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CONTEMPORARY ULTRASOUND METHODS FOR DIAGNOSE AND CLINICAL FOLLOW UP OF PREGNANCIES COMPLICATED WITH PLACENTA PREVIA AND PLACENTA ACCRETA.

THESIS SUMMURY

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Abbreviations

ACOG - American College of Obstetricians and Gynecologist

ART – Assisted Reproductive Technology

b-HCG – Beta human chorionic gonadotropin

CRL - Crown rump length

EW-AIP - European Working Group on Abnormally Invasive Placenta

MoM - Multiple of the median

NICE - National Institude for Health and Clinical Excellence

NT - Nuchal translucency

OICC - Orificium internum canalis cervicalis

PA – Placenta accreta

PAS - Placenta Accreta Spectrum

PP - Placenta previa

PAPP-A – Pregnancy associated plasma protein-A

RCOG - Royal College of Obstetricians and Gynecologists

SMFM – The Society for Maternal-Fetal Medicine

1. INTRODUCTION

The placenta has a fundamental role for growth and health throughout pregnancy. Normal placental function is essential for a healthy pregnancy outcome. A complete ultrasound survey at any stage of the pregnancy should include full assessment of the fetus and placenta.

Timely detection of placental abnormalities can give the clinician the opportunity to make important management decisions. The primary aim is healthy pregnancy outcome. Prenatal diagnosis and correct obstetric management reduce fetal and maternal morbidity and mortality. Familiarity with the normal and abnormal imaging appearance of the placenta is therefore necessary for the obstetricians.

In this study both placenta previa (PP) and placenta accreta spectrum (PAS) anomalies have been evaluated. Placenta accreta (PA) is a histopathological term, which includes three categories, according to the depth of placental villous invasion into uterine wall: placenta accreta, placenta increta and placenta percreta. In most of the studies, for a long period of time, there are differences in the term used for this placenta abnormality, but in our study, we used both terms: PA and PAS, equally.

The association between placenta previa and placenta accreta is well known and placenta accreta is one of the serious obstetrics complications in 21 century. PP and PA are obstetrics complication, which are associated with high maternal and perinatal morbidity and mortality.

In the recent decades, there is a marked increase in the incidence of PP and PA and this has been observed worldwide. This is attributed to the widely used of ultrasound technique for diagnosis on one hand side, and the increasing prevalence of cesarean delivery, multiparity, dilation and curettage, increased maternal age and infertility procedures on the other hand side.

Ultrasound survey at any stage of the pregnancy, including transabdominal and transvaginal examination is essential for the diagnosis of PP and PA. Despite the fundamental role of the placenta for the pregnancy outcome, ultrasound examination of the placenta is often considered secondary to the fetus. Location, size, shape and architecture are easily ascertained with two-dimensional techniques. Three-dimensional techniques and Doppler techniques are more detailed methods for evaluation uteroplacental structure and function.

Most of the reported studies evaluating the role of the risk factors, the role of the ultrasound examination in early diagnosis and estimate the accuracy of a screening strategy for correct management, in pregnancies complicated with PP and PA. The main aim is by reducing the risk factors and early prenatal diagnosis to achieve reducing the rate of the maternal and perinatal morbidity and mortality and optimal outcome of the pregnancy.

The ultrasound method is essential for diagnosis of PP and PA and is initial approach and one of the standard components of the basic obstetric examination, in most pregnant women. Being familiar with characteristic ultrasound appearance of both of the placental pathologies is essential for the correct prenatal diagnosis and optimal obstetric management. Evaluation of the placenta on a routine visit, is not going to prolog or make more expensive a normal ultrasound examination. Despite the fundamental role of the placenta for the pregnancy outcome, ultrasound examination of the placenta is often considered secondary to the fetus.

To conclude early prenatal diagnosis, on the base of characteristic ultrasound appearance in both PP and PA and correct obstetric management are essential for the optimal maternal and perinatal outcome.

2. GOAL AND OBJECTIVES

2.1. Aim of the study: To estimate the incidence, risk factors, ultrasound markers and ultrasound criteria, the sensitivity and specificity of the ultrasound method, optimal time for making the diagnosis and delivery in pregnancy complicated with placenta previa and placenta accreta and to estimate the diagnostic accuracy of proposed obstetric protocols of follow up and management in pregnancies complicated with placenta previa and placenta accreta.

2.2. Tasks:

1. To estimate the incidence of PP and PA in the general population.
2. To estimate the incidence of PA in general population and in high risk for PA group.
3. To define the risk factors for PP and PA and to examine the association between the incidence of PP and PA and number of prior cesarean deliveries.
4. To define the ultrasound criteria and optimal time for making the diagnosis of PP, examining placenta migration and to assess the accuracy of ultrasound markers used in diagnosis of PA.
5. To estimate the sensitivity and specificity of ultrasound method in diagnosis of PP and PA and to estimate the diagnostic accuracy of screening strategy for early prediction of placenta accreta.
6. To create a score system for diagnosis of PA.
7. To examine the average gestational age at delivery in pregnancies complicated with PP and PA and to estimate the diagnostic applicability of the optimal one used for the purpose of the study.
8. To examine the relation between the delivery blood lost in the pregnancies complicated with PP and PA and the time and method of delivery.
9. To create obstetric protocol for clinical follow up and management in pregnancies complicated with PP and PA.

3. MATERIALS AND METHODS

This was a prospective study of women with a singleton pregnancy attending for a routine hospital visit at 11-13 weeks' gestation at King's College Hospital, London, UK, between August 2013 and August 2016.

3.1. Study population

Study population of 22,604 singleton pregnancies with a live fetus and CRL of 45-84 mm. We exclude 1,130 (5%) cases because there was miscarriage, pregnancy termination or no follow-up. Final study population 21,474 singleton pregnancies for the study period.

3.2. Study design

This was a prospective study of women with a singleton pregnancy with a live fetus and CRL of 45-84 mm., attending for a routine hospital visit at 11-13 weeks' gestation. Final study population 21,474 singleton pregnancies for the study period. During this visit, patients fulfilling the following criteria – low - lying placenta, defined as the lower edge reaching to, covering or within 20 mm. from the internal cervical os, independently of previous uterine surgery were referred for follow-up. This group were defined as a study group of PP.

In this study group we defined second one – high risk group for PA. Patients fulfilling the following two criteria were referred to a specialist "Placental clinic" for further assessment : first history of uterine surgery, including Cesarean Section or myomectomy that involved opening of the uterine cavity; and, second, low – lying placenta, defined as the lower edge reaching to, covering or within 20 mm. from the internal cervical os in the case of anterior placenta and reaching to or covering the internal cervical os in the case of posterior placenta. We also designed information leaflet, which was approved by the hospital committee.

3.3. Including criteria

- singleton pregnancy with a live fetus
- CRL of 45-84 mm.
- low - lying placenta, defined as the lower placenta edge reaching to, covering or within 20 mm. from the internal cervical os, independently of previous uterine surgery

- history of uterine surgery, including Cesarean Section or myomectomy that involved opening of the uterine cavity and low – lying placenta, defined as the lower placenta edge reaching to, covering or within 20 mm. from the internal cervical os in the case of anterior placenta and reaching to or covering the internal cervical os in the case of posterior placenta

3.4. Characterization

During the first visit, as a routine hospital visit and after obtaining patient consent, we recorded maternal demographic characteristics and medical and obstetric history and carried out an ultrasound examination for measurement of fetal crown – rump length (CRL) and nuchal translucency thickness, diagnosis of major fetal defects, and placental localization. The ultrasound scan was done transabdominally and transvaginal. Gestational age was determined from CRL. Blood samples were collected for the purpose of the first trimester screening test for chromosomal abnormalities.

During this visit, patients fulfilling the following criteria – low - lying placenta, defined as the lower placenta edge reaching to, covering or within 20 mm., independently of previous uterine surgery were referred for follow-up at 12-16, 20-24, 28-32 and 34-36 weeks' gestation. This group were defined as a study group of PP. Until the examination at 34-36 weeks' gestation we used term low-lying placenta for the purpose of our study and the statistics, after this examination we used term placenta previa, defined as lower placenta edge reaching to, covering or within 20 mm. from the internal cervical os. We used this approach, firstly, because the diagnosis of placenta previa is not a diagnosis of the first half of the pregnancy, which is supported by published studies and secondly, we include the placenta with lower edge within 20 mm. from the internal cervical os in the term "placenta previa", which is also supported of the results of already published studies. This approach is also supported by the fact that there is not lots of differences in the obstetric management and the delivery is mostly cesarean delivery, in this group with lower edge within 20 mm. from the internal cervical os. In the study population of 21,474 pregnancies, 17,778 had low-lying placenta at 12-16 weeks' gestation, 2,405 had low-lying placenta at 20-24 weeks' gestation, 348 had low-lying placenta at 28-32 weeks' gestation and 150 at 34-36 weeks' gestation. Diagnosis placenta previa was done in all the cases, where the lower placenta edge was reaching to, covering or within 20 mm. from the internal cervical os at 34-36 weeks' gestation and this position did not changed at the time of delivery-planned or emergency. Diagnosis

placenta previa was done also, in all cases, where the position of the placenta and vaginal bleeding as a consequence of this position, was the main indication for emergency delivery before the planned visit at any of the gestational age (20-24, 28-32, 34-36 weeks' gestation). Pregnancy outcome was obtained from the hospital records. In our study we had 158 cases of PP. All the ultrasound examinations were performed by operators, certified by Fetal Medicine Foundation.

The delivery of prenatally diagnosed cases with PP, were done by Cesarean Section, with optimal for the aim of the study time of delivery 37+0-37+6 weeks' gestation. We had a lot of variation in this group, because: there were emergency deliveries before the optimal gestational age for delivery, different gestational age, chosen by the obstetric team or patient informed choice. We examined the average delivery blood lost in all of the cases of the group of PP, where we had could obtained information from the hospital records. Figure.1. represent the design of the study in this group.

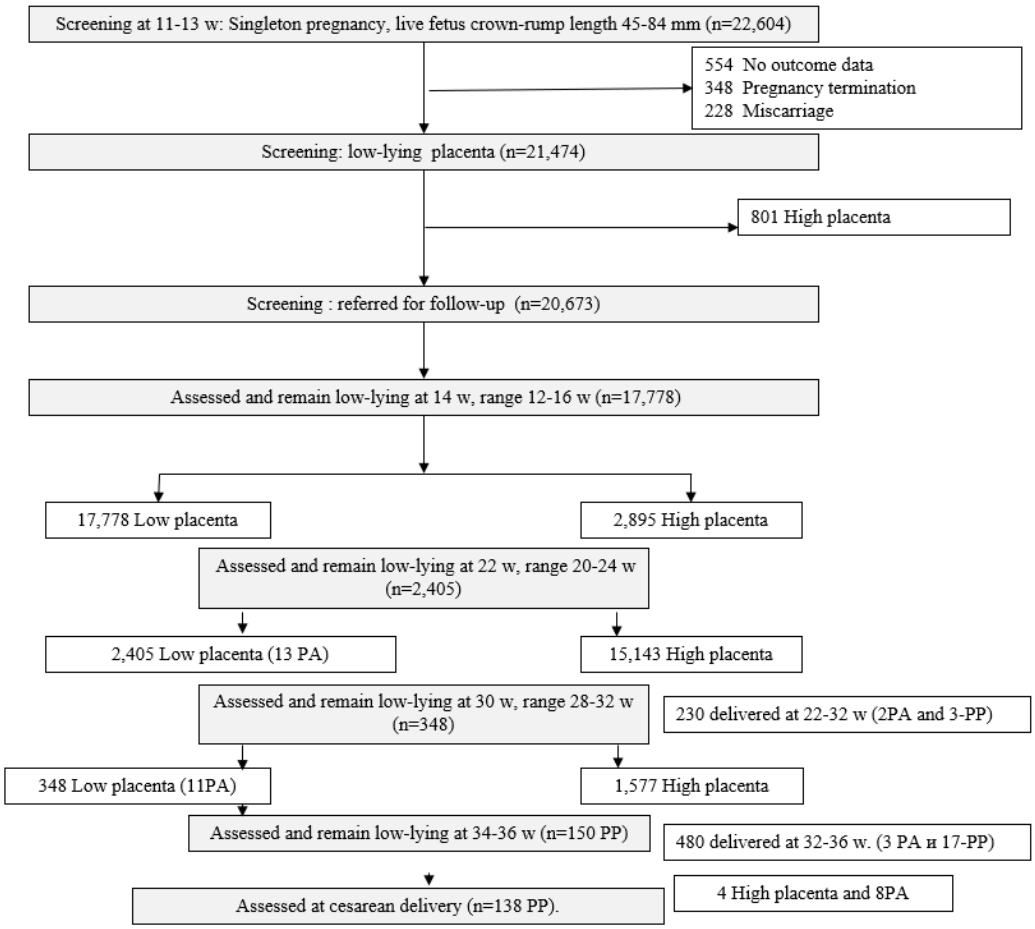


Fig.1. Design of the study in the group of placenta previa.

In this study we defined second group – high-risk group for PA. Patients fulfilling the following two criteria were referred to a specialist "Placental clinic" for further assessment : first history of uterine surgery, including Cesarean Section or myomectomy that involved opening of the uterine cavity; and, second, low – lying placenta, defined as the lower placenta edge reaching to, covering or within 20 mm. from the internal cervical os in the case of anterior placenta and reaching to or covering the internal cervical os in the case of posterior placenta. The follow-up in the "Placental clinic" was done at 12-16, 20-24 and 28-34 weeks' gestation. In the study population of 21,474 pregnancies, 2,961 (13.8%) had previous uterine surgery, 17,778 (82.8%) had low-lying placenta and 1,298 (6%) were considered to be at high-risk for PA, because of both previous uterine surgery and low-lying placenta. These high-risk pregnancies were referred to the "Placental clinic" at 14 (range 12-16) weeks' gestation. The definitive high-risk group after the first follow up in the "Placental clinic" was 1,013.

The examination in the "Placental clinic" was done by one of three operators who received training in the diagnosis of PA. In each visit we recorded the presence or absence of the following features: non-visible cesarean section scar, bladder wall interruption, thin retroplacental myometrial thickness, intraplacental lacunar spaces, retroplacental arterial-trophoblastic blood flow and 3D Power Doppler irregular placental vascularization. The diagnosis of PA was made if there were abnormalities in at least three of the above features.

In 14 cases we suspected PA, the suspicion was confirmed in subsequent visits at 20-24 and 28-34 weeks' gestation, but at the time of Cesarean Section and subsequent histopathological examination the diagnosis PA was made in only 13 of the cases. We had one false positive for PA case and the case was of a PP. In all of the cases suspected for PA we had MRI. MRI confirmed 14 cases of PA, correct diagnose was made in 13 cases and again there was one false positive case. In the case where the diagnosis was not confirmed there was difficult removal of the placenta at the time of cesarean section and hemorrhage of 1200 mL.

In the 13 cases of PA, confirmed at delivery and with histopathological examination, eight had hysterectomy, in 5 of them there was an attempt to manual removal of the placenta and in 3 of them was done hysterectomy, without an attempt to remove the placenta. The rest five cases had partial myometrial resection. We examined the cesarean blood lost in all of the cases. For optimal time of delivery we accepted 35+0-36+0. Figure.2.represent the design of the study in this group.

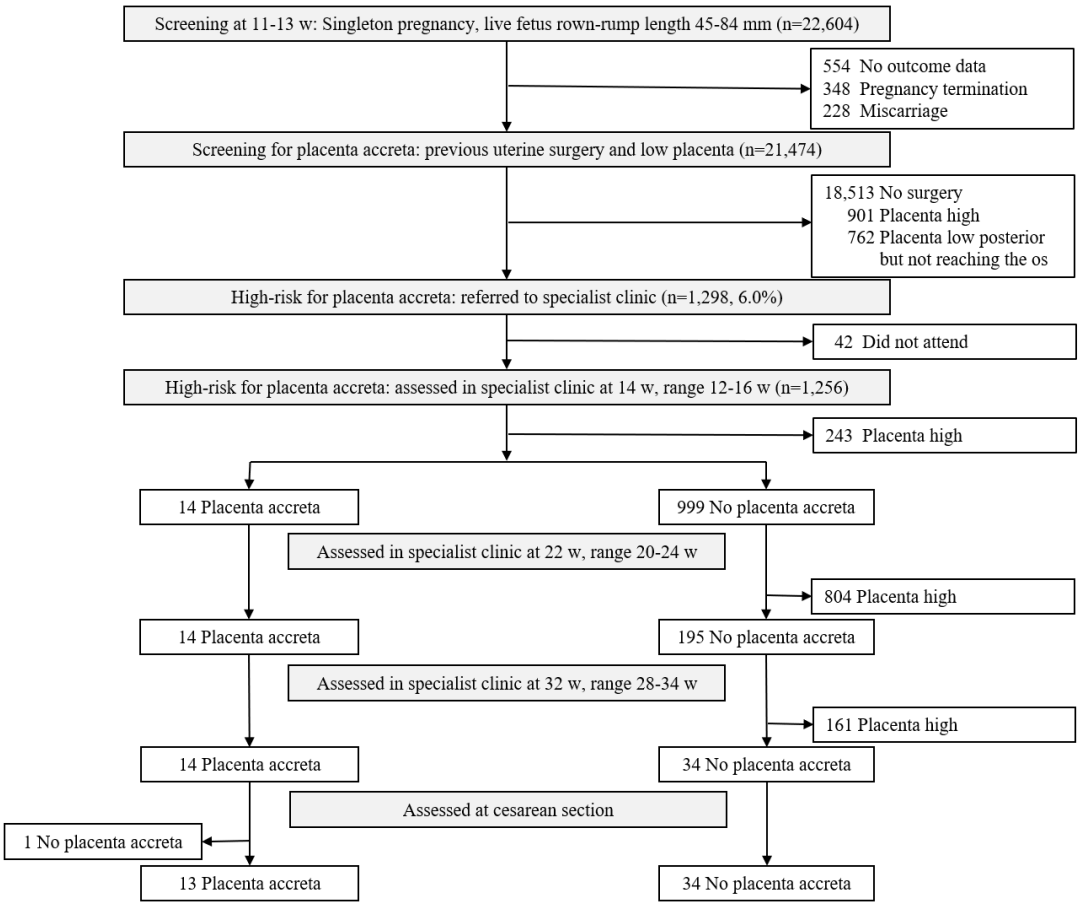


Fig.2. Design of the study in the group of PA

In both group of PP and PA, we examined the following risk factors: maternal age, ethnic disparity, method of conception, maternal smoking, gravidity (previous pregnancies), parity (previous deliveries), previous Cesarean Section, previous Myomectomy with opening of the cavity, previous uterine surgery and fetal gender. The incidence of PP and PA was examined in the general population and in the group with previous Cesarean Section. We also examined: the incidence of PA in high- risk group; the relation between the incidence of PP and PA and the number of prior cesarean deliveries; gestational age at delivery in the group of PP and PA in relation to the general population, altogether and separately; delivery blood lost in pregnancies complicated with PP and PA, in relation to pregnancies without PP and PA; average blood lost, in relation to the gestational age at delivery, in pregnancies complicated with PP – up to 36+6., between 37+0-37+6 and after 38 weeks' gestation.; average blood lost in pregnancies complicated with PP and PA, in relation to average blood lost in cesarean

delivery, without PP and PA. We examined the delivery blood lost in the group of PA according to the operative method with/without attempt of removal of the placenta.

