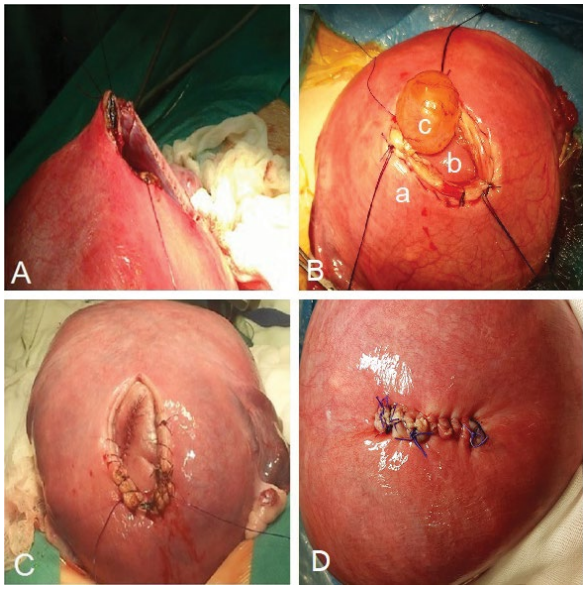

Figure 2. The stages of fMMC repair (A — hysterotomy, B — stabilization of fetus with exposed MMC, a —uterus, b — fetus back, c — MMC sack, C — closed MMC, D — closed uterus); MMC — myelomeningocele

Magnesium sulfate 2 g *i.v* was administered when opening and closing the uterine muscle. The hemodynamic condition of the fetus was monitored by Doppler ultrasound by analyzing FHR and PI indices of the umbilical artery.

After the operation, all women were monitored for signs of intrauterine infection such as: increased basal body temperature, maternal heart rate, fetal heart rate, C-reactive protein, and procalcitonin. Antibiotic prophylaxis was continued until postoperative day 7 with Ceftazidime 2.0 g/24 h *i.v*. Analgesic treatment included Marcaine through an epidural catheter < 7 days. Tocolytic treatment included Nifedipine 20 mg/24 h p.o. and Fenoterol Hydrobromide 20 mg/24 h p.o. The information concerning postoperative management was discussed in detail in our previous study and MOMS study [5, 12].

In the fMMC repair group an elective cesarean section was performed at 37 weeks of gestation, or earlier if the complications threatened maternal or fetal life. The condition of the uterine scar after hysterotomy was assessed during the cesarean section.

RESULTS

Data of the study population is presented in Table 1. Our study group consisted of 74 patients, but because of three fetal death [1 intraoperation fetal death (IUFD) and 2 within 24 hours after fMMC repair (NND)] in the final analysis we took into consideration 71 neonates, except for mortality rate.

Range of gestational age at the time of fetal surgery for MMC was defined as 19^{+0}–25^{+6}, according to inclusion criteria. In our study fMMC repair performed between 22^{+3}–25^{+6} weeks of gestation. Nearly half of the patients were operated in 23^{+6} weeks of gestation. Five (6.8%) patients with low fMMC location < S_1 were exposed to early MRI between 19^{+2}–21^{+3} weeks of gestation and CM II was diagnosed only in a single case. Among the remaining 4 patients, MRI was repeated in 25 weeks and late HH and VM which qualified for fMMC repair were diagnosed.

Table 1. The results of qualification for fMMC repair among CM II patients treated in FSC Bytom (n = 74)

Gestational age at IUMR based on last menstrual period and ultrasound in 11–14 weeks of gestation; mean (range)	$23^{+6} \pm (22^{+3}$–$25^{+6})$
Normal feto-placental function; n (%)	74 (100)
Lower extremities motor function/feet deformity; n (%)	53 (71.6)
Increased lateral ventricles width anterior diameter; n (%)	61 (82.4)
fMMC level; n (%)	
≥ Th_{12}	0
L_1–S_1	66 (89.2)
< S_1	5 (6.8)
Degree of hindbrain herniation; n (%)	
0 — absent	0
I — low	7 (9.5)
II — moderate	64 (86.5)
III — severe	0

The maternal morbidity after fMMC repair encompasses typical complications for surgical operations during pregnancy. Pre-edematous state of pulmonary edema as well as peritonitis was observed only in 1 patient in both current and previous study (accordingly 1.4% vs 2.2%). The need of blood transfusion occured in 4 (5.4%) patients in CFSC group and in 3 (6.5%) patients in PFSC group. Comparing CFSC to MOMS and PFSC, the frequency of complications which could cause serious consequences (pre-edematous state without secondary intubation and ICU treatment, blood loss and peritonitis) were low and comparable (Tab. 2).

The analysis of perinatal results after fMMC repair in CFSC group showed following complications: iatrogenic oligohydramnion 12/71 (16.9%), chorioamniotic membrane separation (CMS) 11/71 (15.5%) and was insignificant compared to MOMS and our previous study PFSC, respectively: 16 (21), 20 (26) vs 4 (8.7%), 8 (17.3%). iPPROM was the most frequent iatrogenic complication after fMMC repair and its frequency in CFSC was 31/71 (43.6%) of similarly high frequency of iPPROM noted in MOMS 36/78 (46.2%) and in our study from the previous period PFSC 24/46 (52.2%). Despite the positive trend, the comparison of the results of all cohorts does not achieve statistical significance. iPTL ≤ 30 weeks of gestation which is a serious consequence of iPPROM occurred in 17/71 (23.9%) patients in our centre where as in 10/78 (12.8%) in Adzick's study. Comparing this value with PFSC 15/44 (34.1%) is not significant. Site evaluation during cesarean section points to a completely healed, hysterotomy site, in the CFSC cohort 63/71 (88.7%) vs MOMS 49/76 (64.5%), $p < 0.001$. In two patients in CFSC and PFSC (accordingly 4,1 % and 6,5%) during cesarean section we observed complete dehiscence of hysterotomy site which needed surgical repair. It was the only complication which we reported during cesarean section in our patients.

Our data indicates that 17/71 (23.9%) of children were born in ≥ 37 weeks of gestation and it was similar in MOMS study. The result of labour ≥ 37 weeks improved compared to our last observation (PFSC) where this value was lower 8/44 (18.2%) vs MOMS 16/78 (20.5%), $p < 0.05$.

Fetal results

HH improvement despite greater number of phenomenon, did not achieve statistical significance in comparing CFSC vs PFSC, respectively for degree: partial ≥ 1° 15/31 (48.4%) vs 13/28 (46.4%), complete 13/31 (41.9%) vs 10/28 (35.7%) and any 28/31 (90.3%) vs 23/28 (82.1%).

Table 2. A comparison of maternal morbidity after fMMC repair (statistical significance vs MOMS)

	CFSC n = 74	MOMS Adzick 2011[5] n = 78	PFSC Zamłyński 2014 [12] n = 46
Maternal results n (%)			
Pre-edematous state of pulmonary edema without secondary intubation and intensive care unit treatment	1 (1.4)	5 (6.4)	1 (2.2)
Preeclampsia/Hypertension	3 (4.1)	3 (3.8)	2 (4.3)
Gestational diabetes mellitus	2 (2.7)	4 (5.1)	1 (2.2)
Blood transfusion	4 (5.4)	7 (9.0)	3 (6.5)
Peritonitis	1 (1.4)	2 (2.6)	1 (2.2)
Amniotic membranes and amniotic fluid n (%)			
Chorioamniotic membrane separation (CMS)	11/71 (15.5)	20 (25.6)	8 (17.3)
iatrogenic oligohydramnios AFI < 5cm, > 21 days	12/71 (16.9)	16 (20.5)	4 (8.7)
iPPROM syndrome	31/71 (43.6)	36 (46.2)	24 (52.2)
Chorioamnionitis	3/71 (4.2)	2 (2.6)	2 (4.3)
Preterm placental abruption	2/71 (2.8)	5 (6.4)	2 (4.3)
Hysterotomy site (evaluation during cesarean section) n (%)			
Completely healed	63/71 (88.7)$^{###}$	49/76 (64.5)	34 (73.9)
Partial dehiscence	4/71 (5.6)	7/76 (9.2)	3 (6.5)
Complete dehiscence	2/71 (2.8)	1/76 (1.3)	2 (4.3)
Fetal extrusion into peritoneal cavity (complete uterine rupture with intact membranes and placenta)	1/71 (1.4)	0	1 (2.2)

$^{###}p < 0.001$

Only in two fetuses with CM II, in both cohorts, was observed HH progression ≥ 1° and in 6 cases HH degree after fMMC repair did not change.

We compared the width of the lateral ventricle before and after IUMR measuring AD in degree: **mild (10–12** mm) or **moderate (12.1–15** mm). It was observed significant inhibition of VM development in CFSC vs PFSC respectively: 25/31 (80.6%) vs 15/28 (53.6%), $p < 0.05$. The comparison of width of the lateral ventricle in MRI during qualification and after fMMC repair (in 30^{+4}–33^{+0} gestational week) point to VM inhibition in the groups CFSC vs PSC in the following way: 25/31 (80.6%) vs 15/28 (53.6%), $p < 0.05$. We did not achieved improvement relative to frequency of progressive VM/HC > 95% comparing our cohorts. In 5 (17.8%) fetuses with MMC localization < S_1, VM was not still observed after fMMC repair.

Neonatal results

In infants born prematurely, advanced neonatal procedures as nCPAP ventilation support 24/71 (33.8%) and mechanical ventilation 19/71 (26.7%) were applied. Comparing CFSC vs MOMS, ventilation support for respiratory distress syndrome was required 43/71 (60.6%) vs 16/77 (21%) infants, $p < 0.001$. Concerning the neonatal outcome the cumulative mortality stands at 4/74 (5.4%) in our centre.

Unexpected, intracranial haemorrhage (IH) I^0–II^0 was observed in a statistically significant frequently in CFSC vs PFSC following: 34/71 (47.9%) vs 4/44 (9.1%), $p < 0.001$. However, IVH I^0 without clinical syndromes were observed using ultrasound examination in near half of cases in the CFSC group 34/71 (47.9%). A high percentage was observed of neonatal infections diagnosed < 7 day of life: CFSC 25/71 (35.2%) and PFSC 12/24 (50%), which could be attributed to the need for invasive neonatal procedures. Despite the improvement of these results, the difference is statistically insignificant. The frequency of a serious complication, sepsis in our cohorts, CFSC 5/71 (7.0%) and PFSC 2/24 (8.3%) was low and is comparable with those reported in MOMS 4/77 (5.2%).

The final effect of changes in the CNS structures in the form of decreasing HH was observed in our study in 28/31 (90.3%) of fetuses with CM II whereas non-progressive VM diagnosed in ultrasonography examination before cesarean section concerned 25/31 (80.6%) of fetuses with fMMC.

DISCUSSION

Up until 1997, only postnatal treatment served as a therapeutic option that eased the consequences of in uterine damage of the nervous system in fetuses with CM II. The first fMMC repair in the US (CHOP and VUMC) has brought surgical procedures to Europe and beyond. The results of these

studies were reported as short term observational studies of cohort groups. The comparison of qualification criteria and surgical protocols remain unanimous [5, 12, 14, 19]. Whereas long-term observation of childhood development after fMMC repair was assessed only in the CHOP study [20, 21].

The maternal morbidity after fMMC repair is typical surgical complications such as blood loss and peritonitis (Tab. 2). Gollombeck et al. [22] in 2006, noted that the most common complications after maternal-fetal surgery was a higher incidence of lung edema and respiratory insufficiency (27.6%), re-intubation (2.3%), and intensive care treatment. The MOMS study and our own experiences, as well as the recent VUMC study, have shown that maternal safety increased significantly [5, 12, 23], in contrast with previous data from Moldenhauer et al. [24] In post-MOMS analysis at the Children's Hospital of Philadelphia, showed lower complication rates than in the actual trial, including pulmonary oedema 2/100 (2%). Furthermore, in our cohorts, the results of maternal morbidity show lower health risk during the intraoperative period. Al-Refai et al. [25], analyzing maternal morbidity associated with various perinatal invasive procedures, concluded that adverse maternal effects are probably rare, when done in an expert center.

Moreover, using atosiban instead of magnesium sulfate in the context of open fetal surgery may significantly improve the maternal safety [26].

Perinatal iatrogenic complications of the uterine-placental-fetal unit are the main limitation of fMMC rehabilitation and they result from the invasive surgical procedure and pharmacological treatment [15]. Pulmonary oedema is the main iatrogenic complications for mother and it results from the use of high doses of magnesium sulfate. Whereas the use of COX-1 and COX-2 inhibitors can lead to oligohydramnions which results from the inhibition of fetal urine production.

In the current studies, iatrogenic iPPROM, iatrogenic oligohydramnion, and CMS were reported in 31/71 (43.6%), 12/71 (16.9%) and 11/71 (15.5%) cases, respectively. Unfortunately, these values remain comparable. CFSC vs PFSC, and insignificant compared to the MOMS results [5]. In the Soni et al. [27] study, frequency of CMS was 21/88 (23.9%) and iPPROM occurred in 27/88 (30.7%) of cases after fMMC repair. In this study, local or global CMS, which was diagnosed by ultrasound, was significantly associated with iPPROM (59.1 vs 21.2%, $p = 0.008$) and earlier gestational age at delivery (32.1 ± 4.2 vs 34.4 ± 3.5 weeks, $p = 0.01$).

In our study, iatrogenic preterm labor, ≤ 30 weeks of gestation, occurred in 17/71 (24) cases as a consequence of iPPROM. 17 (24%) children were born in ≥ 37 weeks of gestation. Many of the unfavorable perinatal outcomes were demonstrated as early experiences of our FSC. In more recent observations the perinatal outcomes have improved as the result of learning curve [15]. It is worth to emphasis that the learning curve has certainly the influence in the reduction of perinatal complication but after achieving some ability, the rate of complications remain on the stable level.

The main results concerning neonates are caused by complications after fMMC repair. In our current study, one fetal death and one miscarriage in 22^{+3} occurred during fMMC repair before uterine muscle closure. Three pregnancies lost in 24^{+2}, 25^{+2} and 24^{+4} weeks occurred up to 48 hours after IUMR due to severe CMS, iPPROM, and placental abruption. In comparison to other researchers, the cumulative postnatal mortality is of acceptable value and much like the MOMS study results and other reports [5, 12, 15]. The total frequency of prematurity ≤ 30 weeks in comparison of our cohorts was the following: CFSC 17/71 (23.9%) vs PFSC 15/44 (34.1%) and it is notably, but not significantly lower. Prematurity contributed to an increase necessity to apply ventilation support for RDS in the following: CFSC 43/71 (60.6%) vs MOMS 16/77 (20.8%) $p < 0.001$ [5].

It is necessary to emphasize that not only prematurity caused by fMMC repair, but also CM II neurological dysfunctions are the independent risk factors for increased intensive neonatal care procedures, even among newborns born at term. Da Silva et al. reported that in 97 newborns delivered ≥ 37 weeks of gestation with untreated CM II, the neurological dysfunction were the reason for nCPAP ventilation in 29/97 (29.9%) (OR 4.55, 95%, CI 1.82–11.41) and newborn intubation in 13/97 (13.4%) (OR 3.94%, CI 1.14–13.59) [28]. At one minute after birth 24 newborns were scored < 7 Apgar points (OR 95%, CI 0.99–7.57) [28].

The main aim of fMMC repair is the neuroprotection of exposed spinal cord nerve fibres from toxic effect of amniotic fluid and secondarily to restrict the evolution of CM II cerebral changes in the form of VM and HH [29].

The evaluation of the brain in magnetic resonance imaging in 30^{+4}–33^{+0} gestational week points to a high percentage of improvement in hindbrain herniation in our cohorts: CFSC 28/31 (90.3%) and PFSC 23/28 (82.1%). Additionally, we obtained significant improvement into fetal conditions in the form of non-progressive VM: CFSC 25/31 (80.6%) vs 15/28 (53.6%), $p < 0.05$.

The evolution of changes in the CNS observed after fMMC repair can prove to restore a normal CSF circulation. Danzer et al. [30] demonstrated that as the pregnancy progressed the lateral ventricular width did not increase in 22 fetuses after fMMC repair, contrary to the fetuses with CM II treated postnatally. In our previous study we observed stationary VM with ventricular width not exceeding the diameter measured at the time of surgical qualification in 53% cases after fMMC repair and in 13% cases without treatment (CI 4.01, 1.05–15.3, $p = 0.04$) [12]. Decreased VM incidence in children that underwent fMMC repair is associated with the

Table 3. A comparison of fetal condition and evolution of CM II and neonatal results after fMMC repair

	CFSC n = 74	MOMS Adzick 2011[5] n = 78	PFSC Zamłyński 2014 [12] n = 46
Mortality, n (%)			
Intrauterine foetal death (IUFD)	1/74 (1.4)	0	0
Neonatal death (NND) < 7 days	3/74 (4.1)	2 (2.6)	2 (4.3)
Cumulative	4/74 (5.4)	2 (2.6)	2 (4.3)
Gestational age at delivery, n (%)			
≤ 30 weeks	17/71 (23.9)	10 (12.8)	15/44 (34.1)
31–33 weeks	16/71 (22.5)	26 (33.3)	11/44 (25)
34–36 weeks	24/71 (33.8)	26 (33.3)	10/44 (22.7)
≥ 37 weeks	17/71 (23.9)	16 (20.5)	8/44 (18.2)
		p < 0.05 vs PFSC for trend	
Evaluation of the brain in magnetic resonance imaging (30^{+4}–33^{+0} gestational week)			
Hindbrain herniation improvement, n (%)			
Partial ≥ 1°	15/31 (48.4)	n.a.	13/28 (46.4)
Complete	13/31 (41.9)		10/28 (35.7)
Any [X]	28/31 (90.3)		23/28 (82.1)
Hindbrain herniation progression, n (%)			
Moderate ≥ 1°	1/31 (3.2)	n.a.	1/28 (3.6)
Severe ≥ 2°[X]	0		0
Lateral ventricles width, n (%)			
Non-progressive VM*	25/31 (80.6)^	n.a.	15/28 (53.6)
Progressive VM/HC > 95%**	6/31 (19.3)		8/28 (28.6)
Neonatal weight, n (%)			
< 3 percentile	3/71 (4.2)	0	1/44 (4.2)
< 10 percentile	12/71 (17)[#]	3 (3.8)	5/44 (20.8)
Fifth minute Apgar score, n (%)			
0–3	6/71 (8.4)	n.a.	3/44 (16.7)
4–7	28/71 (39.4)		8/44 (29.2)
8–10	37/71 (52.1)		13/28 (54.2)
Ventilation support for respiratory distress syndrome (RDS), n (%)			
nCPAP	24/71 (33.8)	n.a.	11/44 (25.0)
Mechanical ventilation	19/71 (26.7)		12/44 (27.3)
Any support	43/71 (60.6)[###]	16/77 (20.8)	23/44 (52.7)
Intracranial haemorrhage (IH), n (%)			
I–II grade	34/71 (47.9)^^^	n.a.	4/44 (9.1)
III–IV grade	2/71 (2.8)		1/44 (2.3)
Any IH	36/71 (50.7)^^^		5/44 (11.4)
Infections < 7 days, n (%)			
Sepsis***	5/71 (7.0)	4/77 (5.2)	2/24 (8.3)
Other neonatal infection	20/71 (28.1)	n.a.	10/24 (41.7)
Any infection	25/71 (35.2)		12/24 (50.0)
MMC wound dehiscence, n (%)	14/71 (19.7)	10/77 (13.0)	n.a.
Foot deformity, n (%)	32/71 (45.1)	39/77 (50.6)	11/44 (45.8)

^ p < 0.05; ^^^ p < 0.001 vs PFSC; [#]p < 0.05; [###]p < 0.001 vs MOMS; [X] — HH improvement was defined as: partial- reduction of HH degree about 1° (from 2° to 1° HH); complete — redaction of HH degree from 2° to 0° or 1° to 0°; [*] Non-progressive VM — was defined as the some VM class before and after fMMc repair (**mild** fetal ventriculomegaly: lateral ventricular AD between **10–12** mm or **moderate** fetal VM: AD **12.1–15** mm); [**] Progressive VM/HC > 95% was defined as increased VM class to **severe** fetal ventriculomegaly also sometimes classified as fetal HC (head circumference > 95% in given gestational age) lateral ventricular AD > **15** mm; *** Sepsis was defined as confirmation on blood culture G (–), G (+) at 7 days

decreased necessity of VPS implantation or EVS [14]. Adzick et al. [6] showed a significantly decreased VPS implantation rates in children treated in utero in their first year of life (40% vs 82% in postnatal group). In a observational study over 53 months published by Zamłyński et al. [12] the necessity of VPS implantation in 18 cases from the fMMC repair group included 5 children (27.8%). In a control group it amounted to 80% (CI 0.35, 0.16–0.75, $p < 0.008$) [22]. In the study of 30 children, aged 5, that underwent fMMC repair without VPS implantation, better cognitive function ($p = 0.02$), enhanced motor function of lower extremities ($p < 0.02$), and an increased number of children to fully care for themselves ($p < 0.01$) were observed (in comparison to the children with postnatal treatment followed by VPS implantation) [22]. In a further study of children who were 10 years old after fMMC repair, in 90% self-reliance and good life quality were affirmed [23].