In the primary group of low-lying placenta, defined as the lower edge of placenta reaching to, covering or within 20 mm. from the internal cervical os, independently of previous uterine surgery, we examined the incidence of low-lying placenta at 12-16, 20-24, 28-32 and 34-36 weeks‘ gestation. The aim was to optimize the time of definitive diagnose of PP.

In a separate group of 2,056, with previous Cesarean Section and low-lying placenta, we examined migration of the placenta: according to the placenta position (anterior, posterior); distance of the lower placenta edge to the internal cervical os within 20 mm., reaching to or covering and according of the degree of the covering (less or more than 20 mm.).

The sensitivity and specificity of ultrasound examination was studied in both of the groups and in the group of PP we did that at 12-16, 20-24, 28-32 and 34-36 weeks’ gestation.

Logistic regression was constructed to assess whether the eight independent variables predict in a statistically significantly way whether the patient had PA. When all eight independent variables are considered simultaneously, they predict in a statistically significant way the presence of PA and the aim was to create a score system for diagnosis of PA.

We also examined the first trimester serum b-HCG and PAPP-A in association with placenta previa and placenta accreta spectrum.

3.5. Demographic characteristics

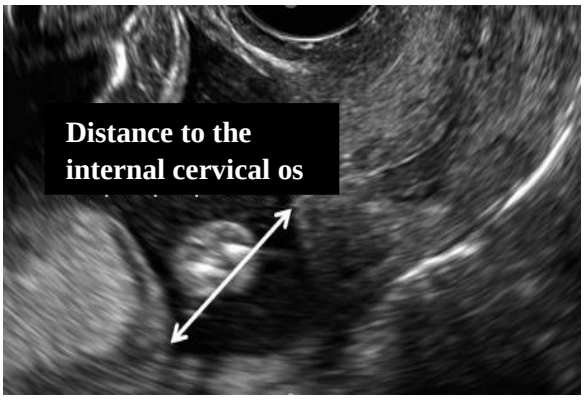
Demographic characteristics-maternal age, ethnic disparity, maternal smoking.

3.5.1. Medical history – chronic disease, previous surrgery.

3.5.2. Obstetric history-previous uterine surgery, including opening the uterine cavity (Cesarean Section, Myomectomy), methos of conception, gravidity, parity.

3.6. Diagnostic methods

Both transabdominal and transvaginal ultrasound examinations was done in the group of PP, to assess placenta position, insertion of the umbilical cord and distance between the lower placenta edge to the internal cervical os at 12-16, 20-24, 28-32 and 34-36 weeks’ gestation. Low-lying placenta was defined as the edge reaching to, covering or within 20 mm. from the internal cervical os. When the edge of the placenta was more than 20 mm. from the internal cervical os, placenta was defined as high placenta. All of the examinations were done with empty and with full bladder and without uterine contraction. (Fig.3,Fig.4)



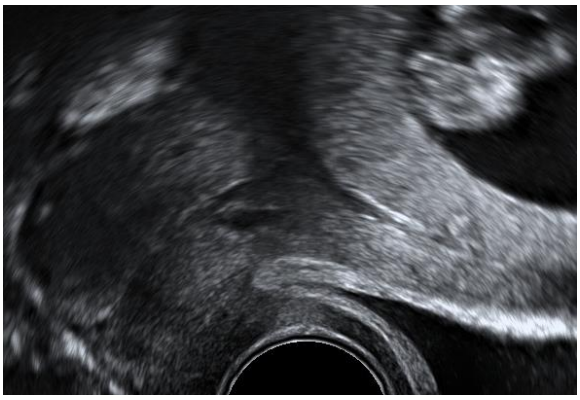


Fig.3. Distance of the lower placenta edge to the internal cervical os

Fig.4. Placenta edge covering internal cervical os

In the “Placenta clinic” both transabdominal and transvaginal ultrasound examinations at 12-16, 20-24 and 28-34 weeks’ gestation, was done, by one of three operators who received training in the diagnosis of PA. In each visit we recorded the presence or absence of the following features: non-visible cesarean section scar, bladder wall interruption, thin retroplacental myometrial thickness, intraplacental lacunar spaces, retroplacental arterial-trophoblastic blood flow and 3D Power Doppler irregular placental vascularization. The diagnosis of MAP was made if there were abnormalities in at least three of the above features.

- Placental lacunae - multiple large, irregular intraplacental sonolucent spaces (ie, placental lacunae) in the center of a lobule or cotyledon adjacent to the involved myometrium replace normal placental homogeneity and give the placenta a "moth-eaten" appearance. Placental lacunae are visible with trnsabdominal and transvaginal ultrasound examinations. Fig.5 and Fig.6 illustrates transabdominal and transvaginal image of placental lacunae, which are shown with white arrow.

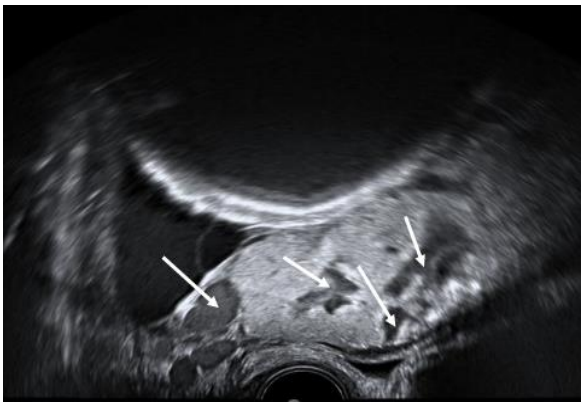


Fig.5. Placental lacunae-transvaginal ultrasound examination

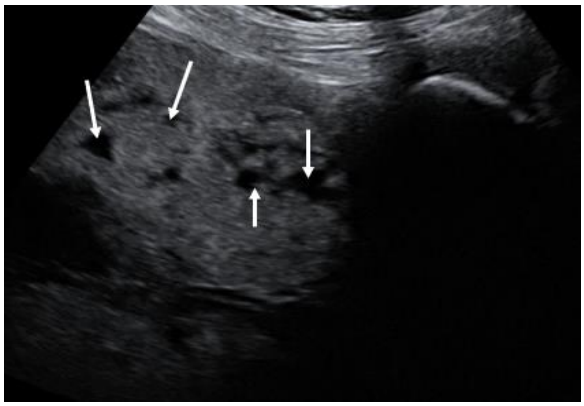


Fig.6. Placental lacunae-transabdominal ultrasound examination

- Retroplacental arterial-trophoblastic blood flow - vessels that extend from the placenta through the myometrium either into the bladder or through the serosa. For the study the pathological blood flow, was defined as a blood flow with velocity more than 20 cm/sec. Fig.7 and Fig.8 illustrate both of the ways - transabdominal and transvaginal .

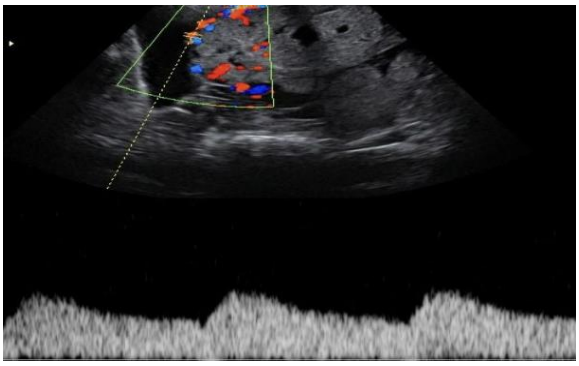


Fig.7. Retroplacental arterial-trophoblastic blood flow with transabdominal examination

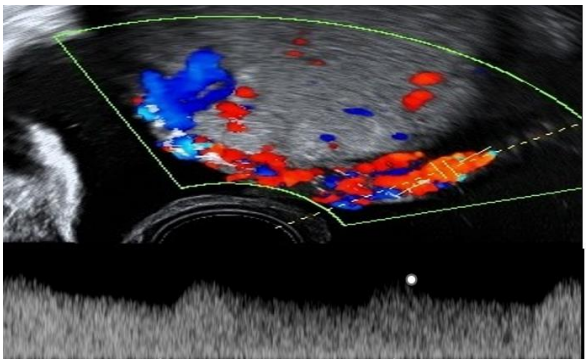


Fig.8. Retroplacental arterial-trophoblastic blood flow with transvaginal examination

- Thin retroplacental myometrial thickness – less than 1 mm. The retroplacental myometrium can be thin (<1 mm) due to either a prior hysterotomy scar or placental invasion. Fig.9 and Fig.10 illustrate transabdominal and transvaginal ultrasound examination. White arrows indicate the zone with thin myometrium.

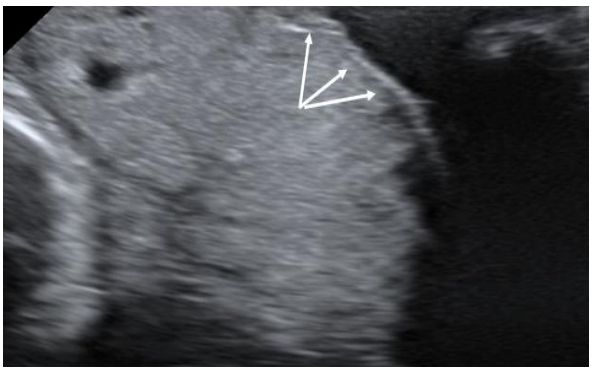


Fig.9. Myometrium less than 1 mm. – transabdominal ultrasound examination

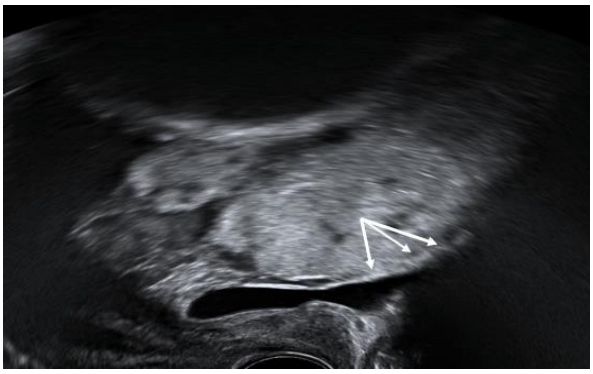


Fig.10. Myometrium less than 1 mm. - transvaginal ultrasound examination

- Non-visible cesarean section scar – sonolucent space, different in shape and size, visualized in the area of the previous Cesarean section. Fig.11 illustrate the scar from the previous Cesarean Section, pointed with white arrows.

- „Bladder wall interruption” - loss or disruption of the normally continuous white line representing the bladder wall-uterine serosa interface (termed the "bladder line") . Fig.12 illustrate “bladder wall interruption”, shown with white arrow.

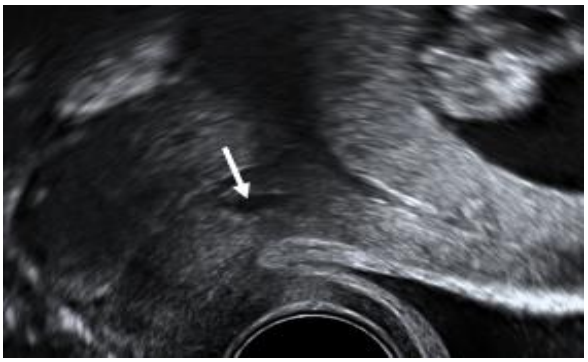


Fig.11. Cesarean Section scar

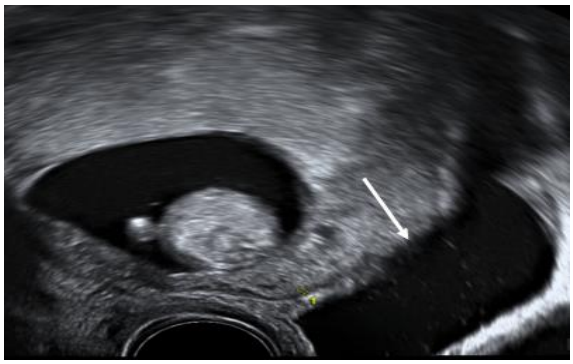
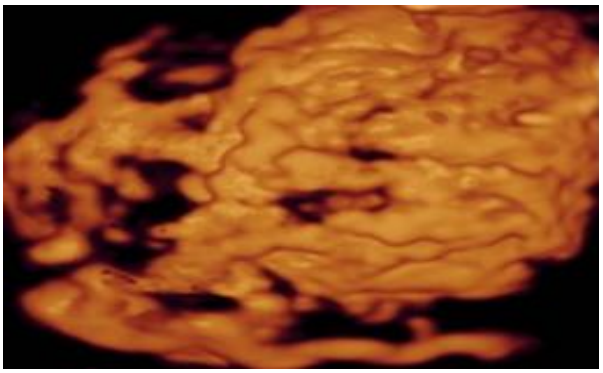


Fig.12. „Bladder wall interruption”

- 3D Power Doppler irregular placental vascularization - Fig.13 and Fig.14.



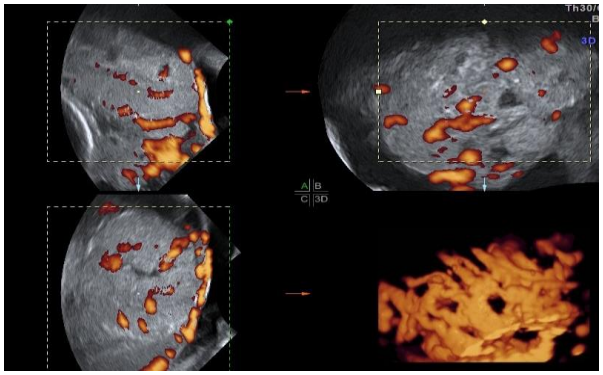


Fig.13 and Fig.14. 3D Power Doppler irregular placental vascularization

3.7. Laboratory methods

Derived for the purpose of the first trimester screening test blood samples, where examined at Harris Birthright Research Center, Kings’s College Hospital, London, UK.

3.8. Statistical methods

The data used in this dissertation was processed with SPSS 26 software and the following analyses were applied:

3.8.1. Descriptive statistics

A. Quantitative variables - mean, median, minimum, maximum, percentiles;

B. Qualitative variables (nominal and ordinal) - absolute frequencies, relative frequencies (in percentages)

C. Graphics

3.8.2. Hypotheses and dependency testing

A. One factor analysis of variance ANOVA - test to compare more than two means of independent samples. The analysis of variance is applied when we want to test whether the effect of one or several factor on another measured variable, called the result, is statistically significant.

B. Tukey HSD post-hoc statistical test - To determine which exact groups have differences, after ANOVA has revealed there is a difference

C. The Student's t-test for two independent samples - to compare the mean values and the distribution of quantitative variables between two groups

D. Chi-square test or Fisher's exact test - seek a relationship between two qualitative variables

E. Kramer's coefficient - to measure the strength of a proven relationship between two variables

F. Discriminant Analysis and Logistic Regression - to determine the weighting of factors in the development of a score system

The critical level of significance used in this work is $\alpha = 0.05$. A relationship or regularity can be claimed when the P value is less than 0.05.

4. RESULTS

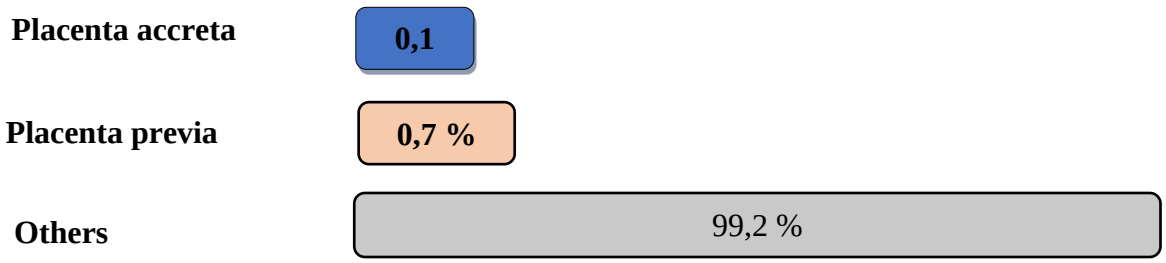
4.1. Incidence of PA and PP

4.1.1. Incidence of PP and PA in the general population

Table 1. Incidence of PP and PA in the general population

Placenta type	Cases (n)	Percentage %
PA	**13**	**0,1%**
PP	**158**	**0,7%**
Others	**21303**	**99,2%**
Total	**21474**	**100,0%**

Graph 1. Incidence of PP and PA in the general population



In the considered cohort of 21,474 patients, the incidence of both placental pathologies was found to be as follows: placenta previa 0,7%, placenta accreta 0,1%. The final number of cases of placenta previa 158 - these are the cases in which the position of the leading placental edge was registered at less than 20mm. from the internal cervical os in the last ultrasound examination and until the time of delivery, in the case of planned delivery or this position and bleeding as a result, are registered in the hospital data base as the main indication for emergency delivery. The final number of cases with placenta accreta was determined at the time of delivery and after available confirmation by histopathological examination. In our study, the final number of cases of PA-13.

4.1.2. Incidence of PP and PA among the patients with and without previous Cesarean Section

Table 2. Incidence of PP and PA among the patients with and without previous Cesarean Section

Placenta type	Previous Cesarean Section			
	Yes		No	
	Cases (n)	Percentage (%)	Cases (n)	Percentage (%)
PA	**13**	**0,4%**	**0**	**0,0%**
PP	**39**	**1,3%**	**119**	**0,6%**
Others	**2904**	**98,2%**	**18399**	**99,4%**
Total	**2956**	**100,0%**	**18518**	**100,0%**

Graph 2. Incidence of PP and PA among the patients with and without previous Cesarean Section

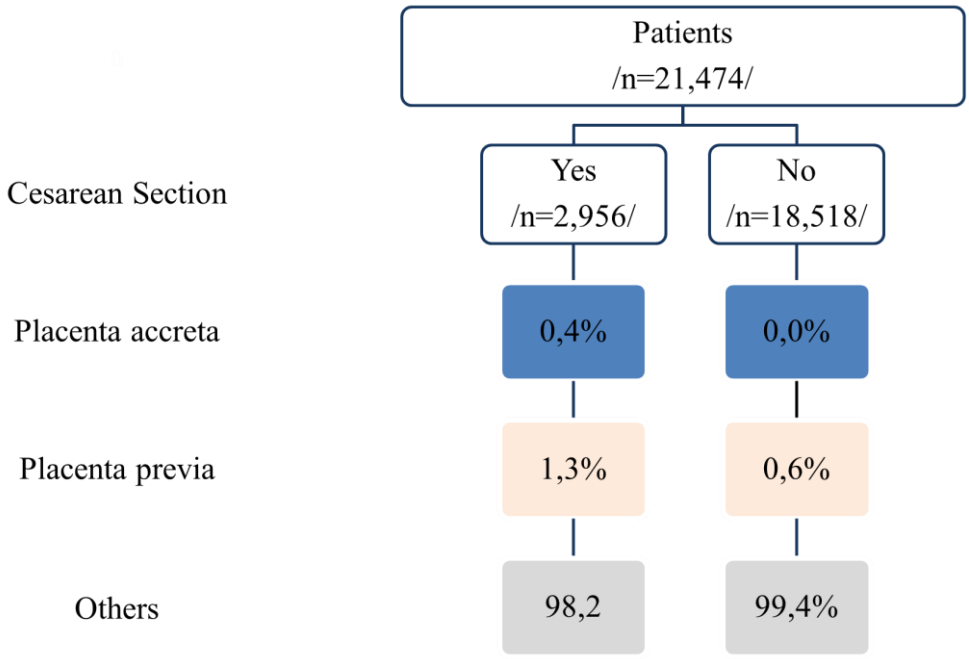


Table.2 and Graph.2. illustrate the incidence of PP and PA among the patients with and without previous Cesarean Section . The number of the cases with previous Cesarean section are 2,956 случаи. The results show that the incidence of PP and PA is higher in the group with previous Cesarean Section.

4.1.3. Incidence of PP and PA in the high-risk for PA group

Table 3. Incidence of PP and PA in the high-risk for PA group

Placenta type	High risk patients	
	Cases (n)	Percentage (%)
PA	**13**	**1,3%**
PP	**35**	**3,5%**
Others	**965**	**95,3%**
Total	**1013**	**100,0%**

Graph 3. Incidence of PP and PA in the high-risk for PA group

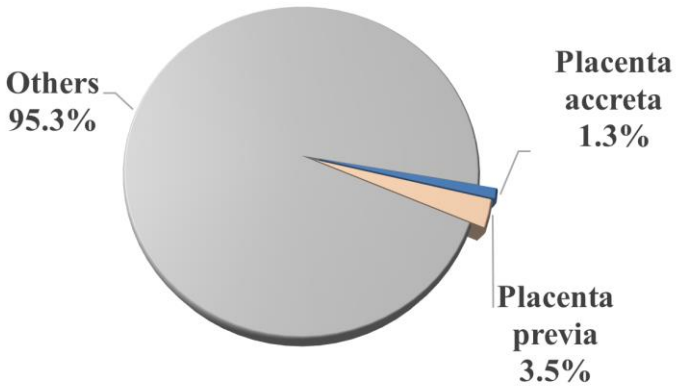


Table.3 and Graph.3 illustrate the incidence of PP and PA in the high-risk for PA group. This is the group with history of uterine surgery, including Cesarean Section and/or myomectomy that involved opening of the uterine cavity and low – lying placenta, defined as the leading placenta edge reaching to, covering or within 20 mm. from the internal cervical os in the case of anterior placenta and reaching to or covering the internal cervical os in the case of posterior placenta.

4.2. Relation between the incidence of PP and PA and the number of prior cesarean deliveries

Table 4. Relation between the incidence of PP and PA and the number of prior cesarean deliveries

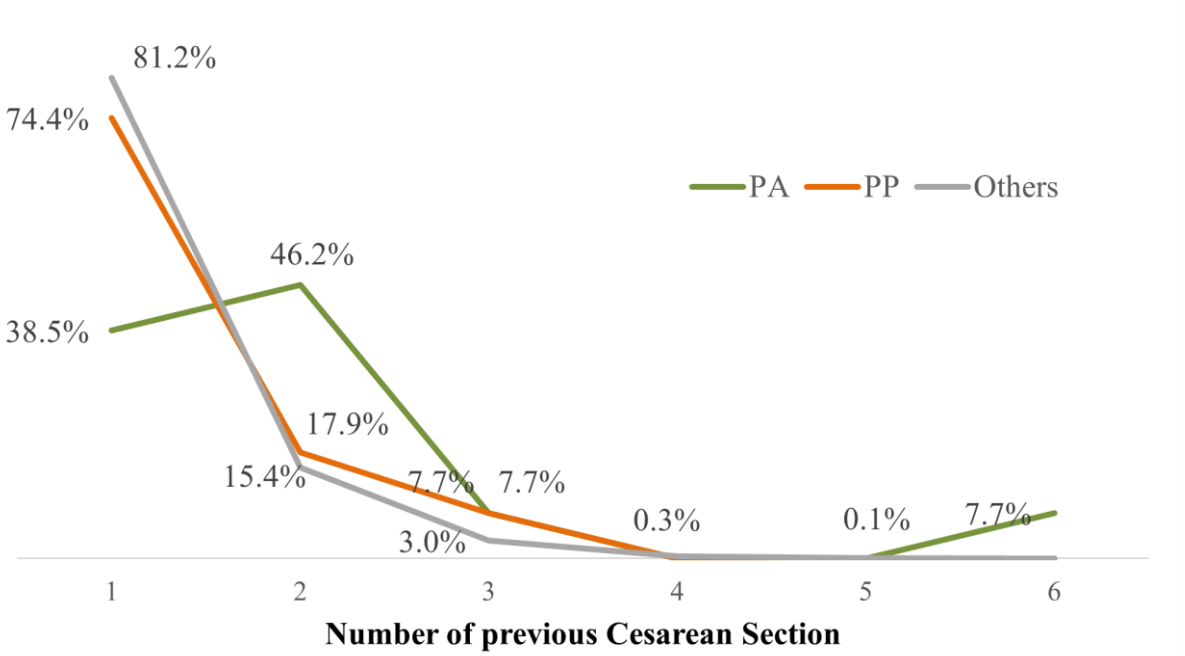
Previous Cesarean Section (n)	Placenta type					
	PA		PP		Others	
	n	%	n	%	n	%
first	5	38,5%	29	74,4%	2358	81,2%
second	6	46,2%	7	17,9%	447	15,4%
third	1	7,7%	3	7,7%	87	3,0%
fourth	0	0,0%	0	0,0%	10	0,3%
fifth	0	0,0%	0	0,0%	2	0,1%
sixth	1	7,7%	0	0,0%	0	0,0%
Total	13	100,0%	39	100,0%	2904	100,0%
Median	2,0		1,3		1,2	
F-statistic (F)	14,664					
Significant (p)	<0,001					

In order to determine whether there is a correlation between the number of Cesarean Sections and the presence of placenta previa and placenta accreta, we have applied one factor analysis of variance (ANOVA). The p-level ($p<0,001$) is lower than the level of significance $\alpha=0,05$, which means that we can assume a correlation between the number of Cesarean Sections and types of placenta. With the help of the Tukey test (Tukey HSD) we will determine which exact types of placenta show a difference:

Placenta type		P	Statistically significance
PA	PP	0,001	yes
PA	Others	0,001	yes
PP	Others	0,567	no

There is no statistically significant difference between PP compared to the number of previous Cesarean Section ($p=0,567$, which is more than от 0,05). For PA we have a statistically significant difference between PP and the rest, due to the P-values close to 0 for both comparisons.

Graph 4. Relation between the incidence of PP and PA and the number of prior cesarean deliveries



4.3. Risk factors for PP and PA

4.3.1. Maternal age and the risk of PP and PA

Table 5. Midian maternal age in relation to the placenta type

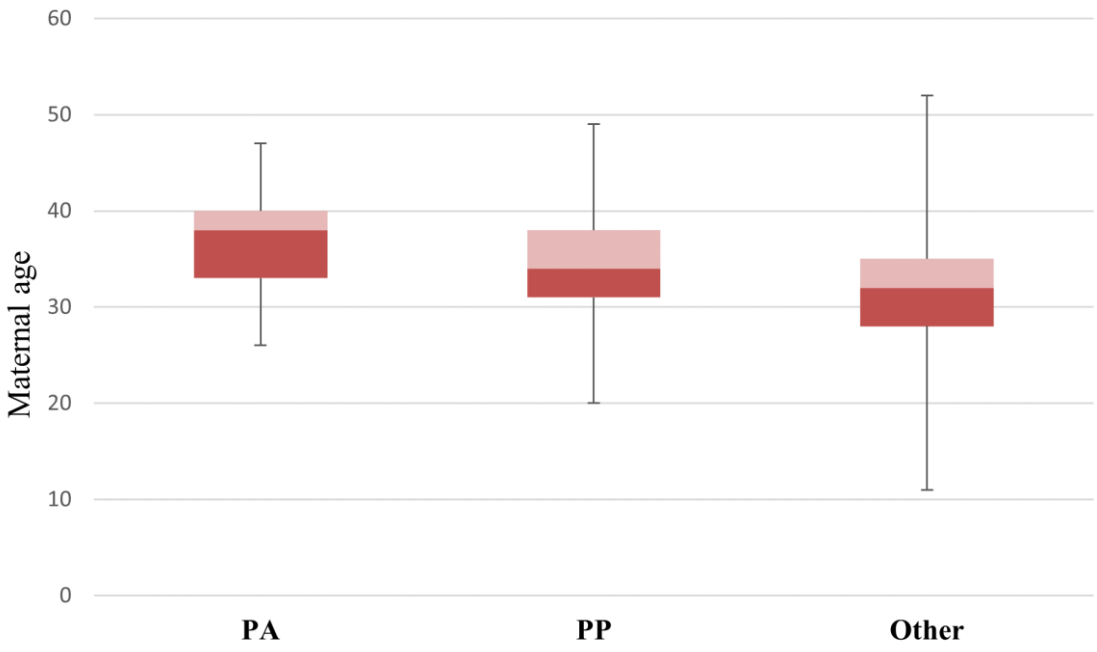
	Placenta type		
	PA	PP	Others
Number (n)	**13**	**158**	**21303**
Average	**37,2**	**34,2**	**31,5**
Standard deviation	**5,2**	**4,9**	**5,3**
Median	**38**	**34**	**32**
Minimal	**27**	**18**	**14**
Maximal	**47**	**49**	**52**

We will use the Student's t-test for two independent samples to check if there are differences in the average age for the different placentas

Placenta type		P	Statistically significance
PA	**PP**	**0,035**	**yes**
PA	**Others**	**0,002**	**yes**
PP	**Others**	**0,001**	**yes**

For the three types of placenta we have statistically significant differences (for all three p<0,05)- the highest average age is for PA (37.2 years), followed by PP (34.2 years). In conclusion maternal age is a risk factor for PP and PA.

Графика 5. Maternal age to the placenta type – PP, PA and others



4.3.2. Ethnic disparity and the risk of PP and PA

A. Ethnic disparity and the risk of PP

The use of the term "race" in the 21st century has become problematic, therefore the term used in our study is ethnic disparity.

Table 6. Ethnic disparity and the risk of PP

PP	Ethnic disparity			Statistic	
	Caucasian	Negroid	Others	X^2	p
n	**14022**	**4983**	**2469**	**1,809**	**0,405**
Yes	**0,8%**	**0,6%**	**0,9%**		
No	**99,2%**	**99,4%**	**99,1%**		
Total	**100,0%**	**100,0%**	**100,0%**		

The $\chi 2$ analysis did not determine difference in the incidence of PP among the various ethnicities - p=0,405, which is higher than α (α=0,05). Ethnic disparity is not a risk factor for PP.

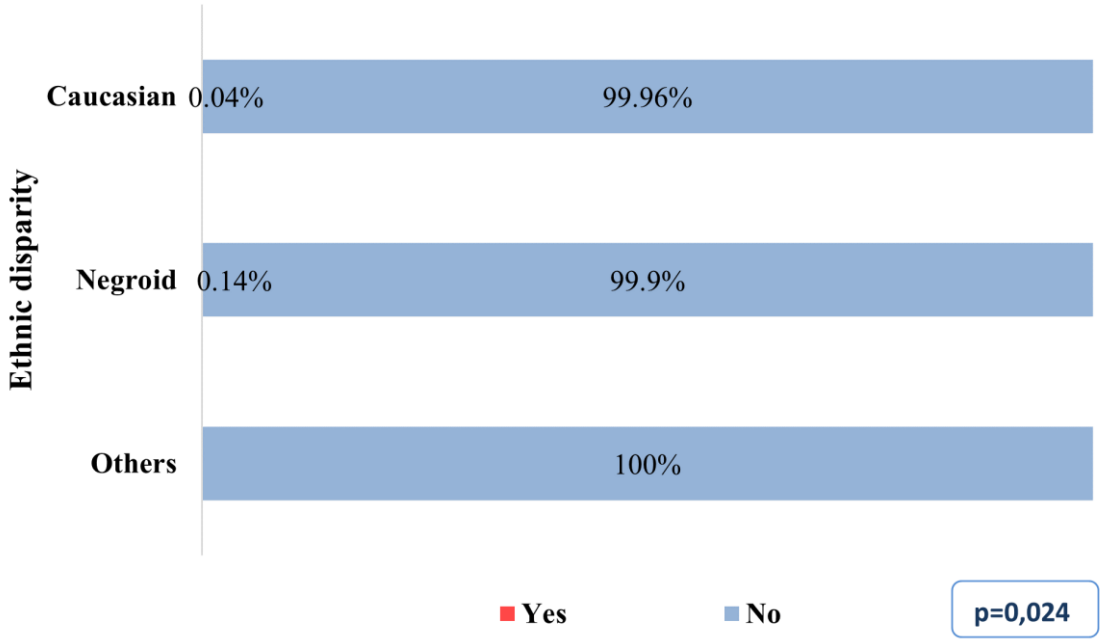
B. Ethnic disparity and the risk of PA

Table 7. Ethnic disparity and the risk of PA

PA	Ethnic disparity			Statistic			
	Caucasian	Negroid	Others	X^2	p	V	V(p)
n	**14022**	**4983**	**2469**	**7,489**	**0,024**	**0,019**	**0,024**
Yes	**0,04%**	**0,14%**					
No	**99,96%**	**99,86%**	**100,0%**				
Total	**100,0%**	**100,0%**	**100,0%**				

The $\chi 2$ analysis determined a difference in the PA incidence depending on ethnicity - p<0,024, which is lower than α. Cramer's coefficient (V=0,019) is statistically significant (V(p)<0,024) and shows a minor correlation between the two variables. In our population negroid ethnic origin is a risk factor for PA.

Graph 6. Ethnic disparity and the risk of PA



4.3.3. Conception type (ART/spontaneous) and the risk of PP and PA

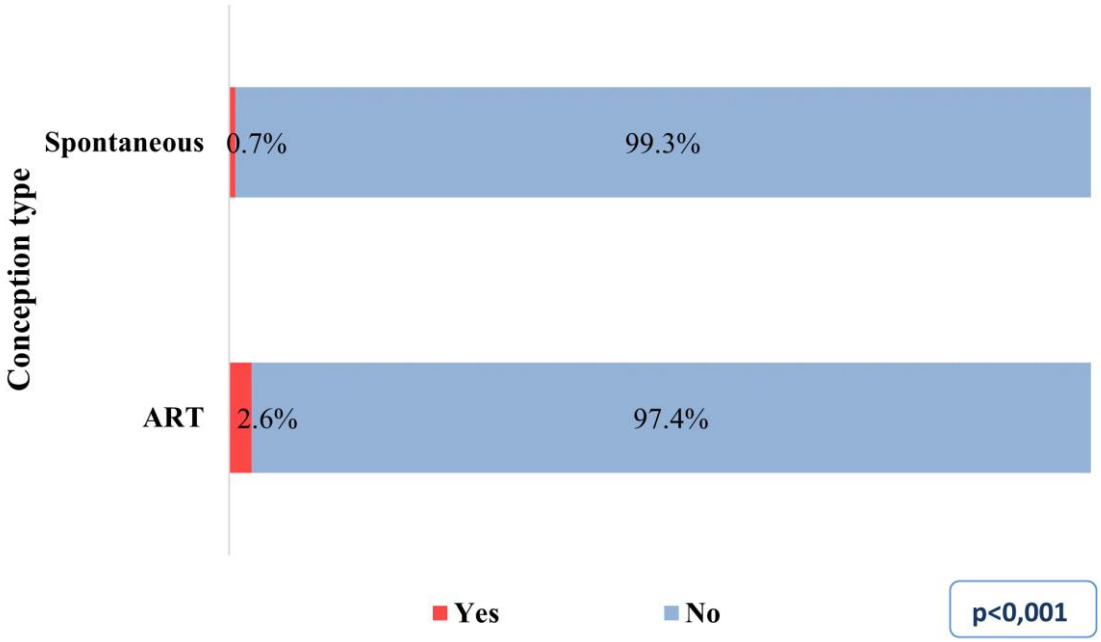
A. Conception type (ART/spontaneous) and the risk of PP

Table 8. Conception type and the risk of PP

PP	Conception type		Statistic			
	ART	Spontaneous	X^2	p	V	V(p)
n	**764**	**20710**	**38,42**	**0,001**	**0,042**	**0,001**
Yes	**2,6%**	**0,7%**				
No	**97,4%**	**99,3%**				
Total	**100,0%**	**100,0%**				

The χ2 analysis determined a difference in the PP incidence depending on the conception method – p<0,001, which is lower than α. Cramer's coefficient (V=0,042) is statistically significant (V(p)<0,001) and shows a minor correlation between the two variables. In conclusion, ART is a risk factor for PP.

Graph 7. Conception type and the risk of PP



B. Conception type (ART/spontaneous) and the risk of PA

Table 9. Conception type and the risk of PA

PA	Conception type		Statistic	
	ART	Spontaneous	X^2	p
n	**764**	**20710**	**0,480**	**0,624**
Yes		**0,1%**		
No	**100,0%**	**99,9%**		
Total	**100,0%**	**100,0%**		

The $\chi 2$ analysis did not determine difference in the incidence of PA depending on the conception method - p=0,624, which is higher than α (α=0,05).

4.3.4. Maternal smoking and the risk of PP and PA

A. Maternal smoking and the risk of PP

Table 10. Maternal smoking and the risk of PP

PP	Maternal smoking		Statistic	
	No	Yes	X^2	p
n	**20515**	**959**	**0,001**	**0,983**
Yes	**0,7%**	**0,7%**		
No	**99,3%**	**99,3%**		
Total	**100,0%**	**100,0%**		

The χ2 analysis did not determine difference in the incidence of PP among smokers and non-smokers - p=0,983, which is higher than α (α=0,05). Maternal smoking is not a risk factor for PP.

B. Maternal smoking and the risk of PP

Table 11. Maternal smoking and the risk of PA

PA	Maternal smoking		Statistic	
	No	Yes	X^2	p
n	**20515**	**959**	**0,317**	**0,448**
Yes	**0,1%**	**0,1%**		
No	**99,9%**	**99,9%**		
Общо	**100,0%**	**100,0%**		

The χ2 analysis did not determine difference in the incidence of PA among smokers and non-smokers - p=0,448, which is higher than α (α=0,05). Maternal smoking is not a risk factor for PA.