The purpose of in utero fMMC repairs that have lasted for three decades was finally proved by the randomized MOMS trial which is considered a milestone in the field of perinatology. This study closes the period of uncertainty concerning fMMC repair validity. The fMMC repair gained a permanent place among perinatal procedures despite iatrogenic complications. In 2013 ACOG published an opinion concerning prenatal MMC repair in CM II, [31]. Additionally, SGOCC suggested in 2014 that due to possibility of prenatal surgery, parents of children with CM II should be fully informed about the procedure and post-operative course of the disease [32].

Historical data and perspectives for fMMC repair in Europe

The Experimental basis for human fMMC repair in animal models was created in Europe and in the US [10]. In the report of Meuli et al. [11] published in 1995, in Nature Medicine, the description of artificial MMC closure in sheep was introduced. It has been proved that intrauterine protection of spinal cord fibres against injury and toxicity of amniotic fluid prevents CNS destruction and worsening of vegetal function [11]. In Europe, the first fMMC repair performed in FSC in Bytom in the year 2005 was followed by the successful procedure in Zurich in 2010, and cases reported in 2014 by Oveare (in Europe, the first fMMC repair performed in FSC in Bytom in the year 2005 was followed by the successful procedure in Zurich in 2010, and cases reported in 2014 by Ovaere from Leuven [33, 34]). In the few centers in the world also in Poland (The University of Warsaw) fetoscopic prenatal surgical repair of MMC is used. This minimally invasive technique is a promising alternative to open fetal MMC repair but still requires improvement.

European medical organizations are trying to work out the consensus and guidelines for patient with MMC [35]. It should presumed that an increasing level of medical acceptance of prenatal therapy and the ability to provide non-directive information for parents of CM II children contribute to an increasing frequency and number of IUMR-centres in Europe.

CONCLUSIONS

FMMC repair is an invasive procedure; however, the level of maternal-fetal surgery safety is quite high. Comparison of fetal condition and neonatal results after fMMC repair: CFSC vs MOMS vs PFSC, points to good effectiveness in reduction of hindbrain herniation (HH) and reduction or prevention ventriculomegaly (VM). The learning curve is positive, mostly decreasing the risk of iatrogenic preterm labor.

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Application of prenatal ultrasonography and magnetic resonance imaging on fetal agenesis of corpus callosum

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ABSTRACT

Objectives: To evaluate the diagnostic value and clinical application of prenatal ultrasonography (US) and Magnetic Resonance Imaging (MRI) for different types of fetal Agenesis of the Corpus Callosum (ACC).

Material and methods: There were 42 cases of fetal ACC discovered by routine US, including complete ACC 18 cases and partial ACC 24 cases, checked by MRI within 1 week. The results were confirmed by head ultrasound after birth or brain biopsy after labor induction.

Results: From prenatal ultrasonic diagnosis, 18 cases were complete ACC and 24 cases were partial ACC. MRI was able to find complete ACC in 11 cases, partial ACC in 16 cases, and non-ACC in 15 cases. Labor induction or birth confirmed that, 11 cases were complete ACC, 14 cases were partial ACC, and 17 cases were non-ACC.The results of different types of ACC were detected by ultrasound and MRI were statistically significant ($p < 0.05$).MRI examination was superior to ultrasound in specificity, positive predictive value, negative predictive value, Youden index, and diagnostic index.

Conclusions: MRI is high specific degrees, diagnostic performance is satisfactory, should be use as a necessary method for prenatal definitive diagnosis of ACC. However, prenatal ultrasound can be tested repeatedly and can be combined with blood flow imaging detection in real time, and it is still the preferred method for screening fetal structural malformation in a comprehensive way, which is suitable for general screening of ACC.

Key words: agenesis of corpus callosum; ultrasonography; magnetic resonance imaging; prenatal diagnosis

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INTRODUCTION

Agenesis of corpus callosum (ACC) is a rare congenital central nervous system malformation, with the incidence rate of about 0.3–0.7%, and often associated with other fetal malformations [1, 2]. ACC can be divided into complete and partial type in morphology, and also Isolated and Compound type with or without other malformations [3, 4], different types of ACC have huge difference in prognosis. The precise function of the corpus callosum is not clear yet, which is currently believed to mainly connect the integrated bilateral motor language centers, motor ataxia area and audio/visual area and other areas [4], and often related to pathogenesis of autism, epilepsy, schizophrenia, dementia and other diseases [2]. High-resolution color Doppler ultrasound is the most important means of prenatal screening for ACC, while the rapid development of fetal magnetic resonance imaging (MRI) has provided a new approach for fetal intracranial studies, with high image resolution and free from the influence of factors such as the position of fetus. The two detection methods have significant differences. This study aims to explore the diagnostic value and application of prenatal ultrasound and magnetic resonance imaging for different types of ACC.

Objectives

The aim of the study was to compare the diagnostic value and clinical application of prenatal ultrasonography(US) with Magnetic Resonance Imaging (MRI) for different types of fetal Agenesis of the Corpus Callosum (ACC), and Provide reference for the formation of standardized consensus of prenatal diagnosis of ACC.

MATERIAL AND METHODS

A total of 42 cases of fetal ACC in ultrasonic or MRI diagnosis in our Hospitals from January 2013 to October

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2017 were performed with fetal magnetic resonance imaging examination within one week after the ultrasonic diagnosis, and followed up to labor induction or birth, maternal age 19 ~ 45 (29.7 ± 4.66) years, gestational age 21 ~ 39 (28.96 ± 4.43) weeks.This study was approved and supervised by the medical ethics committee of the hospital.

Color Doppler ultrasound diagnostic instrument (GE Voluson 8, Accuvix A30), with convex array probe, and the frequency of 2.5 ~ 8.0 MHz were used on ultrasound tests. Informed consent form was signed with the pregnant women before the examination. After examining the fetus according to the system ultrasonic inspection norms, scanning of the craniocerebral cross-section for each layer from the top to the base of the skull was performed for the intracranial abnormal fetuses. Scanning of the craniofacial sagittal section and coronal section was further performed if possible, with careful observation of intracranial arterial blood flow, assessment and classification of suspected cases of ACC, and storage of the related information at the same time.

MRI detected by superconducting magnetic resonance imaging instrument (GE HDX 1.5 T), with 8-channel abdominal surface coils. An informed consent form was signed before the examination. Sequence SS FSE T2W1 and FIESTA coronal, sagittal and axial three-directional scanning was adopted, the fetus was scanned according to fetal size and maternal position, adjusting the scanning parameter TE 100–120 ms. Due to the presence of fetal activity, during the scanning process, images collected at each layer were used as location reference for the scanning of the next layer. After the scan was completed, the image features were evaluated, and classification diagnosis for ACC cases was made.

Ultrasound diagnostic criteria [5]: Direct signs: Complete or partial absence of corpus callosum in the sagittal and coronal planes. Indirect signs: (1) The anterior horn and body of the lateral ventricle expanded outwards, and the bilateral ventricles were parallel; (2) The posterior horn of the lateral ventricle expanded (≥ 10 mm), the anterior horn formed a horn peak, and the lateral ventricle was "Teardrop-like"; (3) The 3rd ventricle showed different degrees of expansion and upward displacement; (4) Transparent septum disappeared; (5) Gyrus echo was presented between the lateral cerebral ventricle and falx cerebri. (6) Pericallosal artery subsidence was observed in ACC fetus from the sagittal section, with the loss of normal arc shape. Ultrasound suspected diagnosis for two of the above indirect signs was partial ACC.

MRI diagnostic criteria [6]: Direct signs: The corpus callosum of median sagittal plane was complete absence (complete ACC) (Fig. 1), partial absence and thinning of the corpus callosum (partial ACC) (Fig. 2); radial distribution of gyri, loss or absence of reed ball-shaped contour in the splenium.

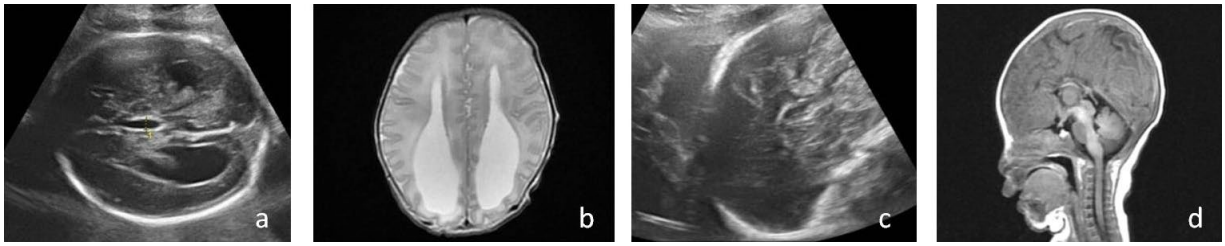

Figure 1. Complete ACC Ultrasound and MRI Comparison (for the same case); **A.** Ultrasonogram Cross-section vie; Lateral cerebral ventricle body outward expansion, loss of normal structure drawn towards the midline, the bilateral ventricles were parallel "Teardrop-like"; the posterior horn of the lateral ventricle expanded (≥ 10 mm), the transparent septum disappeared, the 3rd ventricle showed expansion and upward displacement, and the lateral ventricle was "Teardrop-like"; **B.** MRI image Axial view; The lateral ventricle anterior horn became smaller, with inverted "A" or crescent-shaped separation, the lateral ventricle had near parallel separation, and the 3rd ventricle showed expansion and upward displacement; **C.** Ultrasonogram Longitudinal section view; The cerebral sulci appeared less clear, and gyri echo was not clearly seen; **D.** MRI image Sagittal vie; The corpus callosum was completely absent, and the gyrus showed radial distribution

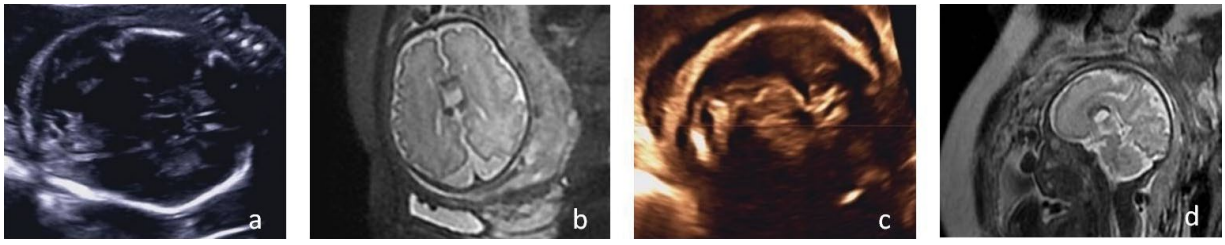

Figure 2. Partial ACC with Arachnoid Cyst Ultrasound and MRI Comparison (for the same case); **A.** Ultrasonogram Cross-section view; The transparent septum disappeared, the 3rd ventricle showed expansion and upward displacement, cyst at left brain midline; **B.** MRI image Axial view; The transparent septum disappeared, cyst near posterior cranial midline, internal separation seen; **C.** Ultrasonogram 3D sagittal section view; The rostrum and genu corporis callosi shown, caudomedial and splenium thinning, and cyst was not shown; **D.** MRI image Sagittal view; Cyst at midline of cranium, rostrum and genu corporis callosi shown, caudomedial and splenium thinning

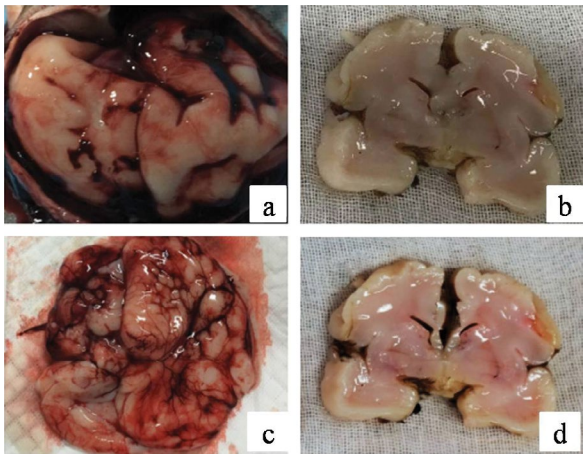

Figure 3. Autopsy chart; **A.** Partial ACC specimens have normal appearance and the brain channel is clear; **B.** The anatomy of the pathological anatomy was edema, and the rear was thinning; **C.** The overall appearance of the complete ACC specimen is uncoupled and unconnected; **D.** The corpus callosum is absent in pathology

Indirect signs: The lateral ventricle anterior horn became smaller, with inverted "A" or crescent-shaped separation; near parallel separation of the lateral ventricle; expansion of the trigone of lateral ventricles and posterior horn; the 3rd ventricle showed expansion and upward displacement; fissurae interhemisphaerica was abnormally near the anterior part of the 3rd ventricle directly or indirectly.

Chi-square test was used to analysis the consistency and difference of the results by SPSS 22.0.

RESULTS

In the 42 cases, from ultrasonic diagnosis, 18 cases were complete ACC and 24 cases were partial. From MRI diagnosis, 11 cases were complete ACC, 16 cases were partial. From the results after labor induction or birth, 11 cases were complete ACC, 14 cases were partial ACC, and rest were normal in the corpus callosum (Tab. 1).

The results should be verified again after birth or after labor induction.In the complete ACC, there were 7 cases of inconformity, 2 cases were partial ACC, 5 cases of callosum were normal. In partial ACC, only 14 cases were diagnosed and 10 cases were misdiagnosed.Ultrasound results show that the specificity, and diagnostic performance are poor and only applicable to the general screening of ACC (Tab. 2).

The results of partial ACC and complete ACC were identified with the results of after birth or labor induction. MRI results showed high sensitivity, strong specificity, strong diagnostic efficacy, high diagnostic value, and suitable for clinical diagnosis of ACC (Tab. 3).

In the 42 cases, 5 cases of brain malformations were misdiagnosis with prenatal ultrasonic diagnosis compared with MRI diagnosis in terms of concomitant intracranial malformations; and 2 cases of limb deformity and 4 cases of heart malformation were detected additionally by ultrasound compared with MRI diagnosis in terms of concomitant extracranial malformations (Fig. 1–3).

DISCUSSION

In this study, the sensitivity of ultrasound and MRI diagnosis of ACC were 100%. While the specificity of ultrasound was 0%, and MRI was 88.24%; the positive predictive values were 59.52% and 92.59%, respectively; the negative predictive values were 0 and 100%; and the Youden indexes were 0 and 0.88, respectively (Tab. 1–3). The results showed that MRI had significant diagnostic value compared with prenatal ultrasound in the fetal ACC diagnosis. The reasons are analyzed as follows, firstly, the total number of cases is relatively small, and no cases of ultrasonic's result is normal but MRI diagnosis as ACC are found yet. In actual work, the

Table 1. Comparison of ultrasound and MRI diagnosis of different types of acc and results after birth or labor induction (unit: case)

Diagnostic Classification	Ultrasound	MRI	After Birth or LaborInduction
Complete ACC	18	11	11
Partial ACC	24	16	14
Non ACC	0	15	17
Total	42	42	42

$X^2 = 40.80$; $p < 0.05$

Table 2. Sensitivity, specificity and diagnostic accuracy of ultrasonic examination

Ultrasonic Diagnosis	After Birth or Labor Induction (Gold Standard)		Total
	ACC	Normal	
ACC	25	17	42
Normal	0	0	0
Total	25	17	42

Sensitivity to ACC, Se = 100%, specificity Sp = 0%; Positive predictive value + PV = 64.29%; negative predictive value — PV = 0; Youden index γ = 0; diagnostic index DI = 100%

Table 3. Sensitivity, specificity and diagnostic accuracy of MRI examination

MRI Diagnosis	After Birth or Labor Induction (Gold Standard)		Total
	ACC	Normal	
ACC	25	2	27
Normal	0	15	15
Total	25	17	42

Sensitivity to ACC, Se =100%, specificity Sp = 88.24%; Positive predictive value + PV = 92.59%; negative predictive value — PV = 100%; Youden index γ = 0.88; diagnostic index DI = 188%

cases that are completely normal in ultrasonic examination usually do not further go through MRI examination, hence there are defects in the inconsistent conditions for inclusion of the two method; next, in the diagnosis of ACC, especially partial ACC, ultrasound has the issue that the standard of diagnosis is too wide, and 11 cases of misdiagnosis are all suspected diagnosis only by the unclear transparent septum, third ventricle or lateral ventricular enlargement, which were confirmed as non-ACC by MRI and after birth examination. Another important reason is that it is very difficult to obtain the direct signs of the corpus callosum by ultrasound, and the image resolution is lower than MRI, the obtaining of indirect signs, for example, the lateral ventricle, the third ventricle, transparent septum and other changes may be caused by other brain malformations.

For the advantages of ultrasound relative to MRI in the blood flow imaging, due to the variable relative position of the fetal head and probe, the sensitivity of deep cerebral blood flow signal decreases, with reliability decreased significantly. The transvaginal ultrasound test is easier to show fetal coronal and sagittal section, but only in the fetal head position and when it is low. For the sagittal view shown by 3D imaging, this study shows that the image resolution still has a certain gap from the 2D ultrasound, the brainstem display rate is low, with the skull acoustic shadow, volume effect and other factors, and can only be used as reference. In addition to the above factors, the ultrasound image itself is influenced by the amniotic fluid, maternal body size, fetal skull, pelvic bone of the pregnant women and the ultrasound equipment limitations, and the result credibility is further reduced. In this study, it is considered that in the ultrasonic diagnosis of ACC, MRI shall be used as a necessary means of detection; if ultrasound cannot obtain satisfactory corpus callosum direct signs, the indirect signs need to meet at least three diagnostic criteria, with follow-up review, and the persistent presence of pathological signs, further MRI examination is performed, so as to reduce the misdiagnosis rate [7].

In this investigation, the diagnostic accuracy of complete ACC is significantly higher than that of partial ACC, indicating that ultrasound has relatively high diagnostic value for complete ACC. Among them, a total of 7 cases of complete ACC misdiagnosis (Tab. 1). Three cases were severe hydrocephalus compression of corpus callosum, transparent septum was not clearly shown, the deep cerebral blood flow signal was poor, resulting in ultrasound misdiagnosis as complete ACC. Two cases were encephalocele with partial ACC to intracranial structural changes, and ultrasound misdiagnosed for complete ACC with encephalocele. Two cases were partial ACC with concomitant septal dysplasia intracranial image changes misdiagnosed as complete ACC, which also shows that the diagnostic scale control of ultrasound in the complete ACC and partial ACC is inferior to MRI.

In this cohort, one case was diagnosed as partial ACC by both fetal prenatal ultrasound and MRI, and the postnatal MRI craniocerebral review was normal. Analysis of reasons show that, for fetal ACC when the gestational age is small (23 weeks of pregnancy in this case), the ultrasound and MRI resolution is lower than in a larger gestational age, whether partial ACC continues the development and improvement process in the uterus, so as to cause misdiagnosis. Therefore, when the gestational age is small, the diagnosis of ACC shall be prudent [8], while the corpus callosum development continues until adolescence. The early over diagnosis of partial ACC can easily increase the psychological burden of pregnant women, hence it should be cautious to make premature conclusions of partial ACC in the fetal period. In this study, it is considered that for complete ACC, ultrasound in the 24 weeks after pregnancy, MRI in the 26 weeks after pregnancy, the intracranial imaging changes are shown more clearly, and the ACC diagnosis has a higher consistency rate. For the diagnosis of partial ACC, ultrasound should be combined with MRI examination, and clear MRI diagnosis shall not be made until it is more than 32 weeks of pregnancy.

MRI detected four more cases of brain malformation than ultrasound, of which three cases were visual — septal dysplasia. In prenatal ultrasonography of severe septal dysplasia, the disappearance of clear septum was almost the only clue, which was easily confused with the ACC misdiagnosis. MRI could accurately identify the type and location of ACC, and could directly display the corpus callosum size, shape and degree of development and other intracranial structural abnormalities. On that account the central nervous system malformations, ultrasound has a greater misdiagnosis rate than MRI. In the extracranial malformation, this group of ultrasound and MRI can both identify the face, kidney, spine, digestive tract malformations, but has detected 2 more cases of limb deformity and 4 more cases of cardiac malformations than MRI. Analysis of the reasons shows that, the current rapid MRI imaging series only solve the problem of fetal movement, while rapid heart movement has not been treated with an appropriate technical means, and ultrasound blood flow imaging combined with structural abnormalities can be better detection of fetal heart malformations. In some limb abnormalities, as the ultrasound can be repeated observation of fetal limb posture changes to determine the more convenient conditions than MRI. Therefore, the current fetal MRI is more for intracranial and static soft tissue examination [9] relative to ultrasound, and ultrasound is currently superior in the above two examinations.