4.3.5. Previous pregnancies (gravidity) and the risk of PP and PA

Table 12. Average numbers of previous pregnancies according to the placenta type and gravidity as a risk factor for PP and PA

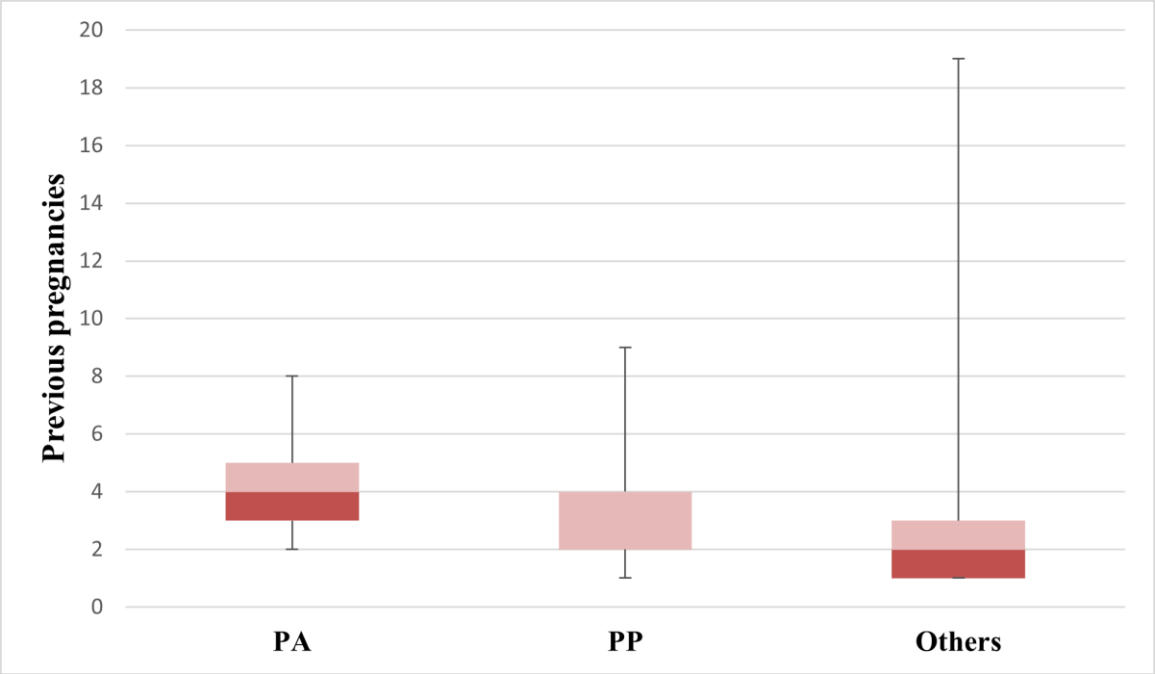
	Placenta type		
	PA	PP	Others
Number (n)	**13**	**158**	**21303**
Average	**4,3**	**2,8**	**2,4**
Standard deviation	**1,8**	**1,7**	**1,5**
Median	**4**	**2**	**2**
Minimal	**2**	**1**	**1**
Maximal	**8**	**9**	**19**

We will use the Student's t-test for two independent samples to check if there are differences for the average number of previous pregnancies between the different placentas.

Placenta type		P	Statistically significance
PA	**PP**	**0,003**	**yes**
PA	**Others**	**0,001**	**yes**
PP	**Others**	**0,001**	**yes**

For the three types of placenta we can observe statistically significant differences (all three $p<0,05$) – the highest average number of previous pregnancies is for PA (4,3), followed by PP (2,8). In conclusion gravidity is a risk factor for both - PP and PA.

Graph 8. Number of previous pregnancies according to the placenta type



4.3.6. Previous deliveries (parity) and the risk of PP and PA

A. Previous deliveries (parity) and the risk of PP

Table 13. Previous deliveries (parity) and the risk of PP

PP	Previous pregnancies		Statistic	
	No	Yes	X^2	p
n	**10184**	**11290**	**2,522**	**0,111**
Yes	**0,6%**	**0,8%**		
No	**99,4%**	**99,2%**		
Total	**100,0%**	**100,0%**		

The χ2 analysis did not determine difference in the incidence of PP among women who have given and who have not given birth - p=0,111, which is higher than α (α=0,05).

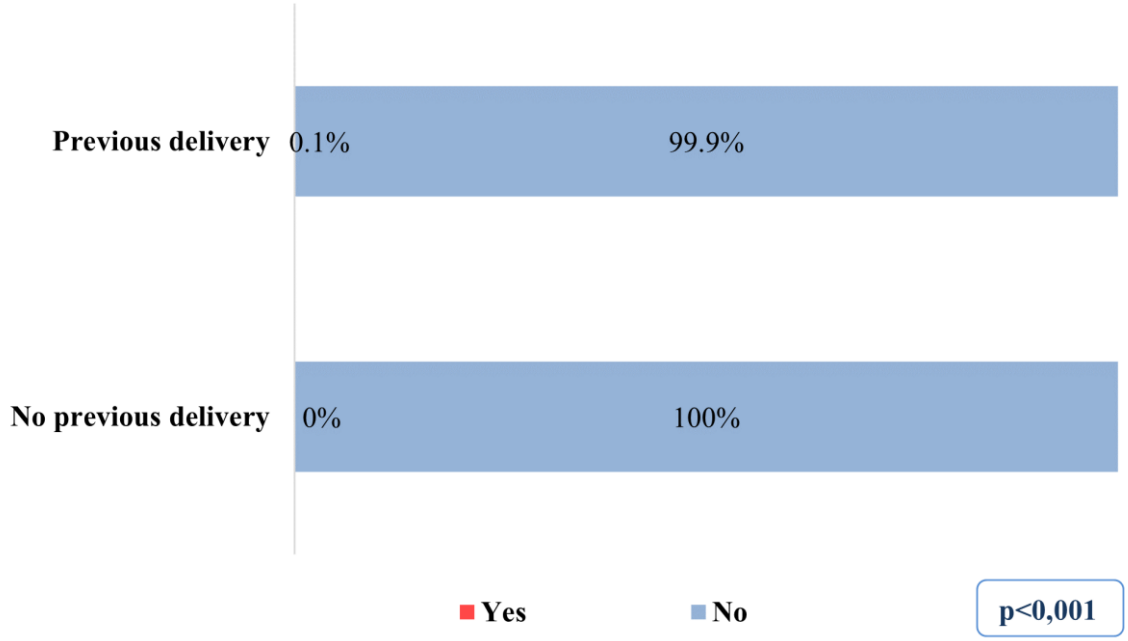
B. Previous deliveries (parity) and the risk of PA

Table 14. Previous deliveries (parity) and the risk of PA

PA	Previous deliveries		Statistic			
	No	Yes	X^2	p	V	V(p)
n	**10184**	**11290**	**11,734**	**0,001**	**0,023**	**0,001**
Yes		**0,1%**				
No	**100,0%**	**99,9%**				
Total	**100,0%**	**100,0%**				

The $\chi 2$ analysis determine a difference in the PA incidence depending on whether women have given birth or have not given birth – $p<0,001$, and is lower than α. Cramer's coefficient ($V=0,023$) is statistically significant ($V(p)<0,001$) and shows a minor correlation between the two variables.

Graph 9. Previous deliveries (parity) and the risk of PA



4.3.7. Previous Cesarean Section and the risk of PP and PA

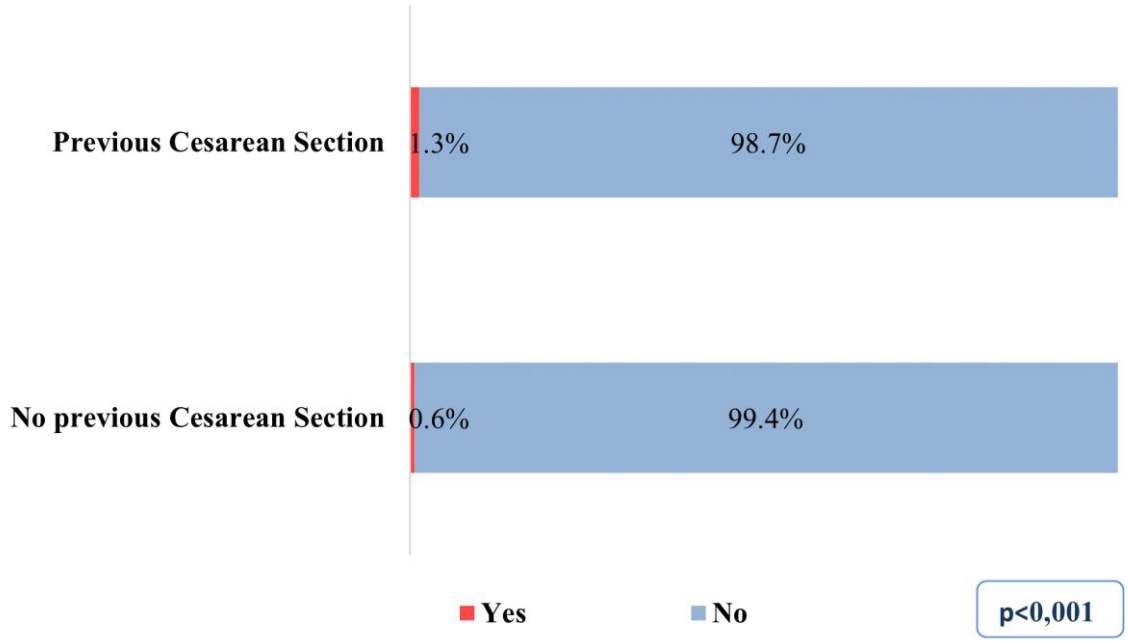
A. Previous Cesarean Section and the risk of PP

Table 15. Previous Cesarean Section and the risk of PP

PP	Previous Cesarean Section		Statistic			
	Yes	No	X^2	p	V	V(p)
n	**2956**	**18518**	**15,984**	**0,001**	**0,027**	**0,001**
Yes	**1,3%**	**0,6%**				
No	**98,7%**	**99,4%**				
Total	**100,0%**	**100,0%**				

The χ2 analysis determine a difference in the PP incidence depending on whether there was a previous Cesarean Section - p<0,001, and is lower than α. Cramer's coefficient (V=0,027) is statistically significant (V(p)<0,001) and shows a minor correlation between the two variables. Previous Cesarean Section is a risk factor for PP.

Graph 10. Previous Cesarean Section and the risk of PP



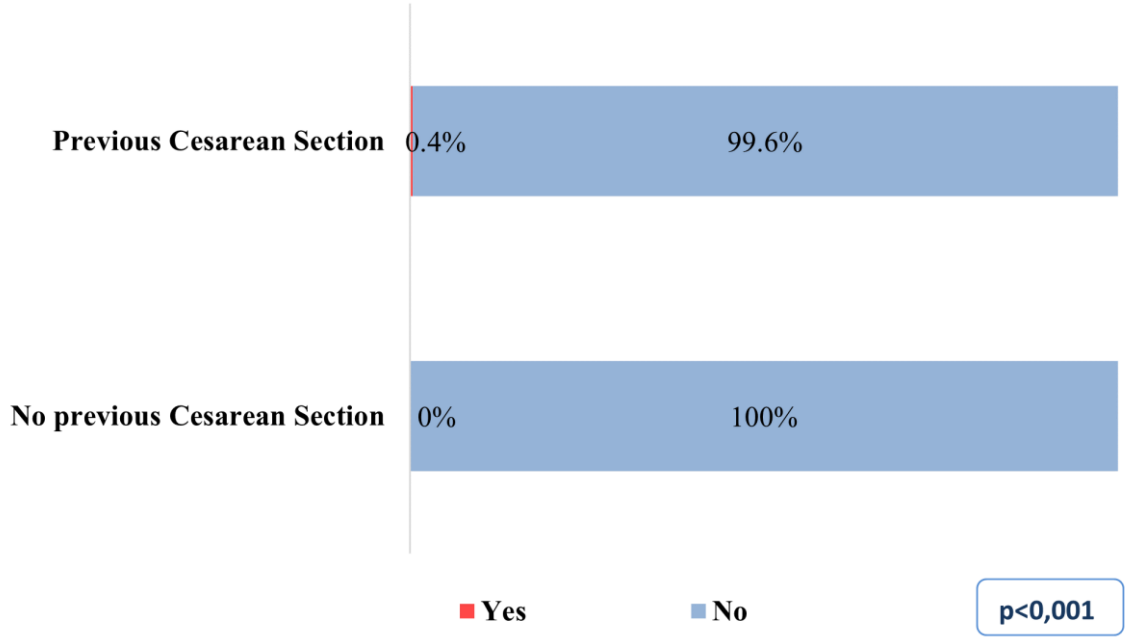
B. Previous Cesarean Section and the risk of PA

Table 16. Previous Cesarean Section and the risk of PA

PA	Previous Cesarean Section		Statistic			
	Yes	No	X^2	p	V	V(p)
n	**2956**	**18518**	**81,488**	**0,001**	**0,062**	**0,001**
Yes	**0,4%**					
No	**99,6%**	**100,0%**				
Total	**100,0%**	**100,0%**				

The $\chi 2$ analysis determined a difference in the PA incidence depending on whether there was a previous Cesarean Section – $p<0,001$, which is lower than α. Cramer's coefficient ($V=0,062$) is statistically significant ($V(p)<0,001$) and shows a minor correlation between the two variables. Previous Cesarean Section is a risk factor for PA.

Graph 11. Previous Cesarean Section and the risk of PA



4.3.8. Previous Myomectomy and the risk of PP and PA

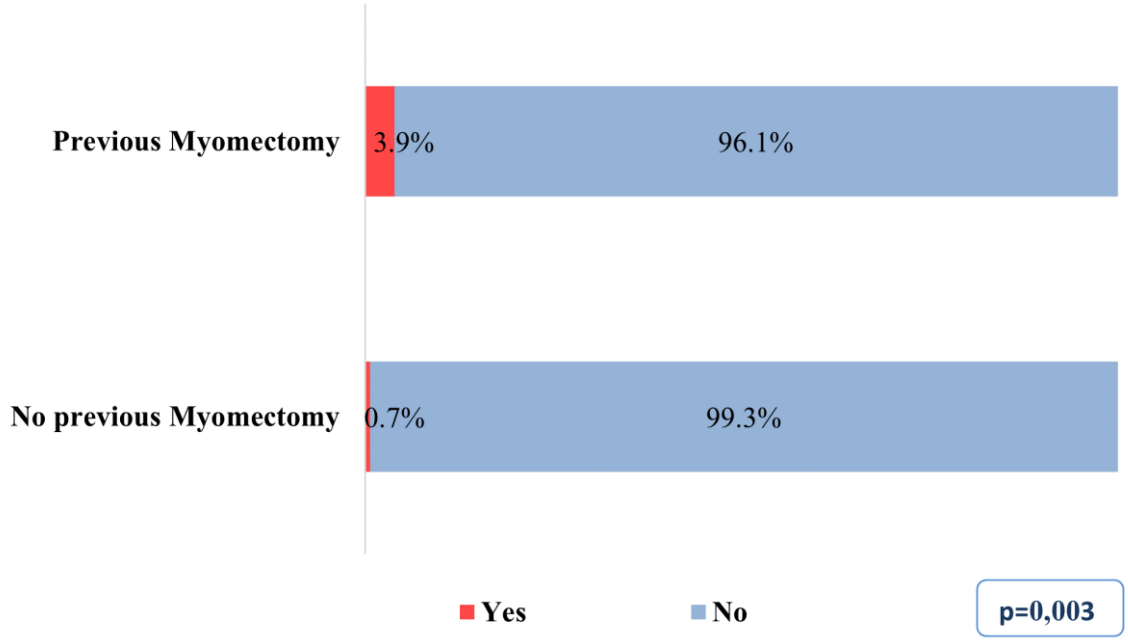
A. Previous Myomectomy and the risk of PP

Table 17. Previous Myomectomy and the risk of PP

PP	Myomectomy		Statistic			
	Yes	No	X^2	p	V	V(p)
n	**128**	**21346**	**17,722**	**0,003**	**0,029**	**0,001**
Yes	**3,9%**	**0,7%**				
No	**96,1%**	**99,3%**				
Total	**100,0%**	**100,0%**				

The χ2 analysis determined a difference in the PP incidence in relation to myomectomy surgery - p<0,003, which is lower than α. Cramer's coefficient (V=0,029) is statistically significant (V(p)<0,001) and shows a minor correlation between the two variables. Previous myomectomy is a risk factor for PP.

Graph 12. Previous Myomectomy and the risk of PP



B. Previous Myomectomy and the risk of PA

Table 18. Previous Myomectomy and the risk of PA

PA	Myomectomy		Statistic	
	Yes	No	X^2	p
n	**128**	**21346**	**0,078**	**0,780**
Yes		**0,1%**		
No	**100,0%**	**99,9%**		
Total	**100,0%**	**100,0%**		

The χ2 analysis did not determine difference in the incidence of PA in relation to myomectomy surgery - p=0,780, which is higher than α (α=0,05).

4.3.9. Previous uterine surgery (Cesarean Section and/or myomectomy) and the risk of PP and PA

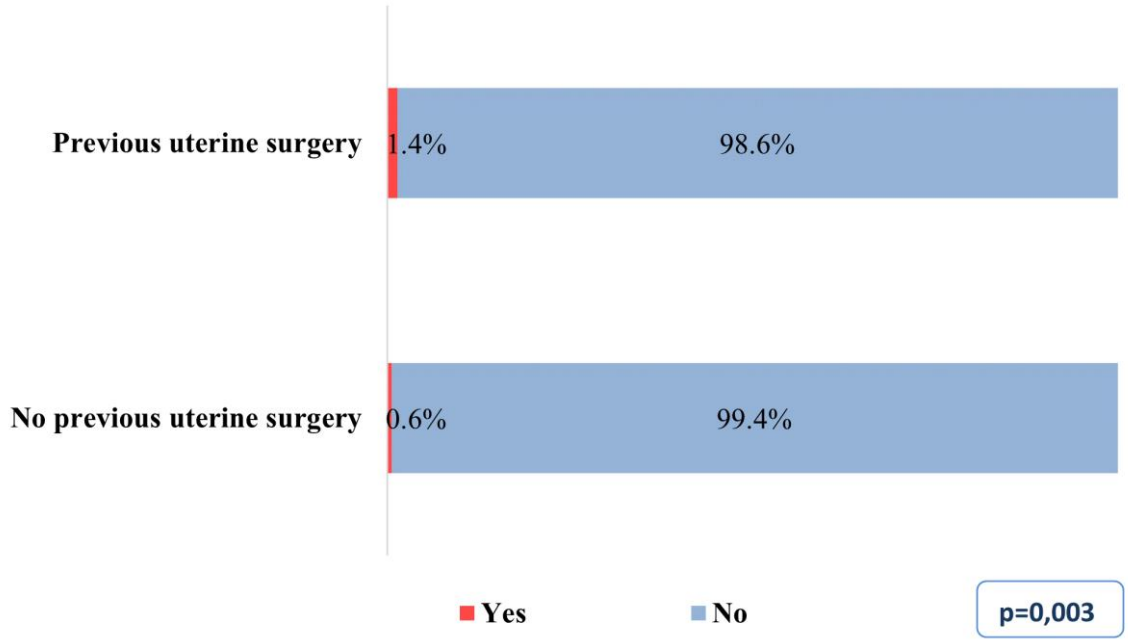
A. Previous uterine surgery (Cesarean Section and/or myomectomy) and the risk of PP

Table 19. Previous uterine surgery (Cesarean Section and/or myomectomy) and the risk of PP

PP	Previous uterine surgery		Statistic			
	Yes	No	X^2	p	V	V(p)
n	**2961**	**18513**	**17,793**	**0,001**	**0,029**	**0,001**
Yes	**1,4%**	**0,6%**				
No	**98,6%**	**99,4%**				
Total	**100,0%**	**100,0%**				

The χ2 analysis determined a difference in the PP incidence depending on whether there was a previous uterine surgery - p<0,001, which is lower than α. Cramer's coefficient (V=0,029) is statistically significant (V(p)<0,001) and shows a minor correlation between the two variables.