In the total 42 cases, 15 cases had chromosome examination, 5 cases were with chromosomal abnormalities, 3 cases were 18-trisomy , 1 case was 21-trisomy and 1 case

was 13-trisomy. The incidence of deformity was 28.57%. In this group of ACC cases, 35 cases had induced labor, most were of other combined malformations (Fig. 3), isolated ACC due to the presence of the risk that the pregnant women could not undertake, the majority selected induction of labor. Seven cases of birth, and 1 case was diagnosed as partial ACC with interventricular septal defect with ultrasonic diagnosis. After birth and performed with MRI encephalic review, no significant intracranial abnormalities were seen, the prenatal diagnosis of ventricular septal defects were confirmed by the review, and in the follow-up currently. Five cases were false positive after birth without significant brain abnormalities by MRI review. One case was with visual-septal dysplasia, the neonatal visual acuity was low, and MRI review confirmed the prenatal MRI judgment.

CONCLUSIONS

In summary, in the diagnosis of fetal ACC, it is necessary to combine the ultrasonic examination with MRI examination, so as to avoid misdiagnosis. The consistency rate of complete ACC diagnosis is relatively high, while there is obvious limitation in the ultrasound diagnosis of partial ACC. There are obvious limitations in the diagnosis of partial ACC ultrasonography, so the diagnosis should be cautious. Although there are many deficiencies in prenatal ultrasound, due to its advantages of safe, economical, convenient, real-time imaging , repeatable check and the ability to detect the blood flow, it is still a good fetal development evaluation imaging method. The prenatal diagnosis of intracranial dysplasia with MRI is superior to that of prenatal ultrasound. The prenatal ultrasound has advantages in the fetal heart malformation, limb malformation diagnosis compared with MRI. ACC is often accompanied by other malformations, so the ultrasonic diagnosis of ACC should be carefully observed to see if there are other malformations. Combined with MRI and chromosome examination, reliable diagnosis can be made, so as to provide an important basis for the decision making of good prenatal and postnatal care.

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Effects of blood pressure level management on maternal and perinatal outcomes in pregnant women with mild to moderate gestational hypertension

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ABSTRACT

Objectives: This study aims to investigate the effects of blood pressure control level on maternal and perinatal outcomes in pregnant women with mild to moderate gestational hypertension (GHp).

Material and methods: A total of 344 pregnant women who initially diagnosed as mild to moderate gestational hypertension were recruited in this study. They were divided into 4 groups according to the stabilized blood pressure level (BPL) during pregnancy. The clinical parameters and the incidence of adverse pregnancy outcomes were compared among the four groups. The association between blood pressure levels and relative factors were analyzed using the χ^2 test. Multivariate logistic regression analysis was adopted for risk factors associated with adverse pregnancy outcomes.

Results: The results showed the prevalence of obesity was significantly associated with blood pressure levels of mild-moderate GHp pregnant women ($p = 0.029$). The incidence of severe GHp, SPE in group A, group B, and group C were statistically significant ($p < 0.001$, $p = 0.041$, respectively). In the patients who used drugs to control BPL, the incidence of severe GHp has a significant association with the initial blood pressure levels ($p = 0.004$). However, no significant difference was found in the incidence of sPE, PE + Upro, and SGA (all $p > 0.05$). Multivariate logistic regression analyses results showed that the gestational factor BPL was an independent risk factor for the incidence of sGHp. The AMA, primigravida, gestational BPL, and edema were risk factors for the incidence of preeclampsia with proteinuria. To the incidence of sPE, gestational BPL is the independent risk factor. Finally, preeclampsia anamnesis and FGR trend are the high-risk parameters to the incidence of SGA.

Conclusions: Timely management and control of blood pressure in pregnant women with mild to moderate GHp were beneficial to reduce the occurrence of severe GHp and sPE, but the incidence of SGA does not affected.

Key words: blood pressure level; pregnancy; maternal outcome; perinatal outcome; preeclampsia; hypertension in pregnancy; adverse pregnant outcomes

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INTRODUCTION

Hypertensive disorder complicating pregnancy (HDCP) is a common complication of pregnancy, with a spectrum of conditions that include chronic hypertension, gestational hypertension (GHp), preeclampsia (PE), severe PE (sPE), eclampsia, and chronic hypertension with preeclampsia. HDCP is one of the main causes of maternal and perinatal morbidity and mortality, which seriously affects the health of mother and fetal [1, 2]. Pregnancy with hypertension affected 6–8% of pregnancies in the USA, and about 5.22% of pregnancies in China [3, 4]. In addition to maternal cerebrovascular and cardiac complications, HDCP is also associated with small for gestational age (SGA) infants and preterm birth [5–7]. Previous study by Buchbinder A et al. [6] showed the adverse perinatal outcomes were higher in women with severe gestational hypertension than in mild preeclampsia. A study by Mudjari NS et al. [8] pointed that the management of hypertension in pregnancy by preventing women from getting the risks of increased blood pressure (BP) can reduce maternal and perinatal morbidity and mortality.

The prevention, early diagnosis, and treatment of HDCP can reduce the risk of maternal and fetal complications [9–11]. In most regions of the world, severe gestational hypertension was diagnosed when the blood pressure during pregnancy is more than 160/110 mm Hg [12–14]. It has reached a consensus on the antihypertensive treatment

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of severe gestational hypertension, and it is necessary to control the blood pressure when the severe gestational hypertension occurs. However, there are still different views on when the treatment of hypertension should be initiated for pregnant women with mild-moderate gestational hypertension (systolic blood pressure 140–159 mm Hg and diastolic blood pressure 90–109 mm Hg). According to the report of the American College of Obstetricians and Gynecologists' Task Force on hypertension in pregnancy, it is suggested that anti-hypertensive medications not be administered for women with mild gestational hypertension or preeclampsia with a persistent blood pressure of less than 160/110 mm Hg [12]. Whereas some other countries, such as Canada, Australia, China, and so on, believe that the treatment of anti-hypertensive can also be considered in women with mild-moderate gestational hypertensive [13–15]. Therefore, to optimize the management of blood pressure in pregnancies with mild-moderate hypertensive is necessary for reducing maternal and perinatal morbidity and mortality.

Objectives

In the present study, we compared the clinical factors associated with GHp and incidence rates of severe GHp, preeclampsia with proteinuria (PE + Upro), sPE and SGA. This study aims to investigate the effects of blood pressure control level on perinatal outcomes in women with mild-moderate gestational hypertension.

MATERIAL AND METHODS

Study Population

A total of 344 pregnant women (aged from 21 to 44, the average age was 30.15 ± 5.15 years; gestational age of 20–32 weeks, the average gestational age was 25.75 ± 2.24 weeks) were included between January 2012 and December 2016 in The Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University (Wenzhou, Zhejiang). Eligible women were those who have had regular antenatal examinations, carried the pregnancy to term, and initially diagnosed with mild to moderate gestational hypertensive. The women with multiple pregnancies, fetal chromosomal abnormalities, placenta previa, spontaneous abortion, or induced abortion before 20 weeks of pregnancy were excluded. The clinical information was collected in this study including maternal age, maternal pre-pregnancy BMI, recurrent spontaneous abortion (RSA), previous history of preeclampsia, and maternal syndrome (such as nephritis and kidney disease syndrome, thyroid disorder, glucose metabolism, immune system disease, and polycystic ovarian syndrome). Obesity is usually classified by BMI. According to the criteria recommended by Working Group on Obesity in China, BMI was grouped into three categories: normal weight (< 24.0 kg/m^2), overweight (≥ 24.0 and < 28 kg/m^2), and obesity (≥ 28.0 kg/m^2). The detailed clinical characteristics were summarized in Table 1 and Table 2. The study protocol was approved by the Ethical Approval of The Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University. All participants signed informed consent.

Definition and classification

According to the stabilized blood pressure level (BPL) during pregnancy, the participants were divided into four groups, including A, B, C, and D group. Group A includes 135 pregnancy women (BPL < 130/80 mm Hg). Group B includes 160 participants with systolic blood pressure between 130 and 139 mm Hg, and diastolic blood pressure between 80 and 89 mm Hg. Group C obtained 46 participants with systolic blood pressure between 140 and 149 mm Hg, and diastolic blood pressure between 90 and 99 mm Hg. Group D includes 3 participants with systolic blood pressure between 150 and 159 mm Hg, and diastolic blood pressure between 100 and 109 mm Hg.

Diagnostic Criteria

The diagnosis of HDCP, including GHp, PE, and sPE, was based on the diagnosis and treatment guideline of hypertensive disorders during pregnancy [16]. Pregnancy complications, obtaining gestational diabetes mellitus (GDM), small for gestational age (SGA), fetal growth restriction (FGR), polycystic ovarian syndrome (PCOS), immune system disease, and other gestational complications, were also analyzed in the study. The diagnosis of GDM was based on the results of an oral glucose tolerance test [17]. Wessel's modified criteria were used to define the SGA infants. The predictive factors of PE mainly include prehypertension, excess body mass (> 0.5 kg per week), edema, hypoalbuminemia, decreased platelet level, and FGR trend. PCOS was defined according to the consensus on women's health aspects of PCOS [18].

Blood pressure control method

The management of blood pressure during pregnancy was controlled using oral drug therapeutic approach (labetalol or nifedipine) and lifestyle interventions. Lifestyle interventions, such as rest, diet control, adjustment of mental and environmental factors, are of proven benefit in gestational hypertensive. Among the participants in this study, there are 48 pregnancy women used therapeutic drug approach to control the blood pressure. What's more, the placental and fetal growth status were detected during the anti-hypertensive treatment.

Statistical analysis

Statistical analysis was carried out using SPSS software (SPSS, Inc., Chicago, IL, USA). Data are expressed as

Table 1. The relationship between blood pressure level and parameters of GHp women

Parameters	Cases (n = 344)	GHp women groups				p
		A (n = 135)	B (n = 160)	C (n = 46)	D (n = 3)	
Gestational age	**25.75 ± 2.24**	**25.93 ± 2.18**	**25.46 ± 2.18**	**26.20 ± 2.71**	**26.33 ± 3.51**	**0.134**
RSA						0.951
No	323	126	151	43	3	
Yes	21	9	9	3	0	
AMA						0.070
No	254	100	125	27	2	
Yes	90	35	35	19	1	
Obesity						0.029
No	301	124	140	35	2	
Yes	43	11	20	2	1	
PE anamnesis						0.182
No	335	134	155	43	3	
Yes	9	1	5	3	0	
Primigravida						0.056
No	169	62	75	29	3	
Yes	175	73	85	17	0	
Primiparity						0.524
No	29	8	16	5	0	
Yes	315	127	144	41	3	
Pregnancy complications						0.370
No	204	82	95	24	3	
Yes	140	53	65	22	0	

RSA — recurrent spontaneous abortion; AMA — advanced maternal age (pregnant women aged 35 years or over)

Table 2. Prevalence of adverse pregnancy outcomes in relation to blood pressure levels

Outcomes	Cases (n = 344)	GHp women groups				p
		A (n = 135)	B (n = 160)	C (n = 46)	D (n = 3)	
Severe GHp						< 0.001
No	322	134	149	36	3	
Yes	22	1	11	10	0	
PE + Upro						0.311
No	242	98	113	28	3	
Yes	102	37	47	18	0	
sPE						0.041
No	296	122	137	34	3	
Yes	48	13	23	12	0	
SGA						0.813
No	314	124	144	43	3	
Yes	30	11	16	3	0	

Severe GHp — severe gestational hypertension; PE + Upro — preeclampsia with proteinuria; sPE — severe preeclampsia; SGA — small for gestational age

mean ± SD. The clinical profile and incidence of severe GHp, preeclampsia with proteinuria (PE + Upro), sPE, SGA were compared among the four groups. The differences between two groups were examined by paired student's t tests. Maternal and perinatal outcomes were compared using χ^2 test and multivariable logistic regression to control for potential

Table 3. Comparison of pregnancy blood pressure levels and prevalence of adverse pregnancy outcomes in 48 mild-moderate GHp women using anti-hypertensive drugs

Outcomes	Cases (n = 48)	Prenatal BPL (mm Hg)			p
		< 130/80	(130–139)/(80–89)	(140–149)/(90–99)	
Severe GHp					0.007
No	31	9	18	4	
Yes	17	1	7	9	
PE + Upro					0.168
No	24	7	13	4	
Yes	24	3	12	9	
sPE					0.042
No	28	8	16	4	
Yes	20	2	9	9	
SGA					0.709
No	39	9	20	10	
Yes	9	1	5	3	

risk factors. P value less than 0.05 was considered to be statistically significant.

RESULTS

Association between blood pressure level and clinical characteristics of pregnant women

In the present study, we compared the clinical characteristics of four groups of pregnant women with mild-moderate GHp. The prevalence of obesity among pregnant women in group A is 8.1% (11/135), 12.5% (20/160) in group B, 23.9% (11/46) in group C, and 33.3% (1/3) in group D, which increased following the rising of BPL. The results showed the prevalence of obesity was significantly associated with blood pressure levels of mild-moderate GHp pregnant women ($p = 0.029$, Tab. 1). However, no positive associations were found with other clinical characteristics, such as gestational age, RSA, advanced maternal age (AMA; pregnant women aged 35 years or over), PE anamnesis, primigravida, primiparity, pregnancy complications (all $p > 0.05$, Tab. 1).

Prevalence of adverse pregnancy outcomes in relation to blood pressure levels

We also analyzed the incidence of adverse pregnancy outcomes in four groups of pregnant women. In group D, there was no occurrence of adverse pregnancy outcome. The incidence of severe GHp in group A (0.7%, 1/135), group B (6.9%, 11/160), and group C (21.7%, 10/46) was statistically significant ($p < 0.001$, Tab. 2). The incidence of sPE was also found (a significant difference among group A, group B, and group C) ($p = 0.041$, Tab. 2). However, there was no significant difference of incidence of preeclampsia with proteinuria (PE + Upro) and SGA (all $p > 0.05$).

The occurrence of adverse pregnancy outcomes in pregnant women with mild-moderate GHp after anti-hypertensive

In the present study, 48 participants were given anti-hypertensive drugs to control blood pressure. Among the pregnant women who used anti-hypertensive drugs, 10 pregnant women had BPL less than 130/80 mm Hg, 25 participants had a BPL of (130–139)/(80–89) mm Hg, and 13 pregnant women had a BPL of (140–149)/(90–99) mm Hg. As shown in Table 3, the incidence rates of severe GHp and sPE in pregnant women with different pregnancy blood pressure levels were significantly different (all $p < 0.05$). Among different pregnancy blood pressure levels groups, there was no dramatical difference in the incidence of preeclampsia with proteinuria and SGA (all $p > 0.05$).

As shown in Table 4, with the increase of initial blood pressure levels, the incidence of severe GHp (3/23, 7/15, 7/10) is significantly increased, which has a significant difference ($p = 0.004$). However, no significant difference was found in the incidence of sPE, PE + Upro, and SGA (all $p > 0.05$).

Risk parameters related to the incidence of adverse pregnancy outcomes

To analyze the risk parameters correlated with adverse pregnancy outcomes, we used the logistic regression analysis. As shown in Table 5, the factors gestational BPL (OR = 2.958, 95% CI = 1.293–6.766, $p = 0.010$) is the high risk parameters that significantly related to the incidence of sGHp. The AMA (OR = 0.112, 95% CI = 0.047–0.265, $p < 0.001$), primigravida (OR = 0.129, 95% CI = 0.070–0.238, $p < 0.001$), gestational BPL (OR = 1.903, 95% CI = 1.224 - 2.959, $p = 0.004$), and edema (OR = 2.698, 95% CI = 1.360–5.351, $p = 0.005$)

Table 4. Comparison of initial blood pressure levels and prevalence of adverse pregnancy outcomes in 48 mild-moderate GHp women using anti-hypertensive drugs

Outcomes	Cases (n = 48)	Initial BPL (mm Hg)			p
		(140–149)/(90–99)	(150–159)/(100–109)	≥ 160/110	
Severe GHp					0.004
No	31	20	8	3	
Yes	17	3	7	7	
PE + Upro					0.651
No	24	13	7	4	
Yes	24	7	8	6	
sPE					0.392
No	28	14	10	4	
Yes	20	9	5	6	
SGA					0.805
No	39	18	13	8	
Yes	9	5	2	2	

Table 5. Logistic regression analysis of factors contributing to adverse pregnancy outcomes

Outcomes	Variables	p	OR	95% CI
sGHp	Gestational BPL	0.010	2.958	1.293- 6.766
PE + Upro	AMA	< 0.001	0.112	0.047–0.265
	Primigravida	< 0.001	0.129	0.070–0.238
	Gestational BPL	0.004	1.903	1.224–2.959
	Edema	0.005	2.698	1.360–5.351
sPE	Gestational BPL	0.030	1.814	1.060–3.104
SGA	PE anamnesis	0.020	6.866	1.347–34.998
	FGR trend	0.004	3.993	1.565–10.189

FGR trend — uterine length and abdominal circumference were all below the 10th percentile for 3 consecutive weeks

are risk factors for the incidence of preeclampsia with proteinuria. To the incidence of sPE, gestational BPL (OR = 1.814, 95% CI = 1.060–3.104, p = 0.030) is the independent risk factor. Finally, preeclampsia anamnesis (OR = 6.866, 95% CI = 1.347–34.998, p = 0.021) and FGR trend (OR = 3.993, 95% CI = 1.565–10.189, p = 0.004) are the high risk parameters that dramatically associated with the incidence of SGA.

DISCUSSION

Gestational hypertensive is one of the common complications in pregnancy, which is initial occurred hypertension after 20 weeks of gestation and will return to normal within 12 weeks after delivery. Light GHp can be asymptomatic or mild dizziness, slightly elevated blood pressure, accompanied by edema or mild proteinuria, severe GHp may cause important organs injury, occur PE or eclampsia. PE and eclampsia are the main cause of adverse maternal and perinatal outcomes, such as intrauterine growth restriction and preterm birth [19, 20]. The study by Schokker SA et al. [21] showed previous hypertensive disorders of pregnancy was an independent risk factor for later vascular morbidity. Therefore, controlling pregnancy blood pressure can avoid organ or placenta injury and reduce the occurrence of serious adverse maternal and perinatal outcomes.

Previous studies have shown that the treatment of severe GHp can minimize the fluctuation of blood pressure during pregnancy and reduce the future risk of vascular (such as cerebrovascular and/or cardiovascular disease) disease [21–25]. A study by Choi DJ et al. [22] showed that a family history of premature cardiovascular disease was significantly associated with gestational hypertensive disease. The study by Abalos E et al. [23] showed that with the use of antihypertensive drugs could reduce the risk of developing severe hypertension, but no clear differences in the risk of other developing outcomes were found. Molvi SN et al. [24] also found antihypertensive therapy was associated with a lower incidence of severe pregnancy-induced hypertension, proteinuria, SGA babies, as well as some other maternal and fetal-neonatal non-fatal adverse events. A previous study suggested that anti-hypertensive treatment when BPL > 140/90 mm Hg, coupled with close fetal monitoring, might result in both improved fetal outcome, as well as decreasing immediate maternal complications and permanent vascular injury [25]. However, whether anti-hypertensive drug therapy for women with mild or moderate GHp is still controversial.

In the present study, we analyzed the clinical parameters of pregnant women with mild to moderate GHp. We found the prevalence of obesity was significantly associated with blood pressure levels of mild-moderate GHp pregnant women. Some studies have indicated obesity was associated

with blood pressure and increased risks of GHp. For instance, Gaillard R et al. [26] suggested maternal obesity and morbid obesity were strongly associated with the risk of gestational hypertensive disorders. Pregnancy is a period of substantial change in blood pressure, with physiological blood pressure decreasing before the middle stage of pregnancy, and then increasing until delivery [27–29]. In this study, we also analyzed the incidence of adverse pregnancy outcomes in pregnant women with different BPL. The results showed that the incidence of severe GHp in group A (0.7%, 1/135), group B (6.9%, 11/160), and group C (21.7%, 10/46) was statistically significant, which showed an increasing trend with the BPL level. The incidence of sPE was consistent with that of severe GHp. But in group D, there was no occurrence of adverse pregnancy outcome, which might be related to only 3 cases, as the small sample size was prone to bias. Then we further investigated the adverse pregnancy outcomes in pregnant women who took BPL medications. Among 48 pregnant women who used anti-hypertensive drugs, 10 pregnant women had BPL less than 130/80 mm Hg, 25 participants had a BPL of (130–139)/(80–89) mm Hg, and 13 pregnant women had a BPL of (140–149)/(90–99) mm Hg. After anti-hypertensive treatment, the incidence rates of severe GHp and severe eclampsia in pregnant women with different pregnancy blood pressure levels were also found significantly different. However, there was no dramatical difference in the incidence of preeclampsia with proteinuria and SGA. The occurrence and development of mild to moderate GHp may be influenced by multiple factors. Multivariate logistic regression analysis results showed gestational BPL was an independent risk factor for the incidence of severe GHp and sPE. Hence, low blood pressure during pregnancy in GHp women can help reduce the occurrence of severe GHp and sPE, and will not lead to increased incidence of SGA.

What's more, we analyzed initial blood pressure levels and prevalence of adverse pregnancy outcomes in mild-moderate GHp women using anti-hypertensive drugs. The results showed that the incidence of preeclampsia with proteinuria, sPE, and SGA have no significant difference with the initial BPL in mild to moderate pregnant women who had anti-hypertensive treatment, and only the difference in the incidence of severe GHp was statistically significant. The results indicated with the increase of initial blood pressure levels, the incidence of severe GHp (3/23, 7/15, 7/10) was significantly increased. According to the multivariate logistic regression analysis results, the initial BPL was an independent risk factor for the incidence of severe GHp, which suggested timely management and control of blood pressure in pregnant women with mild to moderate GHp was beneficial to reduce the occurrence of severe GHp.

The multivariate logistic regression analysis results also showed edema was risk factor that significantly associated with preeclampsia with proteinuria. The pregnant women with edema show a higher incidence of preeclampsia with proteinuria than those without edema. Therefore, it is necessary to observe the occurrence of edema for preventing the incidence of PE. According to the results of detection of placental and fetal growth status during the anti-hypertensive treatment, there was no affection to the incidence of SGA. Multivariate logistic regression analysis results show the factors gestational BPL is the high-risk parameters that significantly related to the incidence of sGHp. The AMA, primigravida, gestational BPL, and edema are risk factors for the incidence of preeclampsia with proteinuria. To the incidence of sPE, gestational BPL is an independent risk factor. Finally, preeclampsia anamnesis and FGR trend are the high-risk parameters that dramatically associated with the incidence of SGA. These results showed that the risk factors influencing the incidence of adverse pregnancy outcomes were very complicated. The gestational BPL was found significantly associated with the incidence of severe GHp, preeclampsia with proteinuria, and sPE. To control the gestational BPL is beneficial to delay the progression of severe GHp, and reduce the incidence of sPE.

In considering the results of this study, some limitations need to be addressed. First, the sample size of patients is limited. A large number of subjects can improve the accuracy of the results. Second, part of the clinical data was not completed, and more parameters can be involved in the further analyses. Due to the limitations, further analyses are necessary for large research cohort and more parameters.

CONCLUSIONS

In conclusion, timely management and control of blood pressure in pregnant women with mild to moderate GHp was beneficial to delay the progression of severe GHp, and reduce the occurrence of sPE. What's more, there is no correlation was found with the incidence of SGA. Meanwhile, due to the regular prenatal examination and the diversification of diagnostic methods, mild to moderate GHp pregnant women can be timely diagnosed.

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Quantitative and qualitative Ductus Venosus blood flow evaluation in the screening for Trisomy 18 and 13 — suitability study

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ABSTRACT

Objectives: The objective of the paper is the suitability assessment of screening for Trisomy 18 and 13 on the basis of nuchal translucency (NT) measurement, Fetal Heart Rate (FHR), double test, quantitative [Ductus Venosus (DV) Pulsatility Index for Veins (PIV)] and qualitative (the A-wave assessment) blood flow evaluation in the DV.

Material and methods: The study was performed in 7296 singleton pregnancies. In each fetus NT, FHR, DV-PIV were examined. Double test from maternal blood was examined. These ultrasound and biochemical factors were in combined screening investigated. Additional doppler ultrasound markers such as abnormal a-wave in Ductus Venosus and Pusatility Index for Veins of Ductus Venosus were and their impact on Trisomies 18 and 13 screening were examined.

Results: Two groups of patients were compared — with chromosomal normal and chromosomal abnormalities — Trisomy 18 and 13. Detection Rate of Trisomies 18 and 13 at the risk cutoff 1/300 using combined screening was 90.2% and FPR was 6%. Detection Rates of examined chromosomal abnormalities using contingent screening were: 92.1% using DV abnormal a-wave and 94.84% using DV-PIV. FPR's for booths parameters 5.8% and 5.4% respectively.

Conclusions: Quantitative analysis of the flow — assessment of DV-PIV in the first trimester significantly influences the improvement of screening values focusing on Trisomy 18 and 13 detection.

Key words: Combined test trisomy 18 trisomy 13; first trimester nuchal translucency thickness; ductus venosus pulsatility index for veins; serum free β-hcg; pregnancy-associated plasma protein a

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INTRODUCTION

Congenital anomalies and chromosomal defects are most common causes of neonatal mortality and morbidity. On that account, in the period of the last dozen years we have been observing the development of scientific research that would enable the early diagnosis of defects and would let provide these defects possible treatment [1].

First trimester screening for chromosomal defects is based on ultrasound examination with assessment of NT (Nuchal Translucency) and "double test" based on free β-human Chorionic Gonadotropin (hCG) and Pregnancy Associates Plasma Protein-A (PAPP-A) concentrations in maternal blood expressed in Multiplies of the Median (MoM).

The essential ultrasound screening performed between the 11 + 0 and 13 + 6 weeks. [corresponding to Crown-Rump Length (CRL) between 45–84 mm] is based on the assessment markers of chromosomal defects with NT being the first. Additional markers are Nasal Bone (NB), Tricuspid Regurgitation (TR) and ductus venosus flow assessment (DV). The latter is more and more often used in screening [2–4].

In 65% of fetuses with Down syndrome and 55% of fetuses with Trisomy 18 or 13, the reversed A-wave, corresponding to atrial contraction, is detected in DV (it is the qualitative assessment of the flow) [5]. Additionally, Pulsatility Index for Veins (PIV), which provides the quantitative

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evaluation, is also taken into consideration. The average value of DV-PIV is 0.94 (range from 0,53 to 1.99) [6].

In first trimester screening for the most common chromosomal defects in general population for trisomy 21, 18 and 13, Fetal Medicine Foundation has developed the algorithm based on maternal age, CRL, NT, fetal heart rate (FHR) free β-hCG and PAPP-A. This screening strategy provides the Detection Rate (DR) of approximately 90% with the False Positive Rate (FPR) of approximately 3–5% [7]. If the assessment of DV flow is added, the test DR increases to 96% for Trisomy 21, to 92% for Trisomy 18 and to 100% for Trisomy 13. FPR for all is 3% [8].

Non-invasive prenatal screening focuses on identifying pregnant women who are at high risk of chromosomal defects and in whom invasive testing would be justified. [9]

Objectives

The objective of the paper is the suitability assessment of screening for Trisomy 18 and 13 on the basis of NT measurement, double test, quantitative (DV-PIV) and qualitative (the A-wave assessment) blood flow evaluation in the DV.

MATERIAL AND METHODS

In total, 7466 fetuses in singleton pregnancies were examined. It should be stressed that the fetuses with other syndromes (Trisomy 21 — 83 , Turner Syndrome — 12, Tetraploidy — 4, Unbalanced translocations — 5 cases respectively) and structural defects with normal karyotype, such as: heart defects — Hypoplastic Left Heart Syndrome — 12 , Atrioventricular Septal Defects - 8, Tetralogy of Fallot — 4 and Transposition of the Great Arteries — 2 cases were excluded from the research. Other structural fetal defects excluding fetuses from the study were: Fetal Hydrops — 13, Spina bifida — 10, Hydrocephalus — 6, Palate or upper lips cleft — 6, Omphalocele — 3 and Gastroschisis — 2 cases. The study was performed in 7296 singleton pregnancies scanned in the Department of Obstetrics and Gynecology in Ruda Śląska and in Outpatient Clinic "GENOM" in Ruda Slaska. All ultrasound examinations at 11^0 a 13^{+6} weeks were performed according recommendations of Polish Gynecological Society (PTG - Polskie Towarzystwo Ginekologiczne) and Fetal Medicine Foundation (FMF)., Assessed parameters were: CRL, FHR, NT and DV-PIV were measured and the qualitative assessment of A-wave in DV was performed according to FMF rules [9]. In all cases CRL was between 45–84 mm.

For the PIV the 95^{th} percentile was designated and it was taken into consideration within the quantitative analysis.

Specialists in obstetrics and gynecology with valid of FMF and PTG certificates performed all scans using GE Voluson Expert 730 or GE Voluson E8 ultrasound machines.

Directly after the scan, all patients had their blood taken for double test. Maternal blood was tested using the FMF-certified Delfia Express Perkin–Elmer and the concentration of the free β-hCG and PAPP-A were converted to MoMs and then the risk of trisomies was calculated by the FMF certified ASTRAIA software.

Patients in high risk for chromosomal defects (≥ 1/300), were offered amniocentesis for karyotyping (total amount of amniocentesis were 337 cases, whereas in 100 cases, parents did not consent to invasive test) . In patients, who declined invasive testing, postnatal follow up was performed. Pregnancy outcome was collected in all cases by the questionnaires (filled and returned by the patients) and the medical history of newborns. The neonatal phenotype was also evaluated. In the cases with no developmental defects and congenial diseases, the newborns were qualified as healthy. In all cases of increased NT in the first trimester and/or development defects suspected on prenatal ultrasound, a newborn baby underwent a detailed examination by a neonatologist, pediatric cardiologist and a geneticist. Karyotyping was performed in all phenotypically abnormal newborns. For the purpose of this paper, only the phenotypically normal newborns (they were approved as healthy) and fetuses that were detected Trisomy 13 and 18 were calculated. In this way two groups were obtained: 7239 normal neonates and 57 cases of Trisomies 18 and 13 respectively.

Statistical analysis: The Statplus Mac Ver 5 and Wizard Version 1.6.8 statistical packages were used to analyze the data. The Shapiro-Wilk test was applied to assess these results distribution. After ascertaining differences in relation to normal results distribution, the Mann Whitney's U test was applied to conduct further calculations. To analyze qualitative parameters, the Chi^2 test was used. The diagnostic threshold value for particular measurements was determined on the basis of the ROC (Receiver Operating Curve). Sensitivity and specificity were calculated for each threshold value. In all tests, the p level of probability, which was lower than the assumed level of significance ($p < 0.05$), was adopted as the level of differences statistical significance. DR and FPR for separate configurations of markers of the first pregnancy trimester: NT, MA, BC and FHR have been compared.

RESULTS

Two groups of patients were compared. The group of healthy women was constituted by 7239 patients whose fetuses were not detected chromosomal aberrations or any other development defects. The group of diseased women included 57 patients whose fetuses had Trisomy 13 or 18 confirmed on the basis of the karyotype examination.

The medians of outcomes of all examined and assessed parameters in both groups of healthy and diseased patients were observed and compared by Mann Whitney's U test (Tab. 1).

Table 1. Medians of outcomes of all examined and assessed parameters in both groups of normal and abnormal karyotypes

	Healthy	Trisomy 18 or 13	P
n	7239	57	
CRL	62.70	59.50	0.0000
NT	1.70	3.90	0.0001
βHCG MoM	1.05	0.51	0.0000
PAPP-A MoM	0.96	0.34	0.0000
FHR	161.0	159.00	0.0000
MA	34.00	30.00	0.0000
DV PIV	1.00	1.80	0.0001

CRL — crown rump length; NT — nuchal translucency; FHR — fetal heart rate; βhCG — free subunit β of human Chorionic Gonadotropin; PAPP-A — pregnancy associates plasma protein-A; MoM — multiple of median, DV PIV — Ductus Venosus Pulsatility Index for Veins; MA — maternal age; p95 — 95 percentile

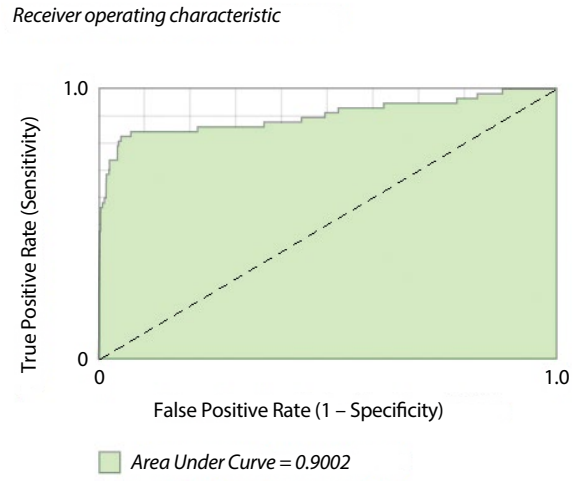

Figure 1. ROC for NT + BC + MA

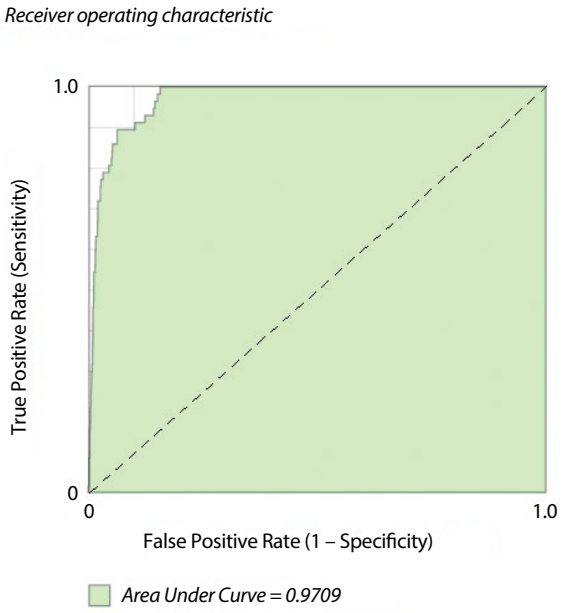

Figure 2. ROC for NT + BC + MA + DVPIV

The test with the lowest DR factor was characterized. It took into consideration the combination of the following basic markers: NT, MA, BC and FHR. In this case this factor amounted 90.02%. The test DR increased to 92.10% after attaching the analysis of a flow in Ductus Venous. However, the highest DR was obtained when, apart from NT, MA, the DV-PIV — Pulsatility Index for Veins in Ductus Venosus was analyzed and then it amounted 81%. FPR amounted respectively: 6.0 for NT + MA + BC, 5.8 for NT + MA + BC + the A-wave and 5.4 for NT+MA+BC+DV-PIV. The above results were obtained for the group risk 1:300.

Comparing mutually all groups of Trisomy 13 and 18 high risk, which is 1:300, 1:200, 1:100 and 1:50, the analysis indicated similar dependencies. In all groups the test diagnostic sensitivity increased after taking into account the quantitative and qualitative assessment of a flow through DV. At the same time the number of FPR results decreased. It appeared that the most advantageous method was the consideration of the flow through a venous ductus together with the qualitative assessment of DV-PIV within the combined test, which was characterized by the highest DR = 89.30%. Additionally, the reduction of the level of Trisomy 18 and 13 risks to the level of 1:200 let maintain similar sensitivity with the decrease of the percentage of FPR results in the analogical group and with the consideration of the qualitative assessment of DV-PIV to 3.5%.

Using statistical analysis sensitivity and specificity for tests that include measurements of NT, biochemistry, mother's age — NT + BC + MA (Fig. 1) as well as for the test enlarged by the measurement of PIV — Pulsatility Index in a Venous Duct — NT + BC + MA + DV-PIV (Fig. 2), the ROC were designated. Comparing both graphs for NT + BC + MA and NT + BC + MA + DV-PIV tests (Fig. 2), great diagnostic suitability of both tests was stated. However, it was noted that analyzing the Area Under Curve (AUC), the diagnostic suitability was bigger for the test extended by the DV-PIV (AUC respectively 0.9002 and 0.9709). Therefore, the most favorable values were obtained for the test in which the combination of MA, NT, double test and DV-PIV, was taken into consideration. Tables 2––4 shows comparison of Detection and False Positive Rates of Trisomies 18 and 13 using examined parameters.

DISCUSSION

During the diagnostic test planning, the highest DR, with a simultaneous reduction of FPR, is tried to be achieved.

Table 2. Analysis of DR and FPR using NT + MA + BC

Risk	1/300	1/200	1/100	1/50
DR [%]	90.02	76.80	66.10	51.80
FPR [%]	6.00	4.70	2.6	1.30

DR — detection rate; FPR — false positive rate

Table 3. Analysis of DR and FPR using NT + MA + BC + A-wave

Risk	1/300	1/200	1/100	1/50
DR [%]	92.10	85.00	80.30	76.00
FPR [%]	5.80	4.10	2.80	2.10

DR — detection rate; FPR — false positive rate

Table 4. Analysis of DR and FPR using NT + MA + BC + DVPIV

Risk	1/300	1/200	1/100	1/50
DR [%]	94.81	89.30	83.90	80.40
FPR [%]	5.40	3.50	2.50	1.40

DR — detection rate; FPR — false positive rate

Therefore, it is aimed at making the noninvasive tests sensitive enough in order to provide the lowest number of patients selected to invasive examinations. The analysis of the blood flow in DV (as Trisomy 13 and 18 additional marker analyzed after obtaining the risk outcomes of a disease calculated according to NT and the double test) lets provide more precise selection of the chromosomal aberration high risk group in the comparison with a method that is based only on the NT measurement and the double test analysis. It should be added that the flow assessment in DV includes two methods: the qualitative method — assessment of the A wave shape (an atrial component) and the semi-quantitative method providing the PIV [3]. In the case of the qualitative assessment, the existence of the retrograde wave in DV is checked. In a situation when the A retrograde wave occurs during a heart contraction, in 80% of cases the fetus's development can be normal but there exists an increased risk of the occurrence of chromosomal disorders, isolated heart defects or even death of a fetus [10]. Literature data show the 60% dependence between the occurrence of the A wave in DV and fetus's heart defects [11]. In their scientific work Maiz and Nicolaides present even 68% of such dependencies [12].

Effectiveness of Trisomy 13 and 18 screening calculated only on the basis of the NT measurement and the double test components lets detect about 91.8% of cases (DR = 91.8%) with the FPR about 2.2% [13]. Within our research in such a case we obtained DR — 90.02% and FPR — 6.0%. After considering the flow in DV, DR increased to 95.4% and FPR decreased to 1.3%. In the case of our results, DR and FPR amounted respectively: 94.81% and 5.4%. Similar outcomes for the assessment of NT and the double test were obtained by Kagan et al [14]: DR 91% for Trisomy 18 and 87% for Trisomy 13 but his FPR was significantly lower and it amounted 0.2% for both aberrations.

The qualitative assessment of the flow (assessment of the A-wave) lets obtain DRT13, 18 at the level of 92.10% with FPR amounting 5.8%. So, slightly better indicators than the Trisomy 13 and 18 risks assessment without the evaluation of the A wave in DV (DR 90.02% and FPR 6.0%) have been obtained. Results of our paper show that it is possible to gain even greater increase of DR to the amount of 94.81% with a simultaneous decrease of FPR to the value of 5.4% when PIV in DV included to the analysis. Similar results — the increase of DR and the decrease of FPR are also gained in the Trisomy 21 screening after including the assessment of the flow in DV. In such a case, Mainz and his partners obtained the following results: DR — 96%, FPR — 3%.

CONCLUSIONS

Concluding, it should be noted that the quantitative analysis of the flow — assessment of DV-PIV in the first trimester significantly influences the improvement of screening values focusing on Trisomy detection. This thesis is confirmed also by Zimmer and his partners' [15] examinations, which indicate that for the test including NT + MA + BC + DV-PIV, the DR increased to 92% whereas for the test without DVPIV analysis of the factor amounted only 84%. Summing up, in comparison with the qualitative assessment of the flow in DV, our research indicates obtaining more effective type of Trisomy 13 and 18 screening with the usage of the assessment of NT, double test and the quantitative analysis of DV flow.

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Minimally invasive surgery for uterine fibroids

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ABSTRACT

The incidence of uterine fibroids, which comprise one of the most common female pelvic tumors, is almost 70–75% for women of reproductive age. With the development of surgical techniques and skills, more individuals prefer minimally invasive methods to treat uterine fibroids. There is no doubt that minimally invasive surgery has broad use for uterine fibroids. Since laparoscopic myomectomy was first performed in 1979, more methods have been used for uterine fibroids, such as laparoscopic hysterectomy, laparoscopic radiofrequency volumetric thermal ablation, and uterine artery embolization, and each has many variations. In this review, we compared these methods of minimally invasive surgery for uterine fibroids, analyzed their benefits and drawbacks, and discussed their future development.

Key words: minimally invasive surgery; uterine fibroid; laparoscopic hysterectomy; laparoscopic myomectomy

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INTRODUCTION

Uterine fibroids comprise one of the most common female pelvic tumors. When including the small, clinically undetectable fibroids and microscopic fibroids, the incidence is approximately 70–75% for those of reproductive age. The cause of uterine fibroids is not clear, and most fibroids present with no symptoms. Only 20–50% fibroids have obvious symptoms, submucous type particularly, for example, abnormal uterine bleeding, urinary frequency or retention, obvious abdominal or pelvic pressure, and infertility. Most fibroids do not need treatment. However, indications for therapy include anemia resulting from metrorrhagia, pelvic pain or pressure affecting daily life, uterine compression, rapid tumor growth, tumor growth after menopause, and infertility [1].