Graph 13. Previous uterine surgery (Cesarean Section and/or myomectomy) and the risk of PP



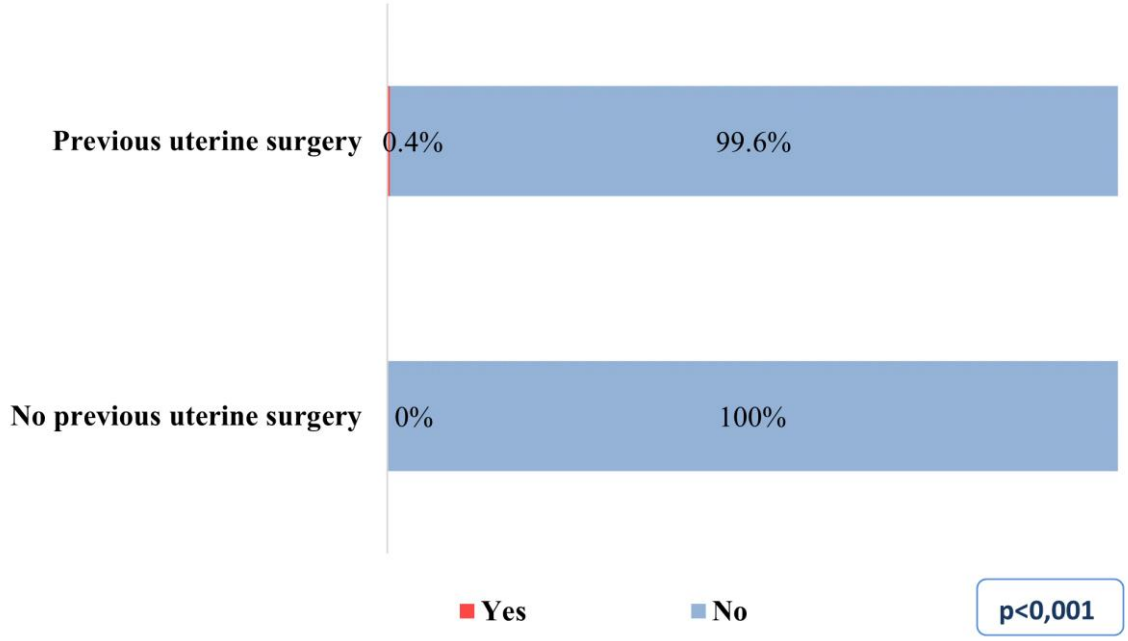
B. Previous uterine surgery (Cesarean Section and/or myomectomy) and the risk of PA

Table 20. Previous uterine surgery (Cesarean Section and/or myomectomy) and the risk of PA

PA	Previous uterine surgery		Statistic			
	Yes	No	X^2	p	V	V(p)
n	**2961**	**18513**	**81,329**	**0,001**	**0,062**	**0,001**
Yes	**0,4%**					
No	**99,6%**	**100,0%**				
Total	**100,0%**	**100,0%**				

The χ2 analysis determined a difference in the PA incidence depending on whether there was a previous operation– p<0,001, which is lower than α. Cramer's coefficient (V=0,061) is statistically significant (V(p)<0,001) and shows a minor correlation between the two variables.

Graph 14. Previous uterine surgery (Cesarean Section and/or myomectomy) and the risk of PA



4.3.10. Fetal gender and the risk of PP and PA

A. Fetal gender and the risk of PP

Table 21. Fetal gender and the risk of PP

PP	Fetal gender		Statistic	
	female	male	X^2	p
n	**10447**	**10989**	**2,553**	**0,111**
Yes	**0,6%**	**0,8%**		
No	**99,4%**	**99,2%**		
Total	**100,0%**	**100,0%**		

The χ2 analysis did not determine difference in the incidence of PP in relation to the gender of the fetus - p=0,111, which is higher than α.

B. Fetal gender and the risk of PA

Table 22. Fetal gender and the risk of PP

PA	Fetal gender		Statistic	
	female	male	X^2	p
n	**10447**	**10989**	**0,550**	**0,583**
Yes	**0,05%**	**0,07%**		
No	**99,95%**	**99,93%**		
Total	**100,0%**	**100,0%**		

The $\chi 2$ analysis did not determine difference in the incidence of PA in relation to the gender of the fetus - p=0,583, which is higher than α.

4.4. Gestational age at delivery in pregnancies complicated with PP and PA, in relation to pregnancies without PP and PA

4.4.1. Gestational age at delivery in pregnancies complicated with PP and PA separately, in relation to pregnancies without PP and PA

Table 23. Average gestational age at delivery in relation to the placenta type

	Placenta type		
	PA	PP	Others
Cases (n)	**13**	**158**	**21285**
Average	**35,7**	**37,6**	**39,6**
Standard deviation	**2,86**	**2,20**	**1,90**
Median	**37**	**38**	**40**
Minimal	**29**	**26**	**21**
Maximal	**39**	**41**	**45**

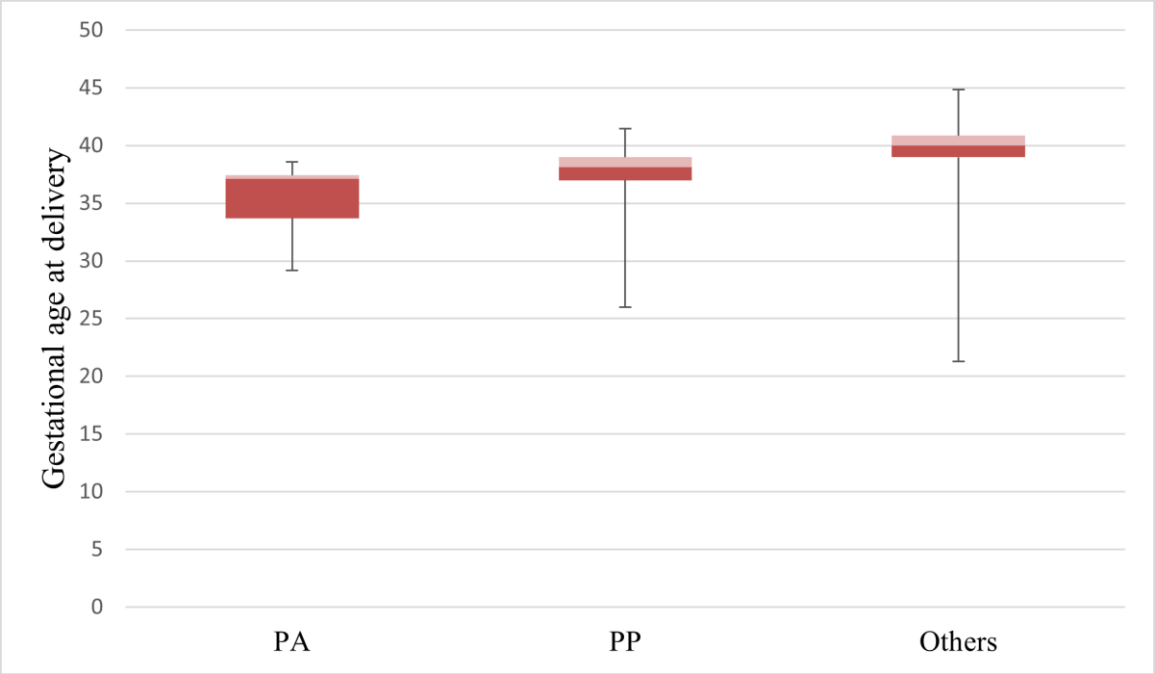
We will use the Student's t-test for two independent samples to check if there are differences between the average gestational age at birth for the different placentas.

Placenta type		P	Statistically significance
PA	**PP**	**0,003**	**yes**
PA	**Others**	**0,001**	**yes**
PP	**Others**	**0,001**	**no**

For all three types of placenta, we have statistically significant differences (for all three $p<0.05$) – the average gestational age at birth is lowest in PA (35,7 weeks' gestation), followed by PP (37,6 weeks' gestation).

The optimal time of delivery, adopted for the aim of the study, was 37+0 - 37+6 weeks' gestation for PP cases and 35+0 - 36+0 weeks' gestation for PA cases. This applies only for the cases, where there were no complications. In all cases with complications there was an individual approach. In the PA group, there were 4 cases (31%) in which the delivery took place earlier than the specified gestational period, and in the PP group, there were 37 cases (23%).

Graph 15. Gestational age at delivery in relation to the placenta type



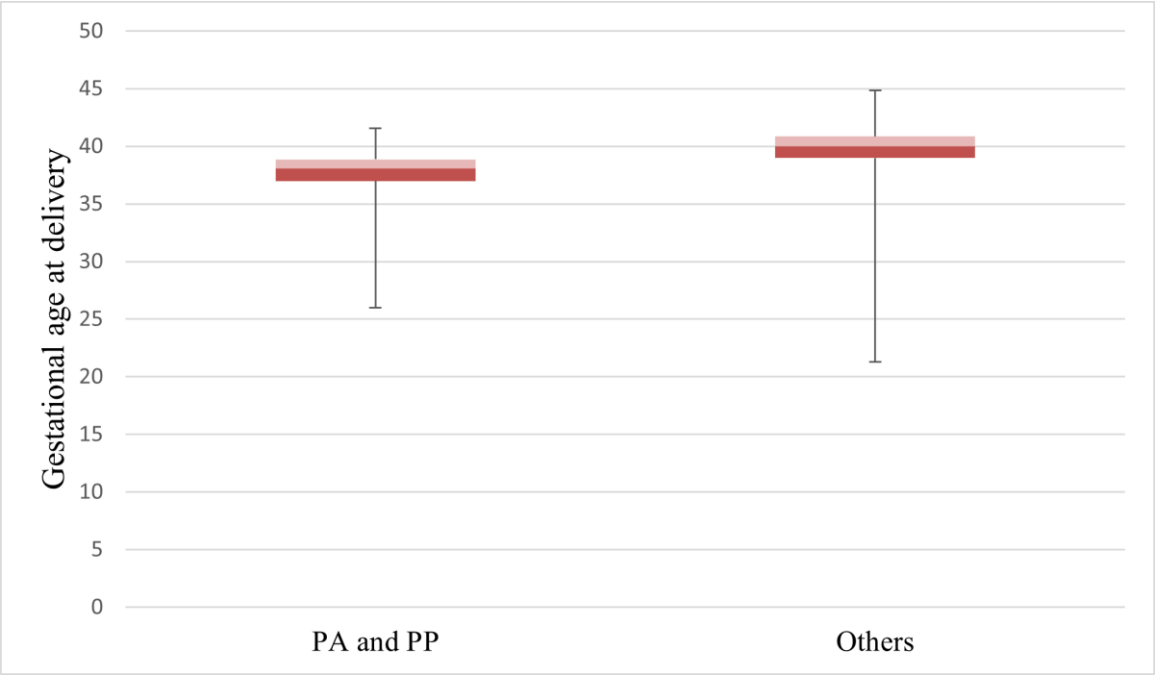
4.4.2. Gestational age at delivery in pregnancies complicated with PP and PA, altogether, in relation to pregnancies without PP and PA

Table 24. Average gestational age at delivery in relation to the placenta type

	Placenta type		t-test	
	PA and PP	Others	P	
Cases (n)	**171**	**21285**	**0,001**	**има**
Average	**37,4**	**39,6**		
Standard deviation	**2,3**	**1,9**		
Median	**38**	**40**		
Minimal	**26**	**21**		
Maximal	**41**	**45**		

The p-value (P<0,001) is lower than α, which means that for patients with PA or PP we can expect earlier childbirth, compared to the rest of the patients without PP and PA.

Graph 16. Gestational age at delivery in relation to the placenta type



4.5. Delivery blood lost in pregnancies complicated with PP and PA, in relation to pregnancies without PP and PA

Only patients in whom reported blood lost was carefully described and recorded in the hospital database were used for this analysis.

Table 25. Average blood lost at delivery in relation to the placenta type

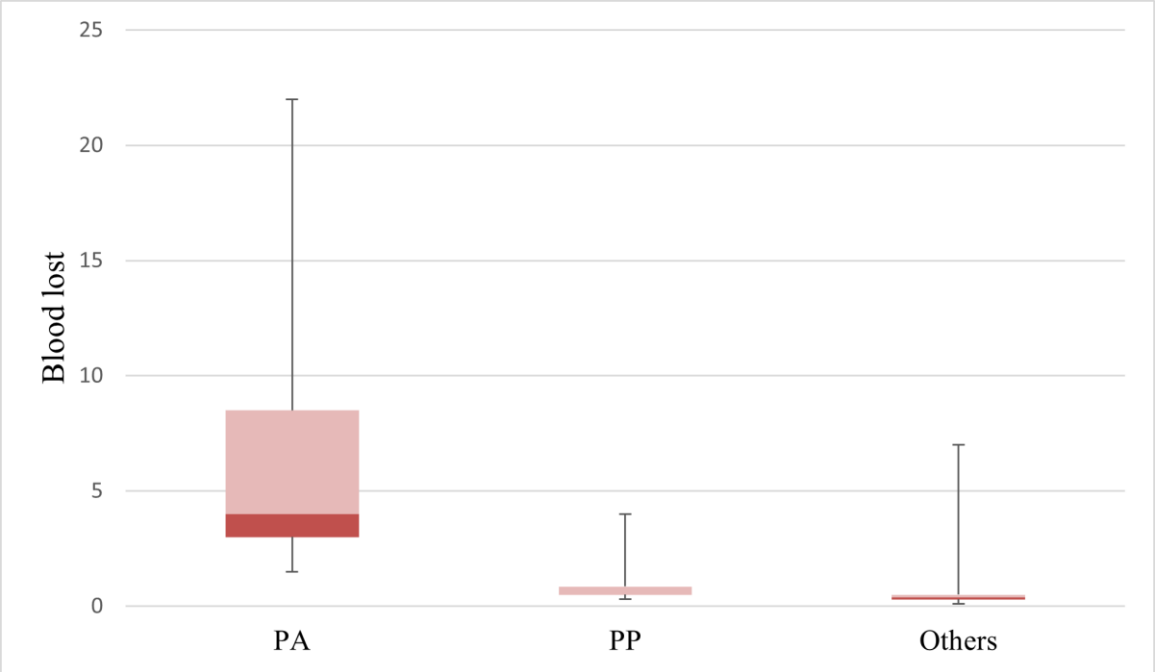
	Placenta type		
	PA	PP	Others
Cases (n)	**13**	**104**	**4382**
Average	**7,77**	**0,75**	**0,48**
Standard deviation	**7,74**	**0,57**	**0,37**
Median	**4,0**	**0,5**	**0,4**
Minimal	**1,5**	**0,3**	**0,1**
Maximal	**22**	**4**	**7**

We will use the Student's t-test for two independent samples to check if there are differences in the average blood lost at the time of delivery for different placentas.

Placenta type		P	Statistically significance
PA	**PP**	**0,007**	**yes**
PA	**Others**	**0,005**	**yes**
PP	**Others**	**0,001**	**yes**

There are statistically significant differences (for all three $p<0.05$) – the lowest blood lost is in cases without PP and PA (0,48 l.), followed by cases with PP (0,75 l.) and cases with PA, for whom the average blood lost is close to 8 litres (7,77 l.).

Graph 17. Blood lost at delivery in relation to the placenta type



In the PA group, the highest blood lost was reported in cases with attempted placenta extraction. These cases were 5 and the corresponding blood loss - 5 l., 8.5 l., 20 l., 21 l., 22 l. In these cases, transfusion of a large amount of blood and blood products and life-saving resuscitation were required. In one of the cases, the patient fell into a severe state of clinical death after resuscitation, permanent brain damage was found at follow-up.

In the PP group, the highest blood lost was reported in cases in which vaginal bleeding was an indication for emergency preterm cesarean delivery. High blood lost was also registered in cases with prolonged pregnancy, after 38 weeks' gestation. This group constituted more than half of the PP cases in our sample, and this is so because the recommendations and protocols for delivery in PP varied with recommendations from 36 up to 39 weeks' gestation. For the purposes of our study, we adopted the period from 37+0 to 37+6 weeks' gestation as an optimal time of delivery in uncomplicated cases of PP.

4.6. Average blood lost, in relation to the gestational age at delivery, in pregnancies complicated with PP

Table 26. Average blood lost, in relation to the gestational age at delivery, in pregnancies complicated with PP

	Gestational age		
	Before 36+6	Between 37+0 - 37+6	After 38
Cases (n)	**23**	**22**	**59**
Average	**0,926**	**0,545**	**0,864**
Standard deviation	**0,712**	**0,174**	**0,583**
Median	**0,600**	**0,500**	**0,600**
Minimal	**0,5**	**0,3**	**0,5**
Maximal	**3,0**	**1,0**	**4,0**

We will use the Student's t-test for two independent samples to check if there are differences in the average blood lost in pregnancies complicated with PP, according to the gestational age at delivery.

Gestational age		P	Statistically significance
Before 36+6	**37+0-37+6**	**0,019**	**yes**
Before 36+6	**38+**	**0,293**	**no**
37+0-37+6	**38+**	**0,043**	**yes**

We have a statistically significant difference in the average blood lost in cases with PP who delivered between 37+0 and 37+6 weeks' gestation, compared to those delivered before (p=0.019) and after this period (p=0.043). The lowest average blood lost (0,54 l.) will be expected in those delivered between 37+0 and 37+6 week's gestation.