The first laparoscopic myomectomy was performed by Semm in 1979 [2], and it may be the first minimally invasive surgery recorded. Since then, there have been numerous advancements in minimally invasive surgery for uterine fibroids. With the increasing of number of surgical methods and development of surgical techniques, uterine fibroid surgery is becoming easier, more feasible, and less invasive and results in fewer complications. Minimally invasive surgery has been considered an advanced approach for dealing with uterine fibroids. In 2014, Chittawar et al performed a meta-analysis to compare minimally invasive surgical techniques and open myomectomy for uterine fibroids. They found that those two kinds of surgery did not have different recurrence risks, but that laparoscopic myomectomy may be associated with less postoperative pain, lower postoperative fever, and shorter hospital stays compared with all other types of open myomectomy [3]. Minimally invasive surgery truly has its own advantages when dealing with uterine fibroids.

In this review, we compared the techniques, methods, and complications of many types of minimally invasive surgery to analyze their indications, advantages, and disadvantages (Tab. 1). We also evaluated their development status and have provided some evidence of the future development of minimally invasive surgery for uterine fibroids.

Laparoscopic hysterectomy

In 1989, Harry Reich performed the first laparoscopic hysterectomy [4]. Laparoscopic hysterectomy has developed into many types, with three of most common being total laparoscopic hysterectomy (TLH), laparoscopic-assisted vaginal hysterectomy (LAVH), and laparoscopic supracervical hysterectomy (LASH).

Total laparoscopic hysterectomy (TLH)

The TLH procedure has some features of laparoscopic surgery and abdominal hysterectomy. The use of the trocar is comparable to that of conventional laparoscopic myomec-

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Table 1. The comparison of different minimally invasive surgery

	Laparoscopic hysterectomy			**Laparoscopic myomectomy**				**Laparoscopic radiofreqency volumetric thermal ablation (RFVTA)**	**Laparoscopic myolysis**	**Uterine artery embolization (UAE)**	**MR-guided focused ultrasound**
The comparision of different minimally invasive surgery	Totally laparoscopic hysterectomy (TLH)	Laparoscopic assisted vaginal hysterectomy (LAVH)	Laparoscopic supracervical Hysterectomy (LSH)	• one of the most common operations in infertile patients • have less effect on overian function, serum pain index and oxidative damage index, and higher succesful pregnancy rate than open abdominal myomectomy but also higher recurrence rate • the maximal size might be 8–10 cm and the numer of uterine fibroids not exceed 4–5 • has the risk of uterine rupturę during pregnancy or labor				• more fibroids can be detect • fit for more kinds of fibroids, such as large fibroids, multiple fibroids and deep intramural fibroids • less blood loss and no laparoscopic uterine suturing • significant reduction in uterine size, reduction of elimination of myoma symptoms, and improvement in quality of life • the reproductiveoutcomes of RFVTA also affirmative • may have equivalence in safety and patent report efficacy with LM	• the diameter of fibroids usually ranged from 3 to 8 cm • patients may have severe pain, uterine abscess and pelvic adhesion after operation • the risk of uterine rupture when pregnancy • fibroids can decrease but may not disappear	• fit for patients with multiple fibroids, very large fibroids, restricted operatibility, or a history of multiple operations • contraindications include viable pregnancy, active infection, and suspected uterine, cervical, or adnexal malignancy • postembliza-tion syndrome may prevent the widespread application • may has lower pregnancy rate higher miscarriage rate and higher reintervention than myomectomy	• required costly equipment • forbidden for patents ongoing pregnancy • may have complications such as skin burns, postoperation pain, nausea and allergic reactions • more clinical research is needed
	• faster recovery, less intraoperative blood loss, enhanced cosmetic appearance than traditional hysterectomy, • may limited by uterine size but related to surgeon's experience • may have some influence on overian function than LSH, • more fit for patients who has pelvic surgery before	• most similar with TLH • don't recommend to patients whose uterine weight over 800 g	• operation procedur pis more simplifield • fit for nuliparous patients, • may have less serum AMH levels decrease, more overian function reserve, low rates of re-operation and better sexual function parameters than THL, • more fit for patients who has cesarean delivery or hysterescopy before	Laparoscopic-assisted abdominal myomectomy	Laparoscopic-assisted vaginal myomectomy	Total laparoscopic myomectomy	Isobaric laparoscopic myomectomy				
				• avoid the laparoscopic suturing, provide multilayer exactly suturing • reduce the complexity of technology and economize much operative time • mostly used to deal with posterior fibroids	• similar with laparoscopic-assisted abdominal myomectomy • determined by the vaginal capacity • mostly used to deal with posterior fibroids • forbidden in nulliparous women	• difficult to operate • limited indications: fundal or subserosal myomas	• the operation is under direct visualization • avoid the side effects and potential risks of CO2 • conventional long laparotomy instrumants can be used to facilitate the procedure • reduction of the operative costrs nad the operating time • more easier to learn				

tomy. Pneumoperitoneum with 10–14 mmHg needs to be created and three trocars are usually needed. The advantages of TLH compared with traditional abdominal hysterectomy include faster recovery, less intraoperative blood loss, less postoperative pain, and enhanced cosmetic appearance. Surgeons have discussed the largest fibroid weight that is still treatable with TLH. In 2017, Antonio et al reported TLH for a uterus containing 5352 g of fibroids [5]. Therefore, uterine size may no longer be a factor that influences whether to use laparoscopic hysterectomy. However, according to a multivariable analysis, there are some factors that present a high risk for conversion to open surgery, such as the surgeon's experience and fibroids with a maximum diameter > 10 cm [6].

Laparoscopic-assisted vaginal hysterectomy (LAVH)

Most LAVH procedures are akin to TLH, except for the vaginal procedure. The vaginal procedure begins after coagulating and resecting the ovarian ducts and proper ovarian ligaments. Surgeons should first dissect the bladder from the surface of the uterine and then open the Douglas pouch. Then, surgeons resect and ligate the cardinal ligament and enter the vesicouterine pouch. The next step is to ligate and resect the uterine arteries so that the uterus can be removed. Finally, hemostasis and suturing of the vaginal walls are performed before proceeding with the normal laparoscopic hysterectomy [7]. The greatest merits of LAVH compared with conventional abdominal hysterectomy are its reduced morbidity and faster recovery. The main factor limiting the use of LAVH is the uterine size. Although the maximum uterine size for LAVH is based on the experience and proficiency of the surgeon, when the uterine weight is more than 800 g, LAVH may not be appropriate because of the significant blood loss or other complications. However, LAVH may be safe for patients with a uterine size ≤ 12 cm [7].

Laparoscopic supracervical hysterectomy (LSH)

The LSH procedure is contrary to that of TLH except for the preservation of the cervical stump and vaginal and uterosacral ligaments; therefore, the operative procedure is obviously simplified and the possibility of accidental injury to the surrounding organs such as the bladder, intestine, and ureter is reduced. Its indications are wider than those for LAVH; they include pain and/or uterine enlargement caused by myomata, dysfunctional uterine bleeding with no response to treatment, suspected uterine adenomyosis, and bleeding after endometrial ablation or resection. LASH is also suitable for nulliparous patients who have not experienced a vaginal delivery. It is a new minimally invasive alternative with low preoperative morbidity for total hysterectomy with benign conditions. Furthermore, LASH has benefits such as shorter hospital stays, faster recovery, and faster return to the workplace [8].

Research has been performed to determine the differences between TLH, LAVH, and LSH. LSH may involve lower serum AMH levels, more ovarian function reserve, low rates of re-operation and spotting, and better quality of life and sexual function than TLH [9–11]. Previous gynecologic conditions were also associated with the type of laparoscopic hysterectomy (LH) performed. Patients with a previous cesarean delivery and previous hysteroscopy are more likely to undergo LSH than LAVH. However, TLH is more suitable than LSH for patients who have undergone previous pelvic surgery. Estimated blood loss, operative time, and length of hospital stay were significantly reduced with LSH. Furthermore, LSH was the most common approach and was associated with significantly less morbidity [12].

Laparoscopic myomectomy

Laparoscopic myomectomy was first described by Semm in 1979; at that time, it was only used for subserous fibroids. In the early 1990s, this procedure was also used for intramural fibroids [13]. Currently, laparoscopic myomectomy is a common procedure for infertile patients. It is indicated for many conditions such as the presence of subserous or intramural fibroids that narrow the uterine cavity, myomas (which can be larger than 3 cm), or multiple fibroids. Compared with traditional open myomectomy, laparoscopic myomectomy may have less of an effect on ovarian function, the serum pain index, and the oxidative damage index, and it may result in higher successful pregnancy rate. However, the recurrence rate with laparoscopic myomectomy might also be higher [14, 15]. The general opinion is that the fibroid must have gradually emerged and have a maximal size of 8–10 cm, and the total number of uterine fibroids should not exceed four or five [16]. Laparoscopic myomectomy is also associated with complications such as uterine rupture during pregnancy or labor, embolism, thrombosis, bowel injury, ureter injury, urinary bladder injury, excessive bleeding, and fistula.

With the constant development of techniques and instruments, the range of application for laparoscopic myomectomy is becoming wider, the procedure is becoming more intricate, and the complications are decreasing. Laparoscopic myomectomy has gradually improved; it results in reduced pain, shorter recovery time, and less ileus time than conventional laparotomy.

There are four different laparoscopic myomectomy approaches: laparoscopic-assisted abdominal myomectomy (LAAM); laparoscopic-assisted vaginal myomectomy (LAVM); total laparoscopic myomectomy (TLM); and isobaric laparoscopic myomectomy.

Laparoscopic-assisted abdominal myomectomy (LAAM)

LAAM was first performed by Nezhat et al. [17] in 1994. There is some concern that laparoscopy cannot be used

to approach the exact wound site and realize the same hemostasis as conventional laparotomy; therefore, hematoma might occur after surgery. With LAAM, the fibroids are isolated, followed by a Mini-laparotomy. Therefore, laparoscopic suturing can be avoided. Compared with conventional laparoscopic myomectomy, LAAM is superior because it provides exact multilayer suturing, requires less complex technology, reduces the operative time, and results in similar recovery time. Furthermore, during laparoscopy, the general use of electrocoagulation hemostasis may injure the uterine tissues.

Laparoscopic-assisted vaginal myomectomy

During LAVM, a guide suture is usually placed to identify the largest tumor after laparoscopic identification of the location of all fibroids. Then, a culdotomy incision was made, through which the guide suture can be taken out of the uterus and placed in the vagina by using a grasper. These procedures usually involve enucleation and removal of the fibroids or repair of the uterine injury and hemostasis [1].

The benefits of LAVM are comparable to those of LAAM. However, there are some differences in the location of the fibroids. Generally, LAAM is used to manage fibroids developing in the anterior uterine or pedunculated fibroids, whereas LAVM is more suitable for posterior fibroids. The difficulty of LAVM is determined by the vaginal capacity. Therefore, LAVM is not recommended for nulliparous women and those with a contracted pelvis.

Total laparoscopic myomectomy

TLM is still considered a difficult laparoscopic procedure because repairing the uterine defect can be challenging. TLM has limited indications, such as fundal or subserosal myomas. Laparoscopic enucleation of large or deep intramural fibroids remains debatable. To solve this problem, Yuen et al. [18] proposed an improved laparoscopic suturing technique that involves the surgeon manually controlling the tail of the suture while sewing laparoscopically. However, this method may be of little value for the skilled surgeons.

Isobaric laparoscopic myomectomy

Most laparoscopic myomectomy procedures use CO_2 to build pneumoperitoneum; however, when the myoma is large (≥ 8 cm), surgery may be hampered because of the increased operative time, risk of preoperative bleeding, and risk of conversion to laparotomy [19]. Hence, a new method called isobaric laparoscopic myomectomy was developed. With this method, surgeons use a laprotenser to lift the abdominal wall so that a vertical intraumbilical incision can be made. Then, primary access is realized by inserting a 10-mm to 11-mm trocar through that incision, and two lower incisions are made without trocars lateral to the rectus muscles. The incision on the right side is 15 mm to 20 mm, and that on the left side is 10 mm [19]. Therefore, under direct visualization, conventional long laparoscopic instruments can be used. An irrigation-suction cannula and bipolar cautery are pivotal for the procedure. Isobaric laparoscopic myomectomy has a few advantages. First, it avoids building pneumoperitoneum, thereby avoiding the side effects and potential risks of CO_2. Second, because the peritoneal cavity does not need to maintain pressure-tight, conventional, long laparotomy instruments, including knives, scissors, and tissue clamps, needle holders can be used. This facilitates several steps of the procedure, including uterine repair. Third, operative costs and operative times are reduced. Furthermore, this method is more easily learned by surgeons who are experienced with laparotomy.

Trocar placement

Correcting the trocar placement is a crucial factor that influences the surgical procedure. Traditionally, surgeons place three portals during surgery. However, with developments in the surgery technique and the higher demand for the operation, more portal sites are being used, and each has its own merits.

Conventional portal sites and the Lee-Huang point

The conventional use of three portal sites is good for medium masses. Video-assisted laparoscopy was performed through the umbilicus using a 5-mm or 10-mm principal trocar. Two ancillary cannulas are placed with the help of video-assisted laparoscopy: one 5-mm trocar in the right lower quadrant beside the inferior epigastric arteries and the other 5-mm trocar in the left lower quadrant [1]. However, with the demand for larger fibroids, Lee et al. introduced new portal sites called the Lee-Huang point. The principal cannula is placed at the midpoint between the umbilicus and the diploid process. Another two 5-mm puncture sites are made at the intersection of the bilateral paramedian line and the level of umbilicus. If three portal sites are not enough, then other trocars can be selected just above the pubic hairline and at the level of the paramedian line.

This type of placement has many advantages. First, the placement of the first trocar (the Lee-Huang point) is much safer for patients with a history of pelvic surgery, potential malignancies, and large pelvic masses. This placement of the cannulas avoids the major bloods vessels and nerves. Second, the incision through the linea alba accesses the abdominal cavity better, provides a better visual field, and increases the accuracy when resecting large myomas. Therefore, using the Lee-Huang point may be the best choice for large masses.

Laparoendoscopic single-site myomectomy

Some research has demonstrated that laparoendoscopic single-site myomectomy (LESS-M) is suitable for patients

with fewer than five myomas and offers outcomes akin to those of conventional laparoscopic myomectomy after surgeons master the technique [20]. However, LESS has not been widely popularized because of its difficult technique that involves limited motion or clashing between instruments. Another challenge for LESS-M is that after the large tissue specimens are removed through the umbilical incision, the uterine walls need multiple sutures; therefore, repair of the uterine wall injuries may be difficult for surgeons with limited experience. Furthermore, difficulties in maintaining adequate tension of the suture line and trying to accurately create a knot increase the operative time and intraoperative blood loss. Only a wound retractor and a surgical glove can fit in a single port entry. A vertical incision of 15–20 mm was made through the umbilicus; then, two 5-mm cannulas and one 12-mm cannula were inserted with the first, third, and fifth fingers of the surgical glove and fixed with silk ligatures. Next, the glove was fixed at the outer ring of the wound retractors. After repair of the myometrium, surgeons use an electromechanical morcellator, which is usually 15 mm, to enucleate myomas, and that device can be placed with one free gloved finger [20].

Although difficult, LESS-M has some advantage. Obviously, its cosmetic benefits are greater than those of other surgery types. Some studies showed that LESS can reduce postoperative pain more than conventional laparoscopic surgery [21]. For instance, the lower abdomen large trocar insertions of conventional laparoscopic surgery may increase the risk of trocar-related sequela, such as incisional hernias [22].

Choi's four-trocar method

In 2006, Choi et al. [23] introduced the four-trocar method, which provides a better operation field for the large uterus. The method uses four trocars for patients whose uterus is same size as it at approximately 16 to 18 weeks of pregnancy. With the guidance of a central 5-mm telescope, the placement of the first trocar is usually the supraumbilical region. Another two 5-mm ancillary trocars are placed lateral to the superior and inferior epigastric vessels in the left and right upper quadrants. The level of the upward shift can be modulated by the uterine size. The fourth trocar is placed 2 cm above the symphysis pubis so that the four 5-mm trocar points can form a V-shape.

This technique has many benefits. First, surgeons can obtain a larger surgical field to exclude the myoma. Second, all the trocars are situated in the "safe zone" to avoid potential injury to the surrounding nerves and vessels, especially the ilioinguinal or iliohypogastric nerves and the inferior epigastric arteries. Third, the risk of intestinal herniation and the scar size are reduced because only 5-mm trocar ports and one 12-mm cannula are used for the myoma screw or morcellator.

However, some believe that because the uterus is large, the placement of the primary trocar in the umbilical region makes the working distance shorter and the operation field smaller. It may be difficult for surgeons to view the whole pelvis, large uterus, and tumors. Therefore, the Lee-Huang point, may be a better option.

Two-port total laparoscopic myomectomy

Two-port total laparoscopic myomectomy (TTLM) was performed using only umbilicus and left inguinal ports. An Olympus 5-mm flexible scope was used to visualize the surgical field, regardless of the insertion angle, and a 12-mm trocar was placed at the umbilical incision. However, for the patients with a history of open abdominal surgery, the ninth intercostal approach is necessary to confirm the absence of any adhesion of the abdominal organs and the umbilicus [24].

The technique has the same technical difficulty as the conventional technique, and it allows exact suturing of the myometrium (2 to 4 layers) assuming the myomas being removed are within the indicated limits. Furthermore, the two-port technique provides a much higher degree of freedom when handling forceps and adjusting the surgical field of view than single-port myomectomy.

Is morcellation an Achilles heel?

Electrical morcellators have been used during laparoscopy; however, they are associated with complications, including major vascular, bowel, ureteric, kidney, and diaphragmatic injuries [25]. These complications are rare. Other less immediately obvious and long-term complications associated with electrical morcellators are more common. A morcellator is in fact a cylinder device with a cutting tip that can rotate rapidly. It cuts the tumor into strips and then collects those strips in its hollow cylindrical body. However, some of the strips will fall out of the device and must be collected and removed individually. However, some small particles or cells in microscopic quantities can spin off and cannot be removed. These may develop into disseminated peritoneal leiomyomatosis in the future. Characteristics of this type of disease include multiple smooth muscle nodules that can develop sub-peritoneally and can be found in any part of the abdominal cavity; although morbidity is rare and most cases remain benign, some may progress to cancer [26]. It may be not worth the risk and lead to a poor prognosis for patients.

An animal model that was established to study the mechanism of the parasite myoma found that estrogen has an important role. Implanted myomas possess more estrogen receptor (ER) and more progesterone receptors (PR), and they have more angiogenesis and proliferative properties compared with non-implanted myomas. Estro-

gen depletion will significantly decrease laparoscopically induced parasite myoma implantation. The implantation, angiogenesis, and proliferation of parasite myomas may be associated with serum E2 levels. Sex steroid hormone modulators and aromatase inhibitors (AI) may also decrease implantation, angiogenesis, and proliferation. These data revealed that angiogenesis and implantation induced by estrogen have an important role in the development of parasite myomas, and that hormonal modulation with AI could potentially prevent laparoscopically induced parasite myomas [27].

In clinical practice, surgeons have created many measures to prevent parasite myomas. A thorough pelvic lavage is required during surgery because it may reduce the cellular load. Some surgeons use a plastic bag to collect morcellation materials and then dilate the navel scar to 3–4 cm so the bag can be removed through the navel [28]. Some experts think that avoiding the use of an electronic morcellator can achieve satisfactory tumor reduction during laparoscopic surgery. Reich et al. introduced a method using conventional surgical tools, such as a scalpel, that can morcellate the largest tumors. This method only requires a small incision in the abdominal wall to insert the device [29]. Another specifically designed morcellator knife has been shown to decrease the loss of the tissue during surgery [30]. Many types of new morcellation tools are in varying degrees of development. For example, devices that can be used outside the abdomen, such as with the vaginal approach, are being developed.

Laparoscopic radiofrequency volumetric thermal ablation (RFVTA)

Laparoscopic radiofrequency volumetric thermal ablation (RFVTA) based on primary liver ablation was developed by Lee in 2002 [31]. The equipment used for RFVTA treatment include a monopolar radiofrequency generator, a handpiece with an electrode tip, two electrode pads, extension cables, an activating foot pedal, and other equipment. Current is delivered to the small electrode tip to ablate the fibroid tissue, which is removed via two large dispersive electrode pads that are usually placed on the patient's thighs. When the electrical current decreases, it results in the oscillation of intracellular ions, thus generating resistive or frictional heating. During the procedure, the heat decreases rapidly with the increasing distance from the electrode. The current continues to flow from the handpiece to the electrode pads; at the same time, the myomas undergo ablation and become coagulative and necrosis. Finally, they are reabsorbed by the surrounding tissues.

As a minimally invasive and uterine-sparing procedure, RFVTA has many advantages that cannot be duplicated. More fibroids can be detected using laparoscopic ultrasound intraoperatively than with either transvaginal ultrasound or contrast-enhanced magnetic resonance imaging (MRI) [32]; therefore, it is suitable for more cases such as large fibroids, multiple fibroids, and deep intramural fibroids [33], but not for type 0 (pedunculated) intracavitary fibroids, which are best suited to undergo hysteroscopic resection. Because RFVTA uses flowing current to coagulate fibroids, there is less blood loss and no laparoscopic uterine suturing, which is difficult for many surgeons. Surgeons only need to use intracutaneous sutures to close the port sites; therefore, patients often have minimal injury and leave the hospital on the same day as the surgery [34]. Furthermore, RFVTA provides significant reductions in uterine size, significant reductions in or elimination of myoma symptoms, and significant improvements in quality of life [35]. The reproductive outcomes of RFVTA are also positive. Berman et al. analyzed the pregnancy outcomes of six women who conceived 3.5 to 15 months after the treatment of one to seven myomas that were between 1.0 and 7.6 cm at the greatest diameter and were of multiple types. Five of the women delivered full-term, healthy newborns and one had a spontaneous abortion during the first trimester. Because RFVTA is a new minimally invasive alternative for uterine myoma, further investigations are needed to determine whether it is appropriate treatment for women who desire future fertility.

Some research has focused on comparing the differences between RFVTA and laparoscopic myomectomy, which is a classic minimally invasive option. It was found that RFVTA results in shorter hospitalizations, less blood loss, and a greater percentage of fibroids treated/excised than laparoscopic myomectomy [36]. Although laparoscopic myomectomy may cause a more significant improvement in health-related quality of life and decreased symptom severity scores, laparoscopic myomectomy and RFVTA may have equivalent safety and patient-reported efficacy [37].

Laparoscopic myolysis

The Nd YAG laser was first considered an alternative to laparoscopic myomectomy in 1989 because for some cases, such as those involving multiple intramural myomas, laparoscopic myomectomy is too difficult or too time-consuming. Indications for laparoscopic myolysis include pelvic pain caused by myoma, compression symptoms, or global uterine volumes equivalent to those between 9 and 12 weeks of pregnancy [38]. The Nd YAG laser technique involves bringing the tissue fiber into the center of the myoma so that the fibroids can be coagulated. The diameter of fibroids suitable for myolysis usually range from 3 to 8 cm. The mean decrease in the myoma diameter after myolysis was 41% after 6 months. However, laparoscopic myolysis also has some complications, such as severe pain caused by coagulation of

the myomas, the risk of uterine rupture during pregnancy, uterine abscesses, and pelvic adhesions [39].

Uterine artery embolization

Uterine artery embolization (UAE) was first created in 1995 to treat typical uterine fibroids [40]. It may be an alternative to traditional treatment, especially for women with multiple fibroids, very large fibroids, restricted operability, or a history of multiple operative procedures in the abdomen [41]. UAE has some contraindications, including viable pregnancy, active infection, and suspected uterine, cervical, or adnexal malignancy [42]. However, UAE has many advantages, such as less blood loss, shorter operative times, and shorter hospital stays [43]. The technique also has some limitations that prevent its widespread application, such as postembolization syndrome, which includes complete amenorrhea [44], subclinical damage of the ovarian function (especially in women older than 45 years) [45], and the potential risk of reintervention or subsequent hysterectomy [46]. Furthermore, the time required for the procedure and the radiation exposure also prevent the application of UAE [47]. UAE is not suitable for women who want to preserve their fertility.

Regarding the prognosis for UAE, Davis et al discussed the reintervention rates among myomectomy, UAE, and endometrial ablation (EA). They found that 5 years after surgery, the reintervention rate for UAE was lower than that for EA but higher than that for myomectomy. Prior anemia, bleeding, pelvic inflammatory disease, and pelvic pain might increase the risk of reintervention [48]. Karlsen et al reported that UAE may lead to lower pregnancy rates and higher miscarriage rates than myomectomy [49]. Therefore, although UAE is a safe method with many benefits, patient selection and counseling are important.

Laparoscopic uterine artery ligation (LUAL)

The principle of laparoscopic uterine artery ligation (LUAL) is similar to that of UAE. Both the right and left uterine arteries need to be ligated by the hemoclips, followed by bipolar coagulation. LUAL can overcome the complications of UAE. However, more research and comparisons, such as with hysterectomy and LAVH, are needed.

Magnetic resonance-guided ultrasound

Magnetic resonance (MR)-guided ultrasound is not widely used because of the costly equipment required. Furthermore, few long-term randomized studies have been performed. MR-guided ultrasound is composed of two parts. MRI is used for treatment planning and synchronous treatment monitoring. Ultrasound is used for necrotizing tissue, which involves heating the fibroids to 60 to 80°C and leads to a reduction in fibroid size. Absolute contraindications for the technique are ongoing pregnancy and all contraindications for MRI. However, large fibroid size itself is not a contraindication. Furthermore, some complications may occur, such as skin burns, postoperative pain, nausea, and allergic reactions [50]. Therefore, more clinical research is necessary to verify the value and safety of this technique.

CONCLUSIONS

Because uterine fibroids are one of the most common female pelvic tumors, the development of operative methods of their treatment will continue. Furthermore, because of the rapid progression of operative techniques and surgical skills, more surgeons and patients prefer minimally invasive methods to treat uterine fibroids. At first, minimally invasive surgery could only be used to treat small subserous fibroids. Now, the indications for minimally invasive surgery are becoming broader, case reports are increasing, fibroid sizes are becoming larger, the number of fibroids is increasing, and fibroid locations are becoming more remote. However, are these surgeries obligatory? Minimally invasive surgery has more shortcomings than traditional laparotomy, such as the longer operative times, the lower suturing accuracy, and the greater potential for pelvic adhesions. More research is necessary to evaluate the indications for minimally invasive surgery to determine whether the outcomes are worth the risks.

Currently, electrical morcellation is a crucial component of minimally invasive surgery because it can help decrease invasiveness and hasten the surgery. However, electrical morcellation has some side effects, such as parasite myomas. Parasite myomas can develop in any part of the abdominal cavity, and multiple smooth muscle nodules can develop sub-peritoneally. Although its morbidity is rare and most cases are benign, some may progress to cancer. Many solutions have been suggested for this complication, but none has been promoted worldwide.

The main purpose of minimally invasive surgery is to decrease injury during surgery and shorten the recovery time. Achieving this goal cannot be accomplished with only minimally invasive surgery. According to enhanced recovery after surgery (ERAS), many measures are necessary, from preparation before surgery to recovery after surgery, such as bowel preparation and adaptive training before surgery, fluid management and temperature control during surgery, and analgesia and retention of the drainage tube after surgery, among others. Minimally invasive surgery should be a component of ERAS so that minimal invasiveness and faster recovery can be realized.

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REVIEW PAPER / OBSTETRICS

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Periodontitis and risk for preeclampsia — a systematic review

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ABSTRACT

Objectives: The aim of the study is to review systematic cohort and randomized trials on the relationship between periodontitis and preeclampsia. Periodontitis is an independent risk factor for preeclampsia (PE), and periodontal treatment could play a significant role in the prevention of this pregnancy complication.

Material and methods: A total of 821 items (published until March 2019), thematically related to the relationship between periodontitis, its treatment and the incidence of preeclampsia, were collected from the databases of PubMed, Scopus, Google Scholar and the Polish Database of Medical Bibliography and analyzed. In the end, 6 cohort studies and 3 randomized controlled trials (from the years 2003–2016) were deemed eligible for the review. The main exclusion criteria were as follows: case-control and cross-sectional studies, medical and dental conditions.

Results: A significant relationship between periodontitis and the risk for developing preeclampsia was demonstrated in 5 cohort trials, which was not confirmed by only 1 study. A total of 2724 pregnant women, including 195 (7.16%) with PE, were analyzed. In 3 randomized trials which assessed the impact of non-surgical treatment (scaling and root planing = SRP) on the occurrence of preeclampsia, the preventive effects of the implemented treatment was not confirmed. A total of 116 women from the group of 1825 pregnant subjects undergoing the non-surgical treatment (SRP) and 116 women from the control group of 1827 pregnant women were subsequently diagnosed with PE, which amounted to 6.30% and 6.35%, respectively.

Conclusions: The cohort studies indicated that periodontitis may result in an increased risk for developing PE. A more detailed analysis regarding the impact of potential risk factors and modification of further studies (clarification of how periodontitis and preeclampsia should be defined in observations, consideration of disease severity, earlier at 12–16 weeks of gestation — implementation of the non-surgical treatment, modification and extension of the classical protocol of the non-surgical treatment of periodontal diseases, as well as conducting European studies), are necessary due to considerable discrepancies in the available literature sources (cohort and randomized observations).

Key words: periodontitis; periodontal therapy; adverse obstetric outcomes; preeclampsia; systematic review

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INTRODUCTION

Periodontitis is a chronic and multifactorial inflammatory disease associated with advanced dysbiosis of the pathogenic bacterial biofilm in periodontal pockets, which leads to a progressive destruction of the periodontal attachment apparatus. Periodontal pathological processes include high biomass of periopathogens (*Porphyromonas gingivalis, Tannerella forsythia, Treponema denticola, Aggregatibacter actinomycemecomitans, Filifactor alocis and Catonella morbi*) in the biofilm on the root surface, progressive character of the inflammatory process in the connective tissue and bone resorption of the alveolar ridge, as well as excessive reactivity of the host immunological-inflammatory response to the bacterial biofilm. Periodontitis is a social disease — the most recent nationwide epidemiological study has demonstrated that it occurs in approximately 30% of the Polish population between the ages of 34 and 45 years [1]. Confirmed risk factors include the non-modifiable (age, sex, race and genotype) and the modifiable (smoking, poorly controlled diabetes, presence of perio-pathogens in the subgingival biofilm, poor oral hygiene, obesity and the metabolic syndrome, osteoporosis, low social and economic status, stress, and poor-quality diet) causes [2]. According to the Polish epidemiological reports, periodontitis is diagnosed in 11–12%

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of all pregnant women [3, 4]. Periodontitis is a risk factor for diabetes and a likely risk factor (evidence from case-control and cohort studies; no evidence from interventional studies) for cardiovascular diseases and their endpoints — myocardial infarction, stroke, CVD mortality, low birth weight and/or preterm birth, and chronic renal failure [5, 6].

Pre-eclampsia (PE) is a hypertensive disorder characterized by signs of damage to another organ system, which typically develops after 20 weeks of gestation. PE has been estimated to occur in 2–8% of all pregnant women and is currently considered to be the second main cause of maternal and perinatal mortality [7, 8]. The most common maternal PE- and hypertension-related complications include a generalized tonic-clonic convulsion, disseminated intravascular coagulation, liver failure and acute renal failure with proteinuria, bleeding to the central nervous system and retina, HELLP syndrome, congestive heart failure, pulmonary edema, placental abruption and cesarean delivery [9]. Fetal PE- and hypertension-related complications include the risk for admission to the neonatal intensive care unit, intrauterine growth restriction, low birth weight, prematurity, intrauterine fetal demise, and early infant mortality [9]. Risk factors for PE include: age (> 35 years), race (African-American), (family) history of PE, multiple gestation, intrauterine growth restriction, obesity, chronic hypertension, pharmacological interventions for the induction of the ovulation, pregestational diabetes mellitus type I or II, gestational diabetes mellitus, systemic lupus, and the antiphospholipid syndrome [9, 10]. Chronic maternal infections (e.g. urinary tract infections) are indicators of PE-related risk. In 2002, Riché et al. [11], were the first to publish the results of a cohort study at Chapel Hill, North Carolina, on the relationship between periodontitis and the development of preeclampsia.

Objectives

The aim of this systematic review is to present cohort and randomized trials on the relationship between periodontitis and preeclampsia. A confirmed role of periodontitis as an independent PE-related risk factor would play a vital role in the prevention of this obstetrical syndrome.

MATERIAL AND METHODS

A systematic review of the literature was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [12].

Questions for the review:

1. Do the adjusted odds ratio values indicate an independent influence of periodontitis on the occurrence of PE in cohort studies about the relationship between periodontitis and preeclampsia?
2. Does periodontal treatment significantly reduce the incidence of PE?

These questions concerned population-based and non-experimental cohort and randomized control trials (CCTs or RCTs).

The review covered all publications in English, German, Polish and Russian about the relationship between periodontal diseases and preeclampsia, as well as the influence of periodontal treatment on PE-related morbidity.

The inclusion criteria were as follows: pregnancy with no PE symptoms before 20 weeks of gestation (blood pressure > 140/90 mm Hg and proteinuria). The exclusion criteria included (family) history of PE, incidence of PE in multiparous women, intrauterine growth restriction, pharmacologically treated hypertension, pharmacologically stimulated ovulation, pregestational diabetes mellitus type I or II, gestational diabetes mellitus, systemic lupus, antiphospholipid syndrome, and fewer than 10 teeth.

All information was obtained from electronic databases. Electronic searches were conducted in PubMed, Scopus, Google Scholar and the Polish Medical Bibliography Databases. All texts were published until the end of March 2019 were figured in. When searching potential papers, the following keywords were used: periodontitis or periodontal disease or periodontal treatment in combination with at least one of the following terms: preeclampsia, pre-eclampsia, pregnancy outcomes, pregnancy complications. The obtained articles were subsequently checked independently by both authors (TK, AZ) against the inclusion and the exclusion criteria.

The first selection eliminated all the abstracts, case descriptions, reviews, animal studies, *in vitro* studies and repeated publications. Subsequently, the texts of the original works were verified against the inclusion criteria (inter alia, with the above definitions of preeclampsia and periodontitis only in accordance with the clinical probing depth and/or clinical attachment loss) and the exclusion criteria (case-control and cross-sectional studies were excluded). If the trial was repeated in the same center, the subsequent study was taken into consideration. The relationship between periodontitis and PE (Odds Ratios — ORs) as well as the effect of periodontal treatment on the risk for developing PE (Risk Ratios — RRs) had to be determined in the studies qualified for the review. The decisions of the authors were compared at the end of the review and the text was included in the analysis only when mutual consensus was reached.

Each study-related entry, independently obtained by both authors (TK, AZ), included the name of the author(s), year of publication, country of study, sample size, age of the examined women, definition of periodontitis, time of study, and in case of the periodontal treatment – time of treatment and its type, OR (RR) as well as 95% confidence interval (CI) values and statistical adjustments for the confounding factors.

RESULTS

The initial review of the literature identified 821 items thematically related to the relationship between periodontitis, its treatment and the development of preeclampsia. After careful analysis, 16 articles, meeting the inclusion and the exclusion criteria, were selected. The last scrutiny excluded 2 cohort studies conducted previously in the same center [11, 13], 3 studies with endpoints which differed from the accepted ones [14–16], and 1 study with inadequate methodology [17]. In the end, 6 cohort studies [18–23] and 3 randomized control trials (RCTs) [24–26] were deemed eligible for the review. The process of selecting works for the systematic review is presented in Figure 1.

Table 1 summarizes the eligible cohort studies conducted between 2003 and 2016. A significant relationship between periodontitis and PE was confirmed by 5 sources [18, 20–23] and not verified by only 1 [19]. A total of 2724 pregnant women were assessed, with 195 (7.16%) diagnosed with PE. These observations were conducted in the USA, India, Korea and Canada. The diversified pool of confounding factors, which were being regarded in the multi-factor analysis of the modelling process, was strongly emphasized.

Table 2 presents 3 randomized studies which assessed the impact of non-surgical treatment (scaling and root planing — SRP) on the morbidity of mothers with PE. None of them confirmed the protective effect of the periodontal treatment on developing PE. Non-surgical periodontal treatment (removal of subgingival deposits with scaling and root planing along with the application of an antiseptic in the

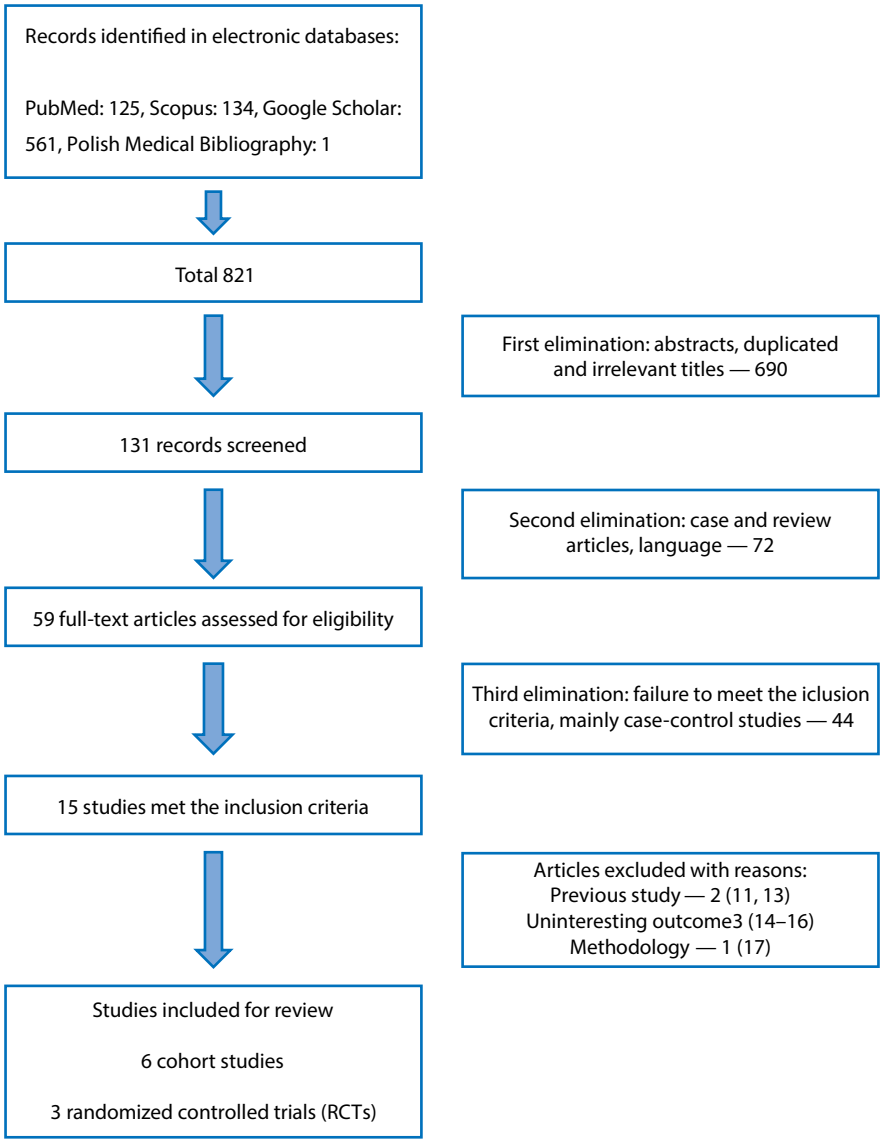

Figure 1. Flow chart of the study selection process for the systemic review

Table 1. Summary of cohort studies included in the present review

Study/Year	Country, city	Sample size, maternal age	Definition of periodontitis	Time of examination	OR (95% CI)	Adjustment of factors
Boggess et al. [18] 2003	USA Chapel Hill	763 women, 39 with PE Age 18–35	PD with BoP > 3 mm	1st visit < 26 weeks, next 26–36 weeks	**2.4** (1.1–5.3) For heavy P	Maternal age, race, insurance, smoking
Srinivas et al. [19] 2009	USA Philadelphia	786 women, 48 with PE Mean age 23.9	PD and CAL ≥ 3 mm	PD and CAL ≥ 3 mm	0.71 (0.37–1.36)	Maternal age, race, smoking, obesity
Shetty et al. [20] 2010	India Mangalore	130 women, 30 with PE Mean age 26.8	PD ≥ 4 mm CAL ≥ 3 mm	1st visit < 26 weeks, next 26–36 weeks and within 2 days after delivery	**5.78** (2.41–13.89)	Maternal age, education, income
Kumar et al. [21] 2014	India New Delhi	504 women, 51 with PE Age 20–35	PD and CAL ≥ 4 mm	1st visit 14–18 weeks, next after 20 weeks	**2.66** (1.32– 5.73)	Maternal age, education, BMI, income
Ha et al. [22] 2014	Korea Seoul	283 women, 13 with PE Mean age 32.8 (25–40)	CAL ≥ 3 mm	1st visit 21–24 weeks, next after 26 weeks	**4.51** (1.13– 17.98)	Maternal age, BMI, health & oral health behaviors
Soucy-Giguère et al. [23] 2016	Canada Quebec	258 women, 14 with PE Mean age 35 (19–45)	PD with BoP > 4 mm	1st visit 15–24 weeks, next after 26 weeks and after delivery	**5.89** (1.24– 28.05)	BMI, smoking

Table 2. Summary of intervention studies included in the present systematic review

Study/Year	Country, city	Sample size of the study and control groups, maternal age	Definition of periodontitis	Kind of intervention	Periodontal treatment time	RR (95% CI)
Michalowicz et al. [24] 2006	USA Minneapolis	IG: 407 (31 PE) CG: 405 (20 PE) Mean age 26	PD ≥ 4 mm CAL ≥ 2 mm	IG: Hand and ultrasonic SRP	Before 21 weeks of gestation, monthly control	1.54 (0.89– 2.66)
Offenbacher et al. [25] 2009	USA San Antonio Tuscaloosa	IG: 880 (67 PE) CG:882 (74 PE) Mean age 25.4	CAL ≥ 3 mm	IG: Hand and ultrasonic SRP	Before 23 weeks of gestation, no follow-up visits during pregnancy	0.9 (0.66–1.24)
Newnham et al. [26] 2009	Australia Perth	IG: 538 (18 PE) CG: 540 (22 PE) Mean age 30.5	PD ≥ 4 mm	IG: SRP and rinsing with 0.12% chlorhexidine mouthwash	20–24 weeks of gestation, 28–31 weeks and control visit 32–36 weeks	0.82 (0.44–1.56)

oral cavity) was performed in 1825 women, out of whom 116 (6.36%) were subsequently diagnosed with PE. In the control group (where only oral hygiene was performed and supra-gingival plaque was removed), 116 (6.35%) out of the 1827 examined women were diagnosed with PE. RCTs were carried out only in the USA and Australia.