According to the result we can conclude, that we have the lowest average blood lost in the group with delivery from 37+0 - 37+6 weeks' gestation. This is the group where we have the lowest percentage of emergency deliveries and the majority of deliveries are planned, after preliminary preparation and discussion of the case. In the group up to 36+6 weeks' gestation, the majority of deliveries were performed as an emergency, when vaginal bleeding was present or after a third episode of profuse vaginal bleeding. In the group after 38+0 weeks'

gestation, we again have a higher than average blood lost and this is due on the one hand to the fact that, again, the majority of deliveries here were performed in an urgent manner, due to the onset of labor and profuse vaginal bleeding , as a consequence of this.

4.7. Average blood lost at delivery in pregnancies complicated with PP and PA, in relation to average blood lost in cesarean delivery, without PP and PA

Table 27. Average blood lost at delivery in pregnancies complicated with PP and PA, in relation to average blood lost in cesarean delivery, without PP and PA

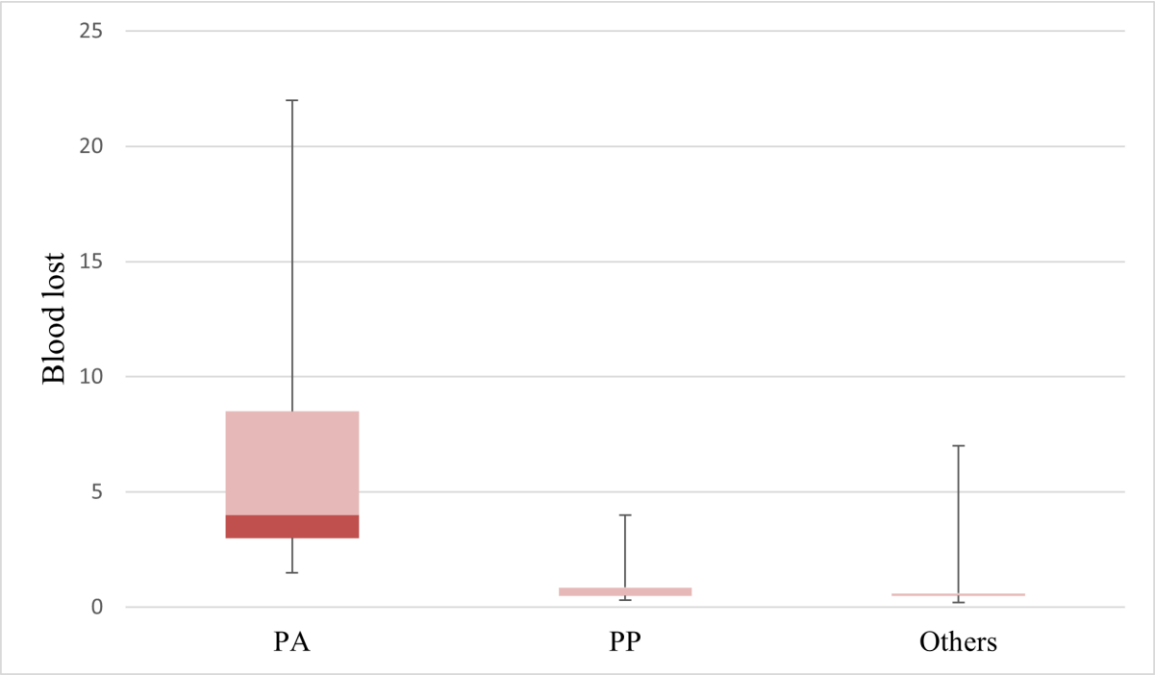
	Placenta type		
	PA	PP	Others
Cases (n)	**13**	**104**	**1561**
Average	**7,77**	**0,75**	**0,57**
Standard deviation	**7,74**	**0,57**	**0,38**
Median	**4,0**	**0,5**	**0,5**
Minimal	**1,5**	**0,3**	**0,2**
Maximal	**22**	**4**	**7**

We will use the Student's t-test for two independent samples to check if there are differences in the average blood lost at the time of delivery.

Placenta type		P	Statistically significance
PA	**PP**	**0,007**	**yes**
PA	**Others**	**0,006**	**yes**
PP	**Others**	**0,002**	**yes**

For all three groups, we have statistically significant differences (for all three $p<0.05$) – the lowest blood lost is for patients who delivered with Cesarean Section, without PP or PA (0,57 l.), followed by patients with PP (0,75 l.) and patients with PA, for whom the average blood lost is close to 8 litres (7,77 l.).

Graph 18. Average blood lost at delivery in pregnancies complicated with PP and PA, in relation to average blood lost in cesarean delivery, without PP and PA



4.8. Sensitivity and specificity of ultrasound in the diagnosis of placenta previa

Table 28. Sensitivity and specificity of ultrasound in the diagnosis of placenta previa at 12-16, 20-24, 28-32 and 34-36 weeks' gestation

Variables	Weeks' gestation			
	12-16	20-24	28-32	34-36
Precision	**0,0089**	**0,0661**	**0,4599**	**0,9718**
Accuracy	**0,1796**	**0,8959**	**0,9914**	**0,9998**
Sensitivity	**1,0000**	**1,0000**	**1,0000**	**1,0000**
Specificity	**0,1735**	**0,8951**	**0,9914**	**0,9998**
True to positive rate	**158**	**158**	**155**	**138**
False to positive rate	**17607**	**2234**	**182**	**4**
False to negative rate	**0**	**0**	**0**	**0**
True to negative rate	**3696**	**19068**	**20895**	**20613**

4.9. Sensitivity and specificity of ultrasound in the diagnosis of placenta accreta spectrum

Table 29. Sensitivity and specificity of ultrasound in the diagnosis of PA

Variables	Values
Precision	**1,00000**
Accuracy	**0,99995**
Sensitivity	**0,92857**
Specificity	**1,00000**
True to positive rate	**13,00**
False to positive rate	**0,00**
False to negative rate	**1,00**
True to negative rate	**21303**

4.10. Placenta migration

The phenomenon of "migration" of the placenta has been described in numerous publications. By following up in each of the investigated gestational periods, we investigated this phenomenon during different gestational periods of pregnancy 12-16, 20-24, 28-32 and 34-36 weeks' gestation.

Table 30. Placenta position at 12-16 weeks' gestation, according to the internal cervical os

	Total		PA		PP		Others	
	n	%	n	%	n	%	n	%
Low placenta	**17778**	**82,8%**	**13**	**100,0%**	**158**	**100,0%**	**17607**	**82,7%**
High placenta	**3696**	**17,2%**	**0**	**0,0%**	**0**	**0,0%**	**3696**	**17,3%**
Total	**21474**	**100,0%**	**13**	**100,0%**	**158**	**100,0%**	**21303**	**100,0%**

Table 31. Placenta position at 20-24 weeks' gestation, according to the internal cervical os

	Total		PA		PP		Others	
	n	%	n	%	n	%	n	%
Low placenta	**2405**	**11,2%**	**13**	**100,0%**	**158**	**100,0%**	**2234**	**10,5%**
High placenta	**19068**	**88,8%**	**0**	**0,0%**	**0**	**0,0%**	**19068**	**89,5%**
Delivered between 12-22 g.w.	**1**	**≈0,0%**	**0**	**0,0%**	**0**	**0,0%**	**1**	**0,0%**
Total	**21474**	**100,0%**	**13**	**100,0%**	**158**	**100,0%**	**21303**	**100,0%**

Table 32. Placenta position at 28-32 weeks' gestation, according to the internal cervical os

	Total		PA		PP		Others	
	n	%	n	%	n	%	n	%
Low placenta	**348**	**1,6%**	**11**	**84,6%**	**155**	**98,1%**	**182**	**0,9%**
High placenta	**20895**	**97,3%**	**0**	**0,0%**	**0**	**0,0%**	**20895**	**98,1%**
Delivered between 22-32 g.w.	**230**	**1,1%**	**2**	**15,4%**	**3**	**1,9%**	**225**	**1,1%**
Total	**21473**	**100,0%**	**13**	**100,0%**	**158**	**100,0%**	**21302**	**100,0%**

Table 33. Placenta position at 34-36 weeks' gestation, according to the internal cervical os

	Total		PA		PP		Others	
	n	%	n	%	n	%	n	%
Low placenta	**150**	**0,7%**	**8**	**72,7%**	**138**	**89,0%**	**4**	**0,0%**
High placenta	**20613**	**97,0%**	**0**	**0,0%**	**0**	**0,0%**	**20613**	**97,8%**
Delivered between 32-36 g.w.	**480**	**2,3%**	**3**	**27,3%**	**17**	**11,0%**	**460**	**2,2%**
Total	**21243**	**100,0%**	**11**	**100,0%**	**155**	**100,0%**	**21077**	**100,0%**

4.10.1. Placenta migration in patients with previous Cesarean section, according to the distance of the lower placenta edge to the internal cervical os (within 20 mm., reaching to or covering)

The examination of the relationship between placenta migration in patients with a previous Cesarean Section, according to the distance of the lower placenta edge to the internal cervical os (at less than 20 mm., reaching, covering) was performed on 2,056 cases. We studied cases with a previous Cesarean Section in which the placenta was recorded as low-lying at the first visit and compared from these cases what proportion remained so until the time of delivery.

Table 34. Placenta migration in patients with previous Cesarean Section, according to the distance of the lower placenta edge to the internal cervical os (reaching to and covering in total)

Placenta position at delivery	Placenta position, according to the internal cervical os		Statistic			
	reaching to+covering	Less than 20 mm.	X^2	p	V	V(p)
n	**1177**	**879**	**21,24**	**<0,001**	**0,102**	**<0,001**
PA or PP	**3,9%**	**0,7%**				
Others	**96,1%**	**99,3%**				
Total	**100,0%**	**100,0%**				

The $\chi 2$ analysis determined a difference in the PA or PP incidence depending on the position of the placenta – $p<0,001$, which is lower than α. Cramer's coefficient ($V=0.102$) is statistically significant ($V(p)<0,001$) and shows a minor correlation between the two variables.

Statistical analysis showed that the probability of "migration" in the group with a previous Cesarean Section in which the leading placental edge reached or covered the internal cervical os was lower than in the group in which the leading placental edge was less than 20 mm., but does not reach it. Accordingly, in the first group the incidence of PP and PA is generally higher.

Table 35. Placenta migration in patients with previous Cesarean section, according to the distance of the lower placenta edge to the internal cervical os (reaching to and covering in separate groups)

Placenta position at delivery	Placenta position, according to the internal cervical os			Statistic			
	reaching to	covering	less than 20 mm.	X^2	p	V	V(p)
n	**974**	**203**	**879**	**50,81**	**<0,001**	**0,157**	**<0,001**
ПА или ПП	**2,8%**	**9,4%**	**0,7%**				
Друга	**97,2%**	**90,6%**	**99,3%**				
Общо	**100,0%**	**100,0%**	**100,0%**				

The $\chi 2$ analysis determined a difference in the PA or PP incidence depending on the position of the placenta– $p<0,001$, which is lower than α. Cramer's coefficient ($V=0.157$) is statistically significant ($V(p)<0,001$) and shows a minor correlation between the two variables.

4.10.2. Placenta migration in patients with previous Cesarean section, according to the placenta position (anterior, posterior), distance of the lower placenta edge to the internal cervical os (within 20 mm., reaching to or covering) and according of the degree of the covering (less or more than 20 mm.)

The analysis of placenta migration in patients with previous Cesarean section, according to the placenta position (anterior, posterior), distance of the lower placenta edge to the internal cervical os (within 20 mm., reaching to or covering) and according of the degree of the covering (less or more than 20 mm.) was done in 2,056 cases, with previous Cesarean Section. We studied cases with a previous Cesarean Section in which the placenta was registered as low-lying at the first visit and we compared of these cases how much remained so until the time of delivery depending on whether the placenta was anterior or posterior and depending on the position of the leading placental edge relative to the internal cervical os (less than 20 mm., reaching to, covering) as well as in the group in which the leading placental edge covers internal cervical os, we further compared the two groups - covers more than 20 mm. and covers less than 20 mm.

Table 36. Placenta migration in patients with previous Cesarean section, according to the placenta position (anterior, posterior) and distance of the lower placenta edge to the internal cervical os (within 20 mm., reaching to or covering)

	Placenta position according to the internal cervical os (n=2056)											
	reaching to (n=974)				less than 20 mm.(n=879)				covering(n=203)			
	Placenta											
	Anterior placenta		Posterior placenta		Anterior placenta		Posterior placenta		Anterior placenta		Posterior placenta	
Placenta at delivery	712		262		118		761		63		140	
	n	%	n	%	n	%	n	%	n	%	n	%
PA/PP	17	2,4%	10	3,8%	2	1,7%	4	0,5%	8	12,7%	11	7,9%
Others	695	97,6%	252	96,2%	116	98,3%	757	99,5%	55	87,3%	129	92,1 %
Total	*712*	*100%*	*262*	*100%*	*118*	*100%*	*761*	*100%*	*63*	*100%*	*140*	*100 %*

Table 37. Placenta migration in patients with previous Cesarean section, according to the placenta position (anterior, posterior) and according of the degree of the covering (less or more than 20 mm.)

	Placenta position according to the internal cervical os-leading placenta edge covering (n=203)							
	Placenta							
	Anterior placenta (n=63)				Posterior placenta (n=140)			
	Degree of covering in mm.							
	< 20 mm.		>=20 mm.		< 20 mm.		>=20 mm.	
Placenta at delivery	34		29		78		62	
	n	%	n	%	n	%	n	%
PA or PP	1	2,9%	7	24,1%	6	7,7%	5	8,1%
Others	33	97,1%	22	75,9%	72	92,3%	57	91,9%
Total	*34*	*100%*	*29*	*100%*	*78*	*100%*	*62*	*100%*

Table 38. Placenta migration in patients with previous Cesarean section, according to the degree of the covering - less or more than 20 mm.

	Placenta position according to the internal cervical os-leading placenta edge covering (n=203)			
	Degree of covering in mm.			
	< 20 mm.		>=20 mm.	
	112		91	
Placenta at delivery	n	%	n	%
PA or PP	7	6,3%	12	13,2%
Others	105	93,8%	79	86,8%
Total	*112*	*100%*	*91*	*100%*

4.11. Incidence of patients with previous cesarean delivery and/or myomectomy in the general population

Table 39. Incidence of patients with previous cesarean delivery and/or myomectomy in the general population

Previous Cesarean Section/Myomectomy	Cases (n)	Percentage %
Yes	**2961**	**13,8%**
No	**18513**	**86,2%**
Total	**21474**	**100,0%**

The ratio of patients who have undergone a previous uterine surgery (Cesarean section and/or myomectomy with opening of the uterine cavity) to women who have not had one is 1:6.

4.12. Incidence of high risk for PA patients, among all patients with previous Cesarean Section and/or myomectomy, with opening of the uterine cavity

Table 40. Incidence of high risk for PA patients, among all patients with previous Cesarean Section and/or myomectomy, with opening of the uterine cavity

High risk for PA	Cases (n)	Percentage %
Yes	**1013**	**34,2%**
No	**1948**	**65,8%**
Total	**2961**	**100,0%**

The ratio of patients at high risk of placenta accreta to women who had undergone previous surgery (Cesarean Section and/or myomectomy with opening of the uterine cavity) but at low risk of placenta accreta was 1:1,9.

4.13. Score system for diagnosis of placenta accreta

In order to test the effect of myometrial thickness, blood flow-arterial/venous, arterial velocity, bladder wall interruption, visible scar of previous Cesarean Section, lacunae, 3D-irregular vascularization in placenta, 3D-hypervascularization of uterine serosa/bladder wall border on the presence or absence of PA, we used logistic regression. Logistic regression was constructed to assess whether the eight independent variables predict in a statistically significantly way whether the patient had PA. When all eight independent variables are considered simultaneously, they predict in a statistically significant way the presence of PA: ($\chi 2 = 144.84$, df = 8, $p < 0.01$). We then used discriminant analysis to determine the severity of each of the markers.

Table 41. Score system for diagnosis of placenta accreta

Ultrasound markers	Points
1. Myometrium thickness	**3**
2. 3D-irregular vascularization	**2**
3. Bladder wall interruption	**2**
4. Velocity of arterial/trophoblastic blood flow	
>=40	**2**
20-39	**1**
5. Lacunae	
More than 3	**2**
1-3	**1**
6. Arterial/trophoblastic blood flow	**2**
7. 3D-hypervascularization on uterine serosa/bladder wall border	**1**
8. Not visible scar from the previous Cesarean Section	**1**
Maximal score	**15**
Very high probability of PA	**From 11 to 15 points**
High probability of PA	**From 6 to 10 points**
Low probability of PA	**From 3 to 5 points**

After calculating the scores for each case and assigning to the corresponding probability group, we identified a complete overlap in patients with "very high" and "high" probability of PA with the results at delivery.

Table 42. Probability of PA according to the score system

Probability of PA	Cases (n) according to the score system	Cases (n) at delivery
Very high probability of PA	**9**	**9**
High probability of PA	**4**	**4**
Low probability of PA	**33**	**0**
Total	**46**	**13**

4.14. First trimester serum PAPP-A (MoM) in association with placenta previa and placenta accreta spectrum

Table 43. First trimester serum PAPP-A (MoM) in association with placenta previa and placenta accreta spectrum

	Placenta type		
	PA	PP	Others
Cases (n)	**13**	**153**	**20949**
Below median	**23,1%**	**26,1%**	**23,3%**
Around median	**15,4%**	**36,6%**	**46,7%**
Above median	**61,5%**	**37,3%**	**30,0%**
Total	**100%**	**100%**	**100%**
Average	**1,704**	**1,269**	**1,189**

The $\chi 2$ analysis determined that there were statistically significant differences in the relative proportions of PAPP-A MoM, depending on the placenta type. In patients without PA and PP we can expect significantly more often the values of this hormone to be around the median ($p= 0.039$ when compared to PA and $p= 0.02$ when compared to PP). We also found that for women with PA we can expect significantly more often the values of this hormone to be above the median ($p= 0.048$ when compared with PP and $p= 0.02$ when comparing patients without PA and PP).

We will use the Student's t-test for two independent samples to check if there are differences in the average values of PAPP-A MoM for the different placentas.

Placenta type		P	Statistically significance
PA	**PP**	**0,052**	**no**
PA	**Others**	**0,005**	**yes**
PP	**Others**	**0,137**	**yes**

We found a statistically significant difference in patients with PA versus patients without PA or PP (p=0.005, which is greater than 0.05). Higher deviations of this hormone can be expected in patients with PA.

4.15. First trimester serum b-HCG (MoM) in association with placenta previa and placenta accreta spectrum

Table 44. First trimester serum b-HCG (MoM) in association with placenta previa and placenta accreta spectrum

	Placenta type		
	PA	PP	Others
Cases (n)	**13**	**153**	**20948**
Below median	**46,2%**	**44,4%**	**44,9%**
Around median	**7,7%**	**20,9%**	**24,7%**
Above median	**46,2%**	**34,6%**	**30,3%**
Total	**100%**	**100%**	**100%**
Average	**1,391**	**1,372**	**1,259**

The $\chi 2$ analysis showed that there are no statistically significant differences in the relative shares of b-HCG MoM, depending on the type of placenta, and the Student's t-test for two independent samples didn't show any differences in the mean values of b-HCG MoM among the different placentas.

Placenta type		P	Statistically significance
PA	**PP**	**0,833**	**no**
PA	**Others**	**0,669**	**yes**
PP	**Others**	**0,212**	**no**

5. RESULTS

5.1. Incidence of PP and PA

The established incidence in the studied population was 0,7% for PP and 0,1% for placenta accreta spectrum anomalies, respectively, is comparable to the studies already published on the subject.[19,58,76,106]

We should note that in our study, a relationship was established between the incidence of both placental pathologies, depending on the presence or not of a previous Cesarean Section, which is also supported by previous studies. For PP, the incidence among cases with a previous Cesarean Section increased to 1.3%, and for PA to 0.4%. This is described in the available literature on the subject and based on this, a previous Cesarean Section is proved as one of the risk factors for both placental pathologies. [76,105,119,181,199,210]

In our study, no relationship was found between the number of previous Cesarean Sections and the incidence of PP. In contrast, the presence of such a relationship in the incidence of PA was found. The incidence of PA increases, depending on the number of previous Cesarean Sections, which is comparable to already published studies on the subject [181].

For the purposes of our study, we investigated the incidence of PP and PA in the high-risk placenta accreta group that met certain criteria, described earlier. In this group, the highest incidence of both placental pathologies was registered, which for PP was found to be around 3,5%, and for PA, respectively, 1,3%.

Based on the study done, we can conclude that the incidence of PP and PA varies in different groups. The highest incidence was registered in the group with a previous Cesarean Section and the presence of a low-lying placenta, which applies to both placental pathologies. In PA, a relationship was established between the number of previous Caesarean Sections and the incidence of the pathology.

5.2. Risk factors

In the studied population, the following risk factors were examined for both placental pathologies, PP and PA – maternal age, ethnic disparity, method of conception, maternal smoking, previous pregnancies, previous deliveries, previous Cesarean Section, presence of previous myomectomy and previous uterine surgery in general.

When examining maternal age as a risk factor, dependence and statistically significant differences ($p<0.05$) were found - the highest was the average age in PA (37,2 years), followed by PP (34,2 years).

Ethnic dparity did not appear to be a risk factor in the PP group, but association was found in the PA group. The analysis found a difference in the incidence of PA according to Negroid ethnicity and showed a weak association between the two variables.

Analysis of the conception type - spontaneous or through methods of assisted reproduction, as a risk factor for PP and PA, found association in the incidence of PP, in relation to the method of conception. In the group of pregnancies that occurred with the ART methods, a higher incidence of PP was reported. Association in the PA group was not found in our study, but this may be due to the smaller number of cases in this group.

In our study, no relationship was found between maternal smoking as a risk factor and the incidence of PP and PA. In our sample, maternal smoking did not prove to be a risk factor for both placental pathologies.

Previous pregnancies (gravidity) in the studied population proved to be a risk factor for both placental pathologies, PP and PA. Statistically significant differences were found ($p<0.05$) – the average number of previous pregnancies was highest in PA (4,3), followed by PP (2,8).

In the studied population, the number of previous deliveries (parity) was also studied as a risk factor for PP and PA. In the PP group, no difference in incidence was found, but such a relationship was demonstrated in the PA group.

Previous Cesarean Section proved to be a risk factor in both PP and PA groups, and in the PA group a relationship between the number of previous Cesarean Sections and the incidence of this placental pathology was found. With previous myomectomy, as a risk factor for PP, a difference in the incidence of PP was found depending on the presence or not of myomectomy. No such relationship was demonstrated in the PA group. When examining the history of previous uterine surgery (previous Cesarean Section and/or myomectomy), we found an association with both placental pathologies, PP and PA, with a higher incidence of both pathologies in this group. We can conclude that previous uterine surgery is a risk factor for the development of PP and PA.

We also examined fetal gender as a risk factor, due to the available publications on the subject, regarding male gender as a risk factor for PP. In our analysis, we found no relationship between fetal gender and the incidence of both placental pathologies. Fetal gender was not a risk factor in our study.

In conclusion, in our study maternal age, method of conception, previous pregnancy, previous Cesarean Section, previous myomectomy and previous uterine surgery were established as risk factors for PP. In the PA group maternal age, ethnic origin, previous pregnancy, previous delivery, previous Cesarean Section and previous uterine surgery were established as risk factors. Results are comparable to a large number of studies published to date. Dependence between the fetal gender and maternal smoking as a risk factors were not proven. [14,23,62,94,96,99,105,107,112,115,152,178,181,210,212]

5.3. Gestational age at delivery in pregnancies complicated with PP and PA, in relation to pregnancies without PP and PA

For the purpose of the study, the following gestational age at delivery was adopted, as recommended for PA 35+0 - 36+0 weeks' gestation and for the PP 37+0 - 37+6 weeks' gestation. This applies only to the cases where there are no complications. In all cases with complications, an individual approach was used. This gestational period, as optimal for planned delivery in both placental pathologies, is supported by numerous publications on the subject. [12,72,166,172,204,213]

In the studied group, statistically significant differences were found in all three groups with PP, with PA and without placental pathology of this type, with the lowest average gestational age at delivery in cases with PA (35,7 weeks' gestation), followed by PP (37,6 weeks' gestation). In the PA group, there were 4 cases (31%), in which the delivery was performed earlier than the specified recommended gestation period, due to the presence of an obstetric emergency (profuse bleeding, labor activity, suspected uterine rupture) and 4 cases in in which due to the presence of focal placenta accreta (which affects less than 30% of the placental volume) prolongation of pregnancy was adopted. In the PP group, in 37 cases (23%), delivery was performed as emergency delivery, before the optimal gestation period, due to an obstetric emergency (hemorrhage, labor). We can conclude that emergency delivery before the recommended gestational age in both placental pathologies is equal to preterm birth (delivery before 37 weeks' gestation) and is observed with greater frequency in both PP and

PA group. The association of PP and PA with preterm birth is described in the literature as one of the serious complications of these placental pathologies. [15,72,126,172,204,213]

5.4. Delivery blood lost in pregnancies complicated with PP and PA

5.4.1. Delivery blood lost in pregnancies complicated with PP and PA, in relation to pregnancies without PP and PA

In the literature, the association of PP and PA with ante-intra- and postpartum hemorrhages has been extensively described. [25,29,56,71,80,84,145,168,176]. In cases of severe and rapid blood lost, rapid intravascular volume loss can occur, leading to hemodynamic instability, hypoxemia, hypoxia, organ damage, and death. Both placental pathologies are perceived as one of the main reasons for life-saving peripartum hysterectomy [25,29,56,80,176].

In our study, in all three groups PP, PA and without placental pathology, we have statistically significant differences - the lowest average blood lost at delivery was in patients who did not have PP or PA (0,48 l.), followed by patients with PP (0,75 l.) and patients with PA, in whom the average blood loss is nearly 8 liters (7,77 l.).

In the PA group, the highest blood lost was reported in cases with attempted for placenta removal. These cases are 5 and the corresponding blood loss - 5 l., 8.5 l., 20 l., 21 l., 22 l. In these cases, massive transfusions of blood and blood products and life-saving resuscitation were required. In one of the cases, the patient fell into a severe state of clinical death after resuscitation and permanent brain damage was found at follow-up.

5.4.2. Delivery blood lost in pregnancies complicated with PP and PA, in relation to pregnancies with cesarean delivery

In the three groups in our study, we found statistically significant differences, the lowest is the average blood lost at delivery in patients delivered by a cesarean delivery, without PP and PA (0,57 l.), followed by PP patients (0,75 l.) and PA patients, where the average blood lost is close to 8 liters (7,77 l.). In the PA group, 8 hysterectomies and 5 partial placental resections were performed at the affected site. The lowest blood lost was reported in the cases with hysterectomy, without attempted of placenta removal, in which the incision on the uterus was preliminarily adjusted to the position of the placenta and was most often performed fundal, respectively 2,5 l., 3 l., 4 l. Less blood lost was also recorded in cases where the affected area

of the placenta was less than 30% compared to cases where we had more than 30% involvement.

5.4.3. Average blood lost, in relation to the gestational age at delivery, in pregnancies complicated with PP

In our study, we divided the cases with PP, in which we had correctly recorded blood lost in the hospital system, into three groups - up to 36+6 , between 37+0-37+6 (optimal period for the purpose of the study) and after 38 weeks' gestation. The groups were analyzed and a statistically significant difference was found in the average blood lost in patients with PP, delivered between 37+0 and 37+6 weeks' gestation, compared to those who delivered before and after this period. The lowest average blood lost (0,54 l.) was recorded in those delivered between 37+0 and 37+6 weeks' gestation. This is the group where we have the lowest percentage of emergency deliveries and the majority of deliveries are planned, after preliminary preparation and discussion of the case. In the group up to 36+6 weeks' gestation the majority of deliveries were performed as an emergency, with vaginal bleeding present or after a third episode of profuse vaginal bleeding. In the group after 38+0 weeks' gestation, we again have a higher than average blood lost and this is due, on the one hand, to the fact that, again, not a small part of the deliveries were carried out in an urgent order, due to the beginning of labor and profuse vaginal bleeding, as a consequence of this. The only case of intrapartum hysterectomy was registered in this group. This group constituted more than half of the PP cases in our sample, and this is so because the recommendations and protocols for delivery in PP varied with recommendations from 36 to 38 weeks' gestation. For the purposes of our study, we adopted the period from 37+0 to 37+6 weeks' gestation as the recommended period for delivery in uncomplicated cases of PP and the analysis of the results reviled that this group is associated with the lowest blood lost at the time of delivery.

5.5. Sensitivity and specificity of ultrasound in the diagnosis of placenta previa and placenta accreta spectrum

In the PP group, we compared each of these indicators at each of the gestational follow-up times (12-16, 20-24, 28-32, and 34-36 weeks' gestation), in order to optimize the time for diagnosis. From the calculations, we concluded that the sensitivity of the ultrasound method is constant in the different periods, but the specificity increases significantly with advancing gestational age, with a maximum value in 34-36 weeks' gestation. This is mostly due to the phenomenon of "migration" of the placenta, which is observed much less often in the third

trimester of pregnancy. If the goal is optimal values, then this gestational period is the most accurate for making a diagnosis of PP, but doing this we will not take into account all cases with PP that will be delivered before 34-36 weeks' gestation, and in our analysis this is 13% of PP cases. After analysis and taking into account the percentage of cases with delivery before this period, the optimal period for making a diagnosis, which combines high specificity and sensitivity, would be 28-32 weeks' gestation. In this period, the phenomenon of "migration" of the placenta was observed less often, and the percentage of emergency deliveries before this optimal period for diagnosis was relatively low, compared to our study 1.9%. These data are consistent with previously published studies. [9,61,70,93]

In the PA group, these indicators were calculated for the accuracy of the ultrasound method, as a screening method in the first trimester of pregnancy, due to the idea of the study to present a screening method for the early prediction of placenta accreta spectrum abnormalities and to create an score system to facilitate of the diagnosis. From the analyzes made, we can conclude that the ultrasound method for diagnosis of placenta accreta spectrum has high sensitivity and specificity. This is comparable to published studies. A meta-analysis including 23 studies showed a sensitivity of 91% and a specificity of 97% for the ultrasound method for the diagnosis of PA. [65] Despite the above, there is wide variation in the accuracy of diagnosis, which is largely determined by the type of ultrasound markers used. Differences in the accuracy of PA diagnosis may also be due to the small sample of patients in most studies, the retrospective design, the different criteria used and differences in the diagnosis - clinically at deliveryor by histopathological examination. [65,105,108]

In our study, MRI was performed on all cases suspicious for placenta accreta, but in the only case with a false positive diagnosis, MRI did not show a difference compared to the ultrasound method. MRI, as a method for diagnosis of placenta accreta spectrum abnormalities, has high sensitivity and specificity, but its application requires highly qualified personnel and significantly increases the cost of diagnosis. It is recommended to carry out MRI in cases that are unclear for ultrasound methods or in case of uncertainty in the diagnosis established by ultrasound examination.

5.6. Placenta migration

In our study we examined the relationship between placenta migration in patient with a previous Cesarean Section, relative to the position of the lower placenta edge to the internal cervical os (less than 20 mm., reaching, covering- up to 20 mm. or by more than 20 mm.)

This was performed on 2,056 patients, all with a previous Cesarean Section. Statistical analysis showed that the probability of "migration" in the group with a previous Cesarean Section in which the leading placenta edge reached or covered the internal cervical os, was lower than in the group in which the leading placenta edge was less than 20 mm. Placenta migration was less likely in the group where the leading placenta edge covered the internal cervical os compared to the group where the leading placental edge was less than 20 mm., which applied to both anterior and posterior placenta. Placenta migration was less likely in the anterior placenta group, in which the leading placental edge overlapped by more than 20 mm. internal cervical os, compared with the posterior placenta group in which the leading placental edge overlapped by more than 20 mm. From the analysis of this sample we found only probability, but no statistically significant differences. This analysis would be relevant for the follow-up of cases with established low-lying placentas and the construction of an adequate protocol for follow-up and obstetric managment during pregnancy.

5.7. First trimester serum PAPP-A and b-HCG (MoM) in association with placenta previa and placenta accreta spectrum

The values of PAPP-A and b-HCG in all patients were obtained for the purpose of the first trimester combined screening for chromosomal abnormalities, which is part of the routine surveillance of pregnancy. Values of both hormones were converted to multiples of the median.

The statistical analysis showed that there were no statistically significant differences in the relative proportions of b-HCG in all three groups PP, PA and others. In PAPP-A, a statistically significant difference was found in patients with PA compared to patients without PA or cases with PP. Higher deviations of this hormone are expected to be observed in women with PA, which is comparable with published studies [214].

5.8. Clinical model protocols for obstetric follow up in pregnancies complicated with placenta previa and placenta accreta

Based on the study and its results, two clinical protocols for obstetric follow-up were developed for PP and PA cases.

5.8.1. Clinical model protocols for obstetric follow up in pregnancies complicated with placenta previa

Placenta previa is one of the conditions in obstetrics, associated with high maternal morbidity, even mortality. The introduction of a follow-up protocol would improve the pregnancy

outcome in these cases. On the basis of our study and its results, a model of clinical protocol for obstetric follow-up during pregnancy was designed. The period for stratification of the patients who will be subject to follow-up was chosen for 20-24 weeks' gestation, due to the fact that in the first trimester of pregnancy, the period between 12-16 weeks' gestation the percentage of cases with a low-lying placenta is very high 82,8%, compared to our study. In the period between 20-24 weeks' gestation, the percentage of cases with a low-lying placenta that will be subject to follow-up is about 1,.2%, according to our study. It is strongly recommended to follow up these cases at 28-32 and 34-36 weeks' gestation. The diagnosis of PP can be made at 28-32 weeks' gestation, but it is strongly recommended to follow up the cases at 34-36 weeks' gestation, because a significant part of them undergo placenta migration, which is observed more often in the cases where the leading placental edge is less than 20 mm., but does not reach the internal cervical os, and this percentage is about 53% of the cases according to our study. It should be considered that in the other groups with placentas where the leading placental edge reaches or covers the internal cervical os, placenta migration also can be seen. Our study showed that in about 13% of PP cases, the pregnancy will end before the age of 36 weeks' gestation, due to a complication, most commonly antepartum hemorrhage, and an emergency cesarean delivery will be performed. The method of choice is the ultrasound examination, in particular the transvaginal ultrasound with an empty bladder and no uterine contraction. The sensitivity and specificity of the ultrasound method, in particular transvaginal ultrasound, in the period 28-32 weeks' gestation is very high, which is of utmost importance and is supported by studies on the subject [122,183]. The optimal time of delivery, which was confirmed by our study, as a period with lower risk of complications, in particular hemorrhage, is 37+0-37+6 weeks' gestation. This gestational age is supported by already published studies [12,166,185]. Figure 15. illustrates a clinical protocol for obstetric follow-up in patients with PP.

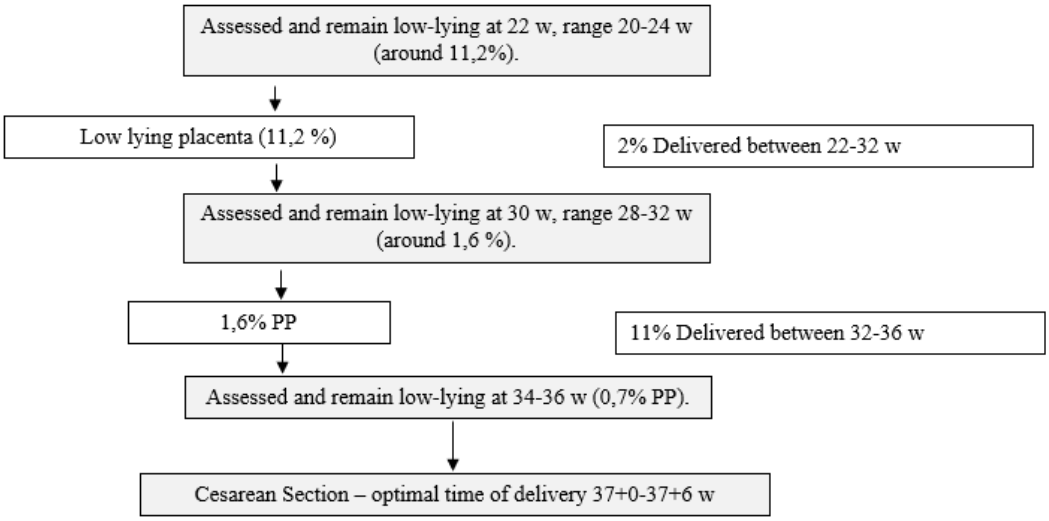


Fig. 15. Clinical protocol for obstetric follow-up in patients with PP

5.8.2. Clinical model protocols for obstetric follow up in pregnancies complicated with placenta accreta

Placenta accreta is associated with maternal morbidity up to 75% and mortality up to 7%. [71,145] Maternal morbidity includes uterine rupture prior to fetal viability, massive hemorrhage, adjacent organ involvement, multiple organ failure, need for blood transfusion, prolonged ICU stay, and need for peripartum hysterectomy. Currently, placenta accreta is one of the main and most common reasons for peripartum hysterectomy [80,176]. Despite modern methods of diagnosis, studies show that the diagnosis of placenta accreta remains unrecognized before birth in about half of cases [20,79], up to two thirds of cases [192].

In the PA group, follow-up was performed in the form of a screening method, in the first trimester of pregnancy, due to the idea of the study to present a screening method for the early prediction of placenta accreta spectrum abnormalities and to create a score system to facilitate the diagnosis. From the analyzes of our study, we can conclude that the ultrasound method for the diagnosis of placenta accreta, has high sensitivity and specificity. This is comparable to studies already published [65]. It should be noted that the majority of studies were in the second and third trimester of pregnancy.