DISCUSSION

It is a well-known fact that cohort and randomized interventional controlled trials have the strongest evidential value in establishing a causal relationship between two pathologies. Therefore, clinical-control and cross-sectional studies were deliberately excluded from this review. The relatively high (over 7%) percentage of women with PE in the included studies resulted from the fact that the study populations comprised non-Caucasian subjects. The cohort trials clearly indicated that periodontitis may result in an increased risk for developing PE in pregnancy (by 5-fold according to some sources). This relationship has also been confirmed by all three meta-analyses carried out in this field [27–29] so far. In all studies included in the meta-analyses, periodontitis was as an independent factor. Sgolastra et al. [27], after taking into account 12 clinical-control trials and 3 cohort studies from 2003–2012 in the random effects model, obtained the OR at the level of 2.17 (1.38–3.41), although with high and significant heterogenicity (only 8 studies confirmed the relevance of this relationship). Wei et al. [28], after including 13 clinical-control trials and 2 cohort studies from 2003–2012, using a random effects model, confirmed that the probability of developing PE among pregnant women with periodontitis was 3-fold higher with respect to gingivitis or healthy periodontium during pregnancy (OR — 2.79, CI — from 2.01 to 3.01). A significant heterogeneity among these studies has also been demonstrated (13 confirmed

the relevance of this association). Also, Huang et al. [29], by including 8 clinical-control and 3 cohort studies from 2003–2013, obtained in their model the OR at the level of 2.69 with a 95% confidence interval of 1.74–4.17. Nine studies reported a statistically significant relationship between periodontitis and PE. The subsequent meta-analysis demonstrated a significant impact of common risk factors (socio-economic status and obesity) on both pathologies, and sample size and the quality of the included studies on the strength of the relationship.

The etiopathological mechanisms providing an explanation for the link between periodontitis and PE remain to be fully elucidated. However, it seems that the destroyed attachment apparatus is the source of direct infection of the uteroplacental organ with perio-pathogens. The presence of *Porphyromonas gingivalis, Fusobacterium nucleatum, Aggregatibacter actinomycetemcomitans, Tannerella forsythia* and *Micromonas micros* in the placental-fetal unit, in chorionic trophoblasts, and in several types of cells such as amniotic epithelial, decidual, vascular and in the amniotic fluid was demonstrated [30]. Extremely significant similarities between the oral cavity microorganisms and the placenta were found [30]. On the other hand, inflammatory mediators, prooxidative factors, endo- and exotoxins and soluble forms of the adhesion molecules, which induce inflammation of the uteroplacental area, hypoxia, oxidative stress, endothelial dysfunctions leading to PE, penetrate into the cardiovascular bed as a result of periodontal inflammation [31].

From the clinical point of view, reduced incidence of PE by modifying the risk factor, in this case the periodontological treatment, is vital. That possibility has not been confirmed by previous studies, which seems to contradict the presented cohort observations or the aggregated results of the clinical-control and cohort studies in the meta-analyses. A meta-analysis of Kunnen et al. [32], based on the same three randomized interventional studies characterized in Table 2, demonstrates, in the randomized effects model, a lack of effect on PE — the overall RR 1.0 (0.78–1.28) with respect to no non-surgical treatment of periodontitis being conducted. This was also confirmed by the subsequent meta-analysis of Iheozor-Ejiofor et al. [33], which included the 2 described studies [24, 25] and the highly questionable study of 2000 — the overall RR was 1.1 (0.74–1.62). Additionally, very poor evidential quality of the combined studies, high risk of an error in a publication, and serious imprecision were emphasized by the authors. The fact that no protective effect of periodontal treatment on the development of PE is observed may be explained in two ways. First of all, it should be noted that the treatment of periodontitis was performed too late to affect the possible development of PE — by way of example, in the study by Newnham et al. [26] the treatment was started between 20 to 24 weeks of gestation. In the case of an early PE, there is no possibility that such treatment will have a preventive effect. Secondly, it remains unclear to what extent the classical protocol of non-surgical treatment of periodontitis (SRP) during pregnancy protects from the exposure to perio-pathogens and proinflammatory biomarkers. Such treatment significantly reduces the number of perio-pathogens in the periodontal pockets, but it does not eradicate them [34], thus failing to eliminate the source of maternal infection. Similarly, such treatment does not significantly reduce proinflammatory biomarkers in the serum and the umbilical cord blood [35] and, as it was indicated in one of the studies, a significant increase in serum TNF-α, IL-8 and MCP1 (monocyte chemotactic protein) was demonstrated after SRP had been performed in pregnant women [36]. If these two suggestions are true, then in the subsequent interventional studies, initiation of the non-surgical treatment between 12 to 16 weeks of pregnancy and improvement of its effectiveness (SRP in combination with supplemental antibiotic administration or antimicrobial photodynamic therapy) may have some effect on PE prevalence. However, methodologically improved interventional tests in pregnant women should certainly be continued, since it is difficult to exclude a positive influence of professional periodontal treatment on various complications of pregnancy.

The present review of the literature about the relationship between periodontitis and preeclampsia is not without limitations. Firstly, there are considerable discrepancies in the definitions of periodontitis, which also applies to Tables 1 and 2. However, if only one definition of periodontitis were to be selected, this would result in rejecting a majority of the analyzed studies. The epidemiological definition of CDC (Center for Disease Control and Prevention) and APP (American Academy of Periodontology) should be preferred, which suggests that at least 2 PD ≥ 4 mm pockets and at least 2 CAL ≥ 3 mm spaces on the contacting surfaces are required for such a diagnosis. Out of the 9 works analyzed in the review, this definition was applied only in one case [20]. Stratification of PE severity would also be of great significance. Secondly, the definition of preeclampsia should also be more precise and differentiated into the early and the late PE (with different risk factors), and it should reflect the degree of clinical advancement. Thirdly, to the best of our knowledge, there are no studies on the subject from Europe, including Poland. Extrapolating the research results of the racially, socio-economically and socio-demographically diverse populations to the Polish one is not prudent. This applies particularly to intervention studies, which have so far been carried out in only two highly developed countries — the USA and Australia. The mere diversity of health care systems between countries can create numerous barriers

for such observations. Next, it is necessary to rigorously monitor as many disruptive factors as possible, including, in particular, common risk factors for both pathologies: maternal age, obesity, socio-economic status and smoking. The development of clear recommendations on the inclusion of these variables in multifactorial analyses in this respect will certainly improve the evidence quality of the studies. Finally, exclusion of publications in Spanish, typically from South America, was a definite limitation.

CONCLUSIONS

It needs to be emphasized that the relationship between periodontitis and preeclampsia remains controversial. The existing incompatibility between the cohort and randomized trials needs to be further clarified. It is necessary to conduct randomized control trials including Caucasian women, with an accurate effort and attempt to improve the methodology. As a result, periodontal treatment would not only have a beneficial effect on the quality of patient life in relation to oral health, but might also play a role in disease prevention, especially PE, which is associated with significant morbidity and mortality. PE constitutes a serious threat to the health and life of both, the mother and the fetus. Thus, any potential modifiable risk factor must be clearly established in terms of strength, dose-effect relationship and reversibility.

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VIA MEDICA

RECOMMENDATIONS

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Recommendations of the Group of Experts of the Polish Society of Gynecologists and Obstetricians in the field of gynecological and obstetric care of young women with physical and intellectual disabilities

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The recommendations present the current knowledge and procedures, which can be modified and changed in some cases, after careful analysis of a given clinical situation, which in the future may become the basis for their modification and updating.

In pediatric gynecology each medical action should be adjusted to patient's age, stage of her physical and mental development, and in case of a disable patient, the type of her disability should be individually taken into consideration.

A person with a disability is defined as a person with a physical or mental impairment that substantially limits one or more major life activities. Mental or physical disability is a crucial factor that impedes the implementation of gynecological and obstetric standards of care, especially in pediatric group of patients. Pediatric gynecologists must not only be characterized by multidisciplinary knowledge but also be able to build good interpersonal relations with young patients.

Women and girls with disabilities have rights to obtain gynecological and obstetric care.

The health awareness of women in Poland is low, and what's more the awareness of women with disabilities is even lower. The necessary element to broaden their knowledge and awareness is to provide each woman with disabilities an easy access to specialists and medical care. In addition, it is important to provide girls with visual impairment a non-stressful and intimate atmosphere during the gynecological visit and physical examination. The second crucial element is to enable women with disabilities to gain reliable and easy-provided medical knowledge, thus these women are often disinformed because of their lower educational status in comparison to general population.

Many findings and observations show, that Polish society is very traditional in terms of many negative stereotypes that are absent in other countries of the European Union. These stereotypes include also an opinion that a person with disability doesn't have sexual needs. Because of that, disabled people are often marginalized in terms of sexual, gynecological and obstetric care. Meanwhile, the World Health Organization emphasizes, that sexual activity in people with disabilities is one of the most one of the most neglected fields and requires the cooperation of specialists from various fields [1].

MEDICAL HISTORY OF A PATIENT WITH DISABILITIES

The strategy of interviewing disabled patients must be individually adapter depending on the type of the disability. The anamnesis of a patient with physical or mental disability differs significantly from interviewing a patient without any disabilities. Medical healthcare providers may not have

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difficulties in interviewing women with isolated physical disabilities, however they have to take into consideration potential information about sensory disturbances due to paralysis or ischemia of some parts of the body.

When discussing the clinical impact of disabilities on women's reproductive health, it's important to remember that these women have the full right to procreation. Providing optimal conditions for conducting pregnancy of a disabled woman, as well as choosing between the natural birth and the cesarean section, requires consideration of specific neurological and orthopedic conditions [2]. The authors' own experiences show, that physicians often do not ask the patients about the presence of genital ailments which maybe a result of the disability. Patients with spinal cord injury often experience oligomenorrhea or amenorrhoea within 12 months after the injury. In this group of women, genital sensory disorders are also common and may negatively affect their sexual activity. Therefore, collecting reliable gynecological history from a disabled woman requires interdisciplinary medical knowledge. During the interview, the patient's specific mental state should be also taken into account, which may be the result of an accident trauma.

Interviewing the physically disabled person does not seem to differ significantly from the standard method of collecting medical records. However, you cannot forget that in some cases, a change in collecting the medical history may be necessary. For example, a girl with cerebral palsy may have impaired speech, so that she may not be understood by the doctor. In that cases, the girls' guardians may play a role of a "translator", while special care should be taken so that he does not create a virtual clinical picture of the patient. Another idea is to prepare a standardized model of collecting medical records from disabled patients.

Speech or hearing dysfunction are another important type of physical disability. The most necessary thing in this situation is the involvement of a professional sign language interpreter. However, this is not possible in the emergency cases and the doctor must deal with the situation. One of the most common mistakes doctors make, is to try to have a written conversation. Unfortunately, this is often a completely ineffective method. Of course, secondary deaf people — after accidents or operations have the ability to read. Unfortunately, deaf people from birth use a much poorer word resource. If we use this method of communication, use simple messages. Simple messages also apply to speech — many patients are great at reading lips. In this situation, we use simple sentences and turn to the patient so that she has the chance to read as much as possible from our lips.

In the contact with a deaf patient, the previously developed gynecological interview questionnaire can be used. In addition, standardized communication cards, such as the one presented in Supplementary Annex 1 (see journal website) [3] are worth to be used. Their guardians can help us in an interview with a deaf person. As long as the guardian is an adult, we use all previously known methods of collecting anamnesis. A communication problem occurs when the interpreter is a child. CODA (Children of Deaf Adults), *i.e.* deaf adults, often accompany deaf parents or siblings in a doctor's office. The conversation mediated by the child is extremely difficult but sometimes it is the only way to contact the patient. Then, any difficult term should be thoroughly explained to the child, bearing in mind that his vocabulary may be severely limited (through constant contact with deaf people and age) so that it can be passed on to the parent as much as possible [4]. Of course, doctors using sign language will find it much easier to communicate with a deaf patient. Despite this, it should be borne in mind that in contact with such patients we use total communication - speech, gestures, drawings, notes. Only in this case the patient has the best chance of understanding the doctor correctly.

Another difficult challenge concerns interviewing a blind person. During the conversation we should remember that she lost a lot of information, *i.e.* on the observation of the intensity of menstrual bleeding.

Subject examination of a patient with intellectual disability depends on its level. People with severe disabilities often communicate in simple, two-word sentences or non-verbally (gestures, facial expressions with vocalization). Speech disorders often significantly distort the statement, which makes it incomprehensible to the environment and often causes the disabled person's unwillingness to communicate. Difficulties also apply to the reception of information, so when talking to an intellectually disabled person, avoid statements that are too complex and contain abstract concepts. Often, disabled patients have disturbances in the functioning of their senses, which is manifested by a delayed reaction or sometimes an inadequate response to a stimulus, *e.g.* in the form of hypersensitivity.

People with severe intellectual disability (IQ below 20) usually communicate non-verbally, using gestures such as pointing, handing objects, leading by the hand towards the desired object. Their health situation causes total dependence on caregivers. In these people, physiological functions such as breathing, sucking, chewing, biting, swallowing and phonation are very disturbed. People with deep disabilities often have many of severe neurological defects, physical defects impairing mobility, epilepsy, and sensory damage. They require specialist health and rehabilitation care to prevent the occurrence of acute recurrent infections [5].

It should be remembered that disabled girls, as particularly vulnerable victims, and they are more likely to experience sexual offenses. **The problem of sexually abused children is a special problem of pediatric gynecology, and even more difficult for disabled girls.**

PHYSICAL EXAMINATION (PE) OF DISABLED PATIENTS

Even the preparation for the physical examination is important. Even such a simple act as undressing is often difficult for disabled patients. This creates psychological discomfort for them, and raises technical problems, which is why you need the help of a caregiver, paramedic, nurse or midwife who works with a doctor.

Gynecological examination concerns the most intimate spheres and problems in a woman's life. Incorrectly conducted, it can cause shame and stress in some patients. This particularly applies to the first gynecological examination in life, because it can affect the behavior of a girl or woman in subsequent stages of gynecological diagnostics, and it may affect her psychosexual development. It is very important for disabled patients to maintain particular intimacy during the examination and to create the right atmosphere of respect for girls' shame and trust. In little girls, cooperation with the mother is necessary. When collecting the interview, the mother may pay attention to the details of the daughter's disability, conditions and her development, which are important for the diagnosis. In addition, the presence of the mother during a gynecological examination can give the child a sense of security

A really important clinical problem is the way the gynecological examination is performed. The main difficulty reported by the patients during gynecological examination is taking appropriate position on the gynecological chair. This is often associated with the technique of moving from a wheelchair to a higher gynecological chair. In addition, in girls and women with spastic paralysis, a big problem is the position of the lower limbs on the footrests or the relaxation of the perineum muscles enabling the examination. The solution to these limitations is to carry out the examination on a couch or wheelchair in positions known in general gynecology and girls' gynecology. In addition, some authors are also considering the possibility of examining disabled patients under anesthesia.

When preparing do perform a gynecological examination of a disabled patient, it should be taken into account that examination of such a patient may require much more time. In addition, it is worth remembering that in the case of patients with cerebral palsy, as well as in some with trauma of the nerve core, the relaxation time is significantly longer. If such examination was not possible to perform, the method of choice is only abdominal ultrasound control.

After the gynecological examination, the physician should record in the documentation the results of the examination, taking into account the patient's age, type of disability, stage of physical development according to the Tanner scale, clitoral size, type of hymen, hygienic condition, type of uterus, data from the gynecological and ultrasound examination of internal genital organs and laboratory tests results.

OBSTETRIC CARE OF A YOUNG PATIENT WITH DISABILITIES

The term "juvenile pregnant mothers" or "teenage mothers" refers to young girls who become pregnant and / or have given birth before the age of 18 [6]. According to WHO, every year, 16 million teenagers between 15 and 19 years old become mothers, and teenage pregnancies primarily affect less educated girls from poorer backgrounds. The pregnancy of adolescent women is not only a medical problem, but also a social and psychological one, and if it concerns an adolescent physically or mentally disabled it is an even more important problem. Women with disabilities are more likely to be victims of physical and psychological violence, sexual abuse, and they are exposed to unstable living conditions, low social status, poor diet and a sedentary lifestyle [7]. An adolescent's pregnancy is usually unplanned and given the fact that disabled girls, as particularly vulnerable victims, and are more likely to undergo sexual offenses, pregnancy may be the result of such violence [8].

Pregnancy in teenage disabled woman still occurs relatively rarely, which makes it difficult to thoroughly analyze the impact of factors directly related to a given disability

Table 1. Recommended positions for gynecological examination of women with physical disabilities

Position	Characteristics	Reccomendation
„Side-knee" position	The patient is lying on the couch on her side. The lower outer limb bent with the knee pulled to the chest and raised by the midwife. The lower inner limb remains visited backwards. This position allows limited palpation, in particular the back wall and posterior vaginal arch are available.	Recommended in situations with severe spasticity
„Diamond/rhombus" position	The patient lies on her back, the feet are joined together, the lower limbs bent at the knee joints, maximally deflected (the outer side of the knee joints rests on the couch). Limbs bent at hip and knee joints form a diamond shape.	Recommended for patients with limited mobility in the hip joint
"M" position	The patient lies on the couch, the lower limbs bent at the knees rest with her feet on the couch. After abducting the limbs forming the letter "M", the position is similar to the classical position of the gynecological examination.	Recommended for pediatric patients
„V" position	The patient lies on her back, the limbs are straightened and extended.	Recommended when PE is performed on a wheelchair

on pregnancy, delivery and the health of the fetus and newborn baby. This provides many difficulties and doubts in perinatal care in this group of patients. According to the literature, pregnant women with physical or intellectual disabilities are more often exposed to such complications during pregnancy and delivery as preeclampsia, small growth gestational age (SGA), preterm delivery, higher perinatal mortality, and venous thrombosis [7]. Casuistic experiences with cooperation with disabled women also confirm the frequent anxiety of obstetricians before undertaking the pregnancy of a disabled patient.

The data available in the the literature clearly show that the pregnancy of a patient with physical disability should always be treated as **a high-risk pregnancy.** In the care of a pregnant woman with a disability, special attention should be paid to [9]:

— greater risk of falling due to disability and weight gain during pregnancy;
— cardiovascular and respiratory disorders occurring during pregnancy, which are further compounded by disability;
— nutritional problems.

The delivery of a disabled woman should be carried out with respect for her rights to make informed decisions regarding the delivery process, choice of delivery site and the person caring during delivery [10].

Most frequently, the factors complicating the course of pregnancy, delivery and puerperium result from the neurological and orthopedic condition of the disabled patient and are specific to the disease which is the primary cause of physical disability. Therefore, the proposed recommendations will be limited to two groups of women with disabilities: patients with spinal cord injuries and patients with multiple sclerosis (MS). From epidemiological data and the authors' own experience, it appears that these are the dominant causes of physical disability of women at the age of greatest reproductive potential.

Obstetric care of a pregnant woman with physical disabilities must be carried out by a multi-specialist team made up of the following specialists: an experienced obstetrician, neurologist, physiotherapist. Constant cooperation should be maintained with the internist who has knowledge of the internist problems of a disabled pregnant woman.

I. Patients after spinal cord injury

Patients after spinal cord injury are not affected by reduced fertility. Both the level of spinal damage and the degree of damage do not affect the woman's monthly cycle. Shortly after spinal cord injury, amenorrhea occurs, however menstruation returns approximately six months after damage. Patients with spinal cord injury may have severe menstrual and premenstrual discomfort [11–13].

The factors influencing the course of pregnancy in a group of patients with spinal cord injury are:

a) Increased incidence of lower urinary tract infections and worsening of neurogenic bladder symptoms that are a direct threat to preterm birth.
b) Reduction of vital capacity of the lungs, problems with proper breathing, impairment of respiratory muscle efficiency. This can lead to more frequent hypoxia and compensatory tachypnoe and tachycardia.
c) Impaired intestinal motility and absorption, leading to frequent constipation and an increased risk of anemia.
d) Circulatory disorders as well as inactivity of the lower limbs greatly increase the risk of venous thromboembolism.
e) Weight gain and a change in its distribution leads to more frequent pressure ulcers, mainly around the sacrum.
f) Occurrence of autonomic dysreflexia in patients with spinal cord injury at Th6 level or above during obstetric examination or delivery. This phenomenon is based on increased autonomic reflexes suggesting the onset of preeclampsia. There is an increase in blood pressure, bradycardia, headache, sweating, edema, induction or intensification of uterine contractions including tetanus contractions. There is also vasoconstriction in the uteroplacental circulation leading to fetal hypoxia.
g) The reduction of deep sensation in patients with spinal injury located above the Th12 vertebra makes it difficult for the patient to feel the fetal movements and contractions predicting delivery.

Little is known about the lactation in women after spinal cord injury. Damage to the spinal core at Th6 or higher may result in shorter lactation time and a reduction in the amount of milk. Patients at risk must also know that irritation of the nipples during feeding may experience autonomic dysreflexia. It is recommended that this group of patients use the assistance of lactation advisers [14].

II. Patients with multiple sclerosis (MS)

MS is most often diagnosed at the age of 20–40, that is at childbearing age. For this reason, the effect of pregnancy on MS is a clinically relevant issue. Patients with MS are not less fertile than healthy women, and no negative impact of MS on pregnancy or delivery has been demonstrated. Pregnancy significantly reduces the risk of MS relapse (especially during the third trimester of pregnancy) [15]. It is recommended to discontinue immunomodulatory therapy during pregnancy and feeding the newborn, and some disease-modifying drugs should be discontinued several months before the planned pregnancy [15]. The risk of recurrence of disease increases 6 months after delivery, so it is recommended that the patient returns to preventative treatment as soon as possible by using immunomodulatory drugs.

CONTRACEPTION IN ADOLESCENTS WITH PHYSICAL OR INTELLECTUAL DISABILITIES

The right to independently plan your own partner life and decide on the number of offspring and the frequency of pregnancies is one of the components conditioning reproductive health. This right only applies if everyone has equal access to a variety of contraceptive methods. The results of world studies and a few Polish works indicate that people with physical or mental disabilities significantly less often use modern methods of contraception.

The wide range of contraceptive methods available in terms of their effectiveness, comfort of use and contraindications has given rise to the need to develop PTGiP recommendations regarding methods of pregnancy prevention, with particular emphasis on hormonal contraception.

All recommendations published so far undoubtedly apply when choosing the contraceptive for a disabled patient. However, specific health conditions that directly result from the nature of disability may constitute additional indications or contraindications for a given method of contraception.

RECOMMENDATIONS FOR PATIENTS WITH PHYSICAL DISABILITIES

According to epidemiological data, the most common causes of physical disability in people of reproductive age are spinal cord injuries, cerebral palsy, and multiple sclerosis. Therefore, the proposed recommendations for patients with physical disabilities were formulated with particular regard to the above-mentioned causes of physical disability.

1. Physically disabled women, depending on severity of the mentioned disability, should adjust both her sexual life and optimal method of contraception, previously seek for sexuological consultation if needed
2. Physical disability often leads to emotional and caring dependence on caregivers. If the presence of a disabled person's guardian is not necessary, the method of contraception should be chosen without the presence of accompanying persons.
3. Regardless of the degree and etiology of physical disability, the choice of contraception method must be preceded by: an interview taking into account information on the cause of the disability and a standard physical examination, also taking into account the severity of motor dysfunction hindering the use of the contraceptive method.
4. The possibility of self-use of the contraceptive method by a patient with physical disabilities should be an important criterion for her choice.
5. An equally important condition for choosing a method should be the frequency of sexual intercourse, which can be much lower when compared to the general population.
6. The use of barrier contraceptives should not be recommended for patients with significant grade of spastic paresis due to difficulties in putting the vaginal ring or condom on properly.
7. The use of low-dose oral hormonal contraceptives is recommended for women with severe physical disabilities, unless otherwise indicated.
8. The transdermal hormonal contraception may cause discomfort to a patient during care treatments performed by the caregiver. An alternative method is to propose a hormonal contraceptive in the form of Depo-Provera.
9. The choice of hormonal contraception method must take into account the patient's level of motor activity. In patients moving on a wheelchair with paraparesi, the use of substances increasing the risk of deep vein thrombosis should be avoided. Monitoring of blood coagulation parameters is also recommended in this patient group.
10. Severe physical disability and the altered sensation in the urogenital area is an absolute contraindication to the use of IUD.

RECOMMENDATIONS FOR PATIENTS WITH INTELLECTUAL DISABILITIES

1. In choosing the appropriate method of contraception for patients with intellectual disabilities, it is important to first determine the degree of mental retardation. The ICD-10 and DSM V classification distinguish four main levels of intellectual disability [16, 17]:
   a) mild intellectual disability
   b) moderate intellectual disability
   c) severe intellectual disability
   d) profound intellectual disability
2. For patients with physical disabilities, the choice of contraceptive method is largely based on the risk of Venous Thromboembolism. Although it is also important for patients with mental retardation, the most important factor affecting the effectiveness of the selected contraceptive method is the possibility of its correct use by the patient and her caregiver. When choosing the right contraceptive method, the Polish Society of Gynecologists and Obstetricians recommends using the following criteria:
   a) The results of previous studies indicate that people with intellectual disabilities, regardless of disability level, experience the sexual attraction and show desire to satisfy it.
   b) The individual disability level is an additional criterion for choosing the appropriate contraceptive, for given patient. Women with moderate disabilities are usually aware of the risk of unwanted pregnancy, although they cannot consciously manage their own fertility. Women with profound disabilities meet their sexual needs at the level of unconditional reflex.

c) In case of a patient with intellectual disability, the person taking care of the patient should also participate in choosing the method of contraception.
d) To ensure adequate health protection, the choice of contraceptive method must be preceded by a standard anamnesis and physical examination. An interview for aggravating risk factors should be collected from the patient caregiver. The physical examination should be expanded to include elements of general examination (e.g. visual evaluation of the vessels of the lower limbs) due to the inability to obtain sufficient information about the patient's medical condition without the medical records. Gynecological examination should also include an assessment of the potential symptoms of sexual abuse.
e) In case of patients with severe intellectual disability, the recommendation to use contraception may be given by the doctor, even if the caregiver does not report such a need. Prevention of unwanted pregnancies in this population is an important aim of gynecological care.
f) For patients with mild or moderate impairment, with well-cooperating caregivers, the use of oral hormonal contraception is recommended. The medicine must be selected individually for the patient so as to minimize the risk of undesirable bleeding, which worsens the maintenance of proper hygiene.
g) In the group of patients with severe intellectual disability it is recommended to use long-acting hormonal contraception.
h) For patients with intellectual disabilities, the use of transdermal contraception is not recommended due to the inability to constantly monitor the patch. However, this method is recommended for patients with physical disabilities.
i) The use of contraception in the form of IUD is recommended by some world experts. The authors of these proposals are less optimistic about patients with intellectual disabilities due to the limited control of potential adverse events associated with the use of IUD by the patient herself.
j) The effectiveness of barrier contraception in patients with intellectual disabilities is significantly lower than the known Pearl Index estimates. Therefore, their use is not recommended in this group of women.

POSSIBILITIES OF BIRTH CONTROL IN PATIENTS WITH PHYSICAL AND MENTAL DISABILITIES

People with physical and mental disabilities have the same right to information and assistance in choosing contraception methods as non-disabled people. PTGiP is of the opinion that modern contraception is the only effective way to prevent the unwanted pregnancies and their termination. That is why the education of the society regarding ways of family planning is so important in Poland. One of the most effective ways of birth control are hormonal contraceptives. There are several possible ways of hormone supply, among them:

1. Oral contraceptives
2. Transdermal hormonal contraceptive system
3. Contraceptive vaginal ring
4. Depot Medroxyprogesterone Acetate (DMPA) injections
5. Hormone-releasing intrauterine device (IUD)

Nowadays, thanks to the above-mentioned methods of contraception, it is possible to choose the appropriate method of administering hormones, individually to the patient, so as to minimize the risk of hormone therapy complications. However, it should be remembered that no hormonal drug is indifferent to one's health.

ORAL CONTRACEPTIVES

The use of oral contraceptives is one of the most effective methods of birth control, characterized by a low Pearl index and a relatively low risk of complications during use.

For many women with disabilities, monthly bleeding is extremely troublesome and often embarrassing. During this time, they require more frequent help in sanitary procedure while menstrual pains only further reduce the patient's comfort.

For this reason, the patient may be offered hormonal contraception in the form of pills taken continuously, without a seven-day break for menstrual bleeding [18]. However, complete amenorrhea is difficult to obtain and is reported only in 62% of patients. Planning withdrawal bleeding every 3 to 4 months may be a more effective method to reduce patient discomfort [19].

Among the main side effects of oral hormonal contraception are: increased thromboembolic risk and increased risk of progression of estrogen-dependent cancers, *e.g.* breast cancer. For this reason, women with a tendency to blood clot formation, with liver failure, elevated cholesterol, diagnosed with estrogen-dependent cancers and reported as smokers are advised against taking hormonal contraceptives [20, 21].

The immaturity of the hypothalamic-pituitary-ovarian axis in adolescents means that hormonal contraception for patients in this age group should be individually considered by a gynecologist. Low-dose contraception is recommended because of its reduced risk of venous thromboembolism (VTE), which is particularly important for physically disabled patients.

Low-dose contraception has a reduced risk of thromboembolism, which is due to the low dose of ethinylestradiol.

These medicine significantly reduce blood coagulability, further reducing fibrinolysis, maintaining the concentration of fibrinolysis for coagulation at the appropriate level. Furthermore, oral estrogens increase HDL cholesterol and lower LDL cholesterol. These properties mean that low-dose contraception is recommended for physically disabled patients. [18].

Girls with disabilities have a higher risk of thromboembolic disease, hence the selection of the contraceptive method should be preceded by tests of coagulation parameters. In people with disabilities, special attention should also be paid to the composition of the hormonal drug and the method of its administration. Low-dose oral contraceptives with third generation progestagens are safer for people with disabilities [22].

TRANSDERMAL HORMONAL CONTRACEPTIVE SYSTEM

Another recognized method of contraception recommended for people with disabilities is hormonal contraception used as a patch (transdermal patch). The contraceptive patch may be the right solution for patients who have difficulty swallowing tablets. What's more, just like birth control pills, it can be glued continuously, without every three weeks of breaks with planned withdrawal bleeding after about 3–4 months of continuous use [23].

The transdermal patch is considered one of the most effective methods of contraception in adolescents. This method reduces the risk of skipping the daily dose of the hormone, and allows to maintain a constant concentration of hormones in the patient's body. Studies show that the main reason for the ineffectiveness of oral contraception is forgetting to regularly take birth control pills [24, 25].

There are no studies that directly address the topic of missed dose when using oral contraception by people with disabilities, although the use of the patch significantly minimizes this risk. The use of transdermal patches requires the attention of the patient or caregiver only once a week, not every day, as is the case of oral contraception.

To avoid possible skin irritation, it is not recommended to stick the patches in the same place for too long. This is especially important in the aspect of skin care for people with disabilities.

Some patients with intellectual disabilities may try to remove the patch, which makes it helpful to place it high on the back or buttocks. However, experts do not recommend the transdermal patch to patients with this type of disability due to the inability to constantly monitor the patch. Notwithstanding, this method is considered extremely beneficial for patients with physical disabilities.

An important advantage of the contraceptive patch is the fact that it does not force changes in a woman's lifestyle and does not hinder rehabilitation. The transdermal patch adheres perfectly to the body and is highly resistant to peeling. This is undoubtedly an advantage for people with disabilities who use a bath, a swimming pool or exercise during rehabilitation.

No less important, however, is the increased risk of blood clots and related complications arising from the use of transdermal patches. The use of patches is associated with a higher concentration of estrogens in the female body than when using oral contraceptives. Considering the above, the use of contraceptive patches is not recommended in people with a disability predisposing to thromboembolism [22].

CONTRACEPTIVE VAGINAL RING

Specialists recommend vaginal rings for all women of childbearing potential, especially those who have a high risk of unplanned pregnancy. This is an excellent method for women who are not disciplined in the daily use of birth control pills or the exposure of transdermal patch is not acceptable to them.

Potentially, contraceptive vaginal ring can be used for women and girls with disabilities who have difficulty taking oral medications or using another method of contraception. Of course, the same as with oral contraceptives and transdermal patches, the ring can be used continuously in exactly the same way as described above [26].

A non-disabled woman places the ring in the vagina by herself on the first day of the cycle and after 3 weeks she also removes it herself. Depending on the limitations of the patient's disability, the ring may be inserted by a caregiver.

However, the use of the ring in disabled adolescents raises some concerns. Self-assembly of the disc requires an appropriate level of agility, which is not always possible to achieve by people with physical disabilities. Moreover, the application method may be unclear for people with intellectual disabilities. The ring insertion performed by the caregiver seriously affects the sense of privacy of the disabled person. All of the above drawbacks have severely limited the use of this method of contraception in the population of people with disabilities [22].

DEPOT MEDROXYPROGESTERONE ACETATE (DMPA) INJECTIONS

Recently, the use of DMPA injections as birth control method in patients with intellectual disabilities is increasingly recommended.

This method involves the intramuscular administration of medroxyprogesterone acetate once every 3 months. This form of contraception is especially recommended for patients with severe mental retardation. These patients are at risk of incorrect use of other forms of contraception, misunderstanding medical prescriptions or skipping subsequent doses of oral contraception.

What is more, DMPA is not only a contraceptive, but also suppresses menstrual bleeding. Amenorrhea in almost 60% of patients occurs after 1 year of using DMPA, and in nearly 80% after 5 years [27].

This method seems to be an extremely beneficial alternative for physically disabled patients who require daily care by a caregiver. The site of hormone injection is invisible to the caregiver, does not interfere during care procedures, and does not require more attention, as is the case with transdermal systems or oral contraception. There are, however, two significant problems in using this form of contraception for physically disabled adolescents.

First, the use of this medicine is associated with weight gain. This problem is troublesome for all teenagers, however, for teenagers with mobility problems, even a slight weight gain can complicate movement and thus reduce their independence [28].

Secondly, the topic of the impact of DMPA on bone mineral density (BMD) is increasingly discussed. The US Food and Drug Administration (FDA) recommends limiting the use of DMPA to a maximum of 2 years. This is especially important for teenagers because girls accumulate about 30% to 40% of their bone mass during puberty. The rate of BMD loss decreases with longer duration of DMPA use. The World Health Organization, ACOG, and Society for Adolescent Health and Medicine advise physicians to individually interpret the recommended 2-year period of use and discuss with the patient and her family the potential risks and benefits of this therapy [29].

In adolescents with disabilities and reduced mobility, bone mineral density may be reduced at the outset, but it is not clear whether this is associated with an increased risk of fractures. Loss of bone density appears reversible upon discontinuation of DMPA in women with disabilities, but there are no data on adolescents with reduced mobility [22].

HORMONE-RELEASING INTRAUTERINE DEVICE (IUD)

Intrauterine devices have been very readily used in adult women for many years, but it has only recently been recommended to use them in teenagers. The intrauterine device contains 20 µg of levonorgestrel, of which 50% is consumed after about 5 years.

IUD has excellent contraceptive effects with a relatively small number of side effects. Due to the lack of estrogen component, it is not associated with such complications as *e.g.* venous thromboembolism. For the same reason, it is recommended for women with disabilities, especially in the case of intellectual disability. The described method also applies to women with physical disabilities associated with immobilization, which are excluded from the use of estrogen [30]. However, it should be borne in mind that significant motor disability, especially with the abolition of sensation in the urogenital area, is an absolute contraindication to the use of IUD.

The intrauterine device is especially recommended for people with intellectual disabilities. It is inaccessible to the patient and thus cannot be removed by herself.

Checking the correct placement of the insert in the gynecological office is extremely simple — ultrasound should be quite sufficient to assess the location of the inserted IUD. This is important in the case of patients who poorly tolerate gynecological examinations [22].

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Magnetic resonance elastography of a uterine fibroid with massive lymphocytic infiltration — an extremely rare finding

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INTRODUCTION

Magnetic resonance elastography (MRE) is a promising tool in pre-treatment diagnostics of uterine tumors. Massive lymphocyte infiltration within a fibroid is an extremely rare finding and its elastogram has not yet been demonstrated.

Case

A 31-year-old woman, nulliparous, with no miscarriage in her medical history, was admitted for surgical treatment because of a uterine myoma. The patient had been suffering from excessive menstrual bleeding for over 12 months. A pelvic ultrasonography confirmed a heterogenous intramural tumor of the uterus, approximately 50 mm in diameter. A 1.5 T MR scanner (Optima, GE Healthcare) was used to perform the experimental MRE examination. The research protocol was approved by the Bioethics Committee of the University of Rzeszów, Poland (Reg. No. 19/04/2016). The MRE system includes special acquisition and processing software, as well as hardware consisting of an active and passive driver. The passive driver is a small plastic device that was placed over the uterus to transmit mechanical vibrations into the tissue. The passive driver is connected via flexible tubing to the active driver, which generates pressure pulses (at 60 Hz frequency). The MRE acquisition was performed using a 16-channel abdominal phase array coil. Shear wave imaging was conducted using a modified 2D gradient–recalled echo-based pulse sequence. The resulting wave images were then automatically processed to generate quantitative images depicting tissue stiffness (elastograms). Region of interest (ROI) were drawn manually on the uterine fibroid, using corresponding T2 images as a guide. From the ROI, mean stiffness (kPa) and standard deviation were reported. Finally, a laparotomy was performed on the patient and the uterine tumor was excised. The last menstrual bleeding appeared 10 days before the surgery.

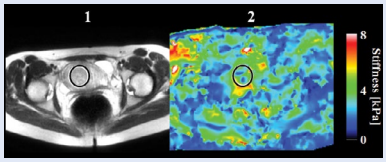

Figure 1. T2w MR image of leiomyoma with massive lymphoid infiltration (1) and its elastogram (2)

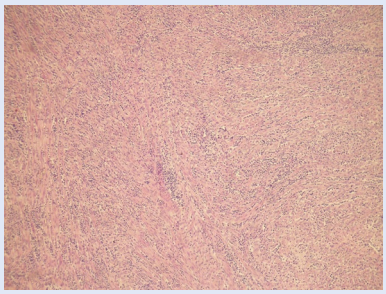

Figure 2. Leiomyoma infiltrated by immune cells. HE

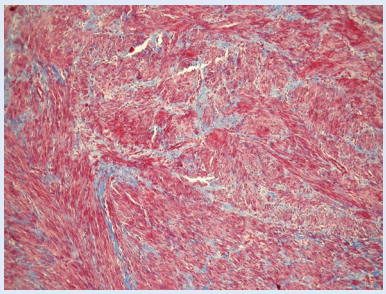

Figure 3. Trichrome Stain: fibrous tissue content less than 5%

RESULTS

The median stiffness of the uterine tumor was 3.36 ± 1.21 kPa (Fig. 1). Macroscopically, it had uterine smooth muscle wall consistency. A microscopic examination revealed leiomyoma infiltrated by lymphocytes, few scattered plasma cells, eosinophils and mast cells (Fig. 2). The concentration of extracellular components in the tumor was less than 5% (Fig. 3). Upon immunohistochemistry, in the lymphocytic infiltrate the T mature lymphocytes (CD3+/CD5+/TdT-) prevailed, whereas B lymphocytes (CD20+/CD5-/TdT-) were innumerous and present in nodular aggregates. The final diagnosis: leiomyoma with massive lymphoid infiltration.

DISCUSSION AND CONCLUSIONS

Massive lymphocytic infiltration in a myoma is an unusual feature. The recognition of its distinct histological features is paramount in avoiding a possible misdiagnosis. Some of them raise a strong suspicion of malignancy, especially lymphoma. The leading treatment method for uterine tumors is surgical excision allowing for their histopathological evaluation. Since most surgical techniques involve different types of morcellation, there is a risk of spreading undiagnosed neoplastic tissue within the operating field, which can negatively impact the patient's prognosis [1]. Hence, there is an urgent need for improvement of the preoperative differential diagnostics of uterine tumors, to enable the choice of the optimal treatment option. Magnetic resonance elastography offers an interesting new possibility. Malignant transformation of the tumor usually alters its mechanical property, which can be detected by MRE and potentially used in the differential diagnostics. The mean stiffness value of common leiomyomas is about 4.81 kPa [2], depending on the concentration of the fibrotic tissue. Uterine sarcomas tend to be more "celullar", which may probably refer to other "unusual" types of myomas, also with premalignant potential [3]. The concentration of extracellular components in the presented leiomyoma with massive lymphoid infiltration was less than 5% and translated into a relatively low stiffness value of 3.36 kPa. This confirms the hypothesis, that the mechanical property of the uterine tumor may be an element of its preparative evaluation and supports the potential role of MRE in pre-treatment diagnostic algorithms.

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