Based on our study, we propose a protocol of obstetric managment, in the form of a screening method, which, in its first phase, aims to separate high-risk patients based on a previous history of the presence of a previous Cesarean Section and/or myomectomy, with opening of the uterus cavity and transvaginal ultrasound examination to diagnose the position of the leading placental edge in relation to the internal cervical os. All cases with previous uterine surgery of this type and placenta - anterior where the leading placental edge is less than 20 mm. reaching or covering the internal cervical os or posterior in which the leading placental edge reaching or covering the internal cervical os, are defined as high risk. These cases are subject to follow-up and evaluate for the presence or absence of the following ultrasound markers characteristic of placenta accreta spectrum. On every visit, it is mandatory to examine the presence or absence of the following ultrasound markers suspicious for this placental pathology: the presence of placental lacunae, increased vascularization at the uterine/bladder serosa border and the presence of pathological trophoblastic/arterial blood flow, thin myometrium (under 1 mm.), "bladder wall interruption", impossible visualization of the previous cesarean scar and pathology on the 3D images of the placental vascularization with Power Doppler. The diagnosis should be made based on the presence of a minimum 3 markers. Optional is the use of the designed score system for diagnosis, which will be discussed in the next chapter. We offer an optimal time for delivery at 35+0-35+6 weeks' gestation, which is supported by numerous studies [72,172,204], but with a previously prepared operative plan that has been discussed with the patient. There are two main approaches during delivery in PA: conservative and operative, with a series of variations observed in each. It is recommended that both approaches will be discussed with the patient before delivery, and it is optimal to choose an approach before delivery itself. Each specific case must always be considered. In our study, MRI was performed on all cases of suspected placenta accreta patients, but in the only case with a false positive diagnosis, MRI did not show a difference compared to the ultrasound method. MRI, as a method for diagnosis of placenta accreta spectrum abnormalities, has high sensitivity and specificity, but its application requires highly qualified personnel and significantly increases the cost of diagnosis. It is recommended to carry out MRI in cases that are unclear for ultrasound methods or in case of uncertainty in the diagnosis established by ultrasound examination.

In conclusion, the key to an optimal pregnancy outcome in placenta accreta spectrum abnormalities is early prenatal diagnosis, followed by timely discussion and patient consultation. A series of ultrasound examinations during pregnancy until birth is necessary.

Prenatal diagnosis is made by ultrasound examination and is highly accurate, especially in cases with anterior placenta previa and previous cesarean section. Combination of ultrasound markers are used to make a correct diagnosis. MRI is most often used to confirm the diagnosis, in posterior placenta or to determine the degree of invasion. [65,66] Complications that occur as a result of massive blood loss are significantly lower in elective compared to emergency delivery [72,172,204]. When the above proven information is taken into account, the majority of births are planned as late elective preterm births at 35-36 weeks' gestation or early term births at 37 weeks' gestation, with prior fetal corticosteroid prophylaxis [49]. The presence of a multidisciplinary team is of utmost importance for a better pregnancy outcome. Figure 16 illustrates a model protocol/screening method of obstetric managment in pregnancies, complicated with PA.

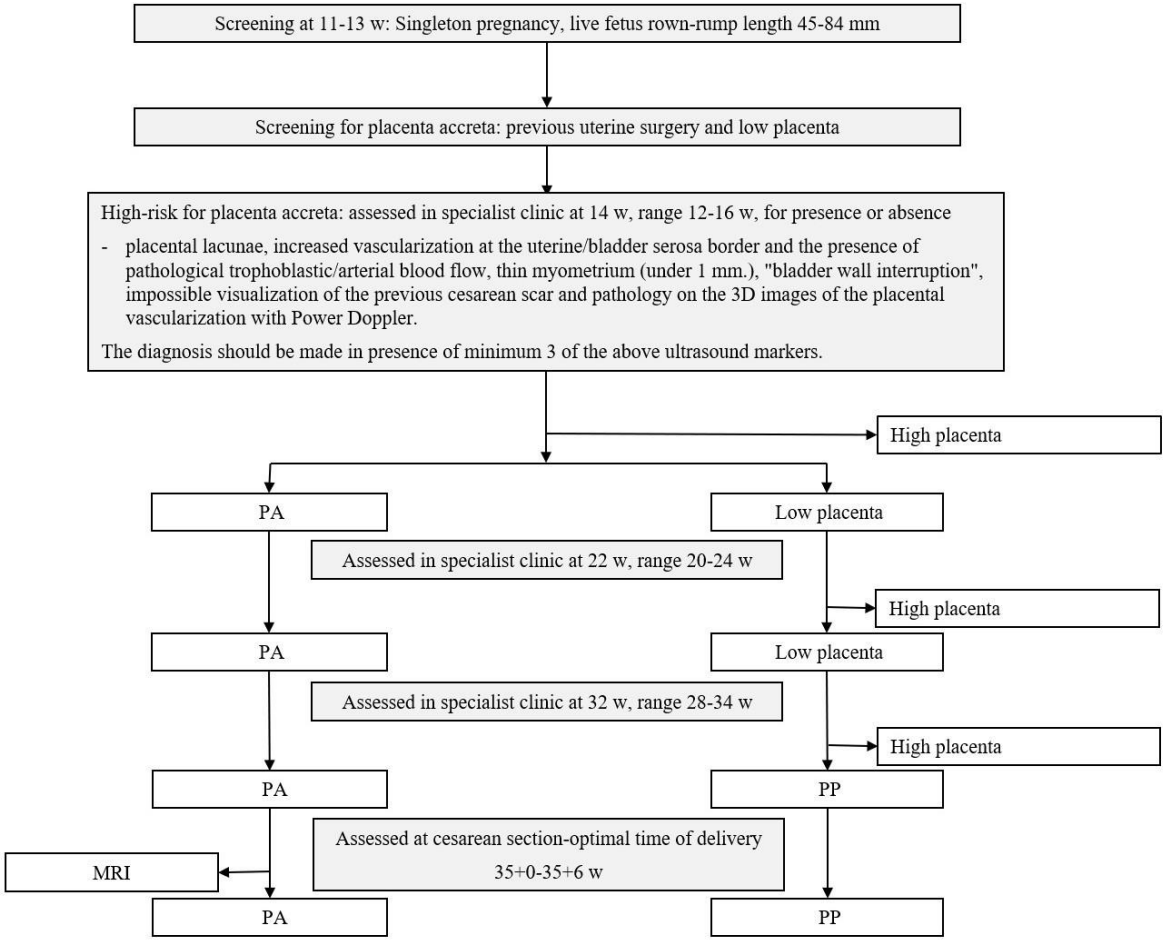


Fig. 16. Clinical protocol/screening method of obstetric managment in pregnancies, complicated with PA

5.9. Score system for diagnosis of placenta accreta

In the studied population, the percentage of cases with previous uterine surgery, including previous Caesarean Section and/or myomectomy, was 13.8%. The ratio of patients who have undergone previous surgery to women who have not had one is 1:6,252. The ratio of patients with prior surgery at high risk for PA to women with prior surgery at low risk for PA was 1:1,923. The incidence of PA among high-risk patients was 1.3%. From our study, we can conclude that the incidence of PA is high among properly stratified, high-risk cases of placenta accreta spectrum abnormalities. Due to the severity of this pathology and the consequences, which we have discussed in detail, the main goal is an early diagnosis, which is very often not made. To improve this, we developed a score system that we tested. The construction of the score system is detailed in Section 4.13, and Tables 41 and 42 illustrate this.

Table 41. Score system for the diagnosis of placenta accreta

Ultrasound markers	Points
1. Myometrium thickness	**3**
2. 3D-irregular vascularization	**2**
3. Bladder wall interruption	**2**
4. Velocity of arterial/trophoblastic blood flow	
>=40	**2**
20-39	**1**
5. Lacunae	
More than 3	**2**
1-3	**1**
6. Arterial/trophoblastic blood flow	**2**
7. 3D-hypervascularization on uterine serosa/bladder wall border	**1**
8. Not visible scar from the previous Cesarean Section	**1**
Maximal score	**15**
Very high probability of PA	**From 11 to 15 points**
High probability of PA	**From 6 to 10 points**
Low probability of PA	**From 3 to 5 points**

After calculating the scores for each case and assigning to the corresponding probability group, we identified a complete overlap in patients with "very high" and "high" probability of PA with the results at delivery.

Table 42. Probability of PA according to the score system

Probability of PA	Cases (n) according to the score system	Cases (n) at delivery
Very high probability of PA	**9**	**9**
High probability of PA	**4**	**4**
Low probability of PA	**33**	**0**
Total	**46**	**13**

The aim of creating a score system was to improve the diagnosis and obstetric management of cases suspected of PA.

6. SUMMARY

After processing and analyzing the data from out study, the incidence of PP in the studied population was found to be 0,7%, and for PA – 0,1%. In the group with a previous Cesarean Section, the incidence of both pathologies was higher for PP 1,3%, and for PA, respectively, 0,4%. An interesting fact is that the highest incidence of PP and PA was registered in the high-risk group, which for PP was found to be around 3,5%, and for PA, respectively, 1,3%.

In the examined population, the following risk factors were examined for both placental pathologies, PP and PA – maternal age, ethnic origin, method of conception, maternal smoking, previous pregnancies, previous deliveries, presence of a previous Cesarean Section, presence of a previous myomectomy, previous uterine surgery in general, gender of the fetus and biochemical markers (PAPP-A and b-HCG).

In conclusion, in our study – maternal age, method of conception, previous pregnancies (gravidity), previous Cesarean Section, previous myomectomy and previous uterine surgery were established as risk factors for PP. In the PA group – maternal age, ethnic origin, previous pregnancies (gravidity), previous deliveries (parity), previous Cesarean Section and previous uterine surgery were established as risk factors. Results are comparable to a large number of studies published already. Relationship between fetal gender and maternal smoking as risk factors was not proven in both placental pathologies. Previous Cesarean Section proved to be a risk factor in both PP and PA groups, and in the PA group a relationship between the number of previous Cesarean Sections and the incidence of this placental pathology was demonstrated. The increase in the number of previous Cesarean Sections leads to an increase in the incidence of PA. The statistical analysis showed that there were no statistically significant differences in the relative shares of b-HCG in the group of PP, PA. In PAPP-A, a statistically significant difference was found in patients with PA compared to patients without PA or patients with PP. Higher deviations of this hormone are expected to be observed in patients with PA, in the first trimester of pregnancy.

After analyzing our study, we came to the conclusion that the diagnosis of PP can be made at 28-32 weeks' gestation, but it is strongly recommended to follow up the cases at 34-36 weeks' gestation, because a not small part of them undergo placenta migration, and this is more often seen in cases where the placental leading edge is less than 20 mm. and does not reach the the internal cervical os and this in percentage is about 53% of the cases, according to our study. Our study showed that in about 13% of PP cases, the pregnancy will end before

36 weeks' gestation, due to a complication, most commonly antepartum hemorrhage, and an emergency cesarean delivery. The first method of choice for the diagnosis of PP is the ultrasound examination, and more precisely - the transvaginal ultrasound examination, with an empty bladder and absence of uterine contraction. The sensitivity and specificity of the ultrasound method, in particular transvaginal ultrasound, in the period 28-32 weeks' gestation is very high, 1,0000 and 0,9914 respectively. For the purpose of our study, we combined the term low-lying placenta, where the leading placental edge is less than 20 mm. from the internal cervical os and placenta, where the leading placental edge reaches or covers the internal cervical os, under the term PP, which is an approach also described by other authors. Statistical analysis, in the group analyzed for the probability of placenta migration, showed that this probability was lower in the group with a previous Cesarean Section, in which the leading placental edge reached or covered the internal cervical os, than in the group in which the leading placental edge was of less than 20 mm., but does not reach the internal cervical os. Placenta migration was less likely in the group where the leading placental edge covered the internal cervical os compared to the group where the leading placental edge was less than 20 mm., which applied to both anterior and posterior placenta. Placenta migration was less likely in the anterior placenta group, in which the leading placental edge overlapped by more than 20 mm. internal cervical os, compared with the posterior placenta group in which the leading placental edge overlapped by more than 20 mm. internal cervical os. Analysis of this sample showed probability, but no statistically significant differences were found.

Our study proved that the use of a screening method for stratification of high-risk patients in the first trimester of pregnancy, combining data from the anamnesis and ultrasound examination, lead to a correct diagnosis of the majority of cases with anomalies of the placenta accreta spectrum. In our study, all PA cases were found in the high-risk group. For the purpose of our study, we used ultrasound markers established in the literature for the diagnosis of placenta accreta spectrum abnormalities, most of which are described in the second and third trimesters of pregnancy. All cases from the high-risk placenta accreta group were examined in each of the investigated gestational periods for the presence or absence of the markers. At each visit, the presence or absence of ultrasound markers suspicious for this placental pathology were noted as follows: the presence of placental lacunae, increased vascularization at the uterine/bladder serosa border, and the presence of pathological trophoblastic/arterial blood flow, thin myometrium (under 1 mm.), "bladder wall interruption", impossible visualization of the previous cesarean scar and pathology on the 3D

images of the placental vascularization with Power Doppler. The diagnosis of PA was made when a minimum of 3 markers were present.

In the PA group, based on the ultrasound markers used and the prenatal diagnosis in the first trimester, the accuracy of the ultrasound method as a screening method in this early period of pregnancy was calculated. This was done for the purposes of the study to investigate the accuracy of a screening method for the early prediction of placenta accreta spectrum abnormalities and to establish a score system to facilitate the diagnosis. From the analyzes performed in our study, we can conclude that the ultrasound method using the combination of the above-described ultrasound markers characteristic of placenta accreta spectrum abnormalities has high sensitivity and specificity.

In order to create a score system, the effect of each of the ultrasound markers used was investigated: the presence of placental lacunae, increased vascularization at the uterine/bladder serosa border and the presence of pathological trophoblastic/arterial blood flow, thin myometrium (less than 1 mm.), "bladder wall interruption", impossible visualization of the previous cesarean scar and pathology of the 3D images of the placental vascularization with Power Doppler (3D-irregular vascularization in the placenta, 3D-hypervascularization at the serosa/bladder wall border) on the presence or absence of PA. Logistic regression was used. Logistic regression was constructed to assess whether the eight independent variables statistically significantly predicted whether a particular case had PA. When all eight independent variables are considered simultaneously, they statistically significantly predict the presence of PA. The severity of each of the markers was also established. After calculating the score obtained for each case and assigning it to the corresponding probability group, a complete overlap was found in women with "very high" and "high" probability of PA with postpartum outcomes.

For the purpose of the study, the following gestational periods were adopted, as recommended for delivery - 35+0 - 36+0 weeks’ gestation for PA and, accordingly, 37+0 - 37+6 weeks’ gestation for PP. This applies only to cases where there are no complications. In all cases with complications, an individual approach was adopted. In the PA group, 4 cases (31%) were registered, in which the delivery was performed earlier than the recommended gestation period, due to the presence of an obstetric emergency (profuse bleeding, labor activity, suspected uterine rupture) and 4 cases in which due to the presence of focal placenta accreta (which affects less than 30% of the placental volume) prolongation of pregnancy was

adopted. In the PP group, in 37 cases (23%), deliveries were performed emergency, before the optimal gestation period, due to an obstetric emergency (hemorrhage, labor activity). In the studied population, the lowest average gestational age at birth was found in cases with PA (35,7 weeks' gestation), followed by PP (37,6 weeks' gestation).

Statistically significant differences were found in all three groups in our study, with the lowest mean blood lost at delivery in patients with no PP or PA, delivered by a Cesarean Section (0,57 l.), followed by patients with PP (0,75 l.) and patients with PA, in whom the average blood lost is nearly 8 liters (7,77 l.).

In our study, we divided the cases with PP, in which we had correctly recorded blood lost in the hospital records, into three groups - up to 36+6 weeks' gestation, between 37+0-37+6 weeks' gestation (optimal period for the purpose of the study) and after 38 weeks' gestation. The groups were analyzed and a statistically significant difference was found in the mean blood lost in patients with PP, delivered between 37+0 and 37+6 weeks' gestation, compared to those delivered before and after this period. The lowest average blood lost (0,54 l.) was found in those delivered between 37+0 and 37+6 weeks' gestation. This is the group where we had the lowest percentage of emergency deliveries and the majority of deliveries are planned, after preliminary preparation and discussion of the case. In the group up to 36+6 and after 38 weeks' gestation the majority of deliveries were performed as an emergency, when vaginal bleeding was present. In the group after 38+0 weeks' gestation, the only case with intrapartum hysterectomy was registered. This group constituted more than half of the PP cases in our sample, and this is so because the recommendations and protocols for delivery in PP varied with recommendations from 36 up to 38 weeks' gestation. From the analysis and the above, our chosen optimal period of delivery in PP is also the period that is associated with the lowest incidence of emergency deliveries and the lowest reported blood lost.

In the PA group, 8 hysterectomies and 5 partial placental resections were performed at the affected site. The lowest blood lost was reported in hysterectomy cases without attempted of the placenta removal, in which the incision on the uterus was pre-adjusted to the position of the placenta and was most often performed fundal. We can conclude that in PA cases, the average blood lost is largely determined by the operative approach during delivery.

From the results of our study we can concluded that designed clinical protocols used are characterized by relatively high sensitivity and specificity in the diagnosis of PP and PA. The

proposed way of follow-up in the PP group would not increase the cost or prolong a routine ultrasound examination. Adopting this approach in the follow-up, from 20-24 weeks' gestation, in the PP group, until the end of pregnancy will diagnose the majority of cases and will lead to optimal management of each case, with the main goal - optimal outcome of the pregnancy.

Our study and its analysis showed that the application of a screening method in the first trimester of pregnancy, including parameters from the anamnesis and an ultrasound examination, determining the position of the leading placental edge relative to the internal cervical os, will define with high accuracy a high-risk group for placenta accreta anomalies. In our study, all cases of PA occurred in this group. This is the group that will be subject to follow-up and specialized ultrasound examinations for the presence or absence of ultrasound markers suspicious for PA. Our study demonstrated that the use of this approach has high sensitivity and specificity in the diagnosis of PA, and this is of primary importance. Early prenatal diagnosis of this placental pathology will minimize maternal and perinatal morbidity and mortality due to the possibility of proper obstetric management of each case and the mandatory involvement of a multidisciplinary team.

In conclusion, the described ultrasound technique as a method of diagnosis of these placental pathologies is fundamental, and it is also the method that is routinely used to monitor each pregnancy. Knowing the characteristic ultrasound images of PP and PA is extremely important for making a diagnosis, which will lead to correct obstetric managment during each pregnancy. Evaluation of the placenta at each routine ultrasound examination during pregnancy would not increase the cost or prolong the examination. However, at present, evaluation of the placenta is very often neglected, which leads to a number of complications.

7. CONCLUSIONS

1. The incidence of PP in the studied population was 0,7%. The incidence significantly increased in the group with previous Cesarean Section and was 1,3% respectively. In the high risk PA group, an increase in the incidence was registered again and was up to 3,5%.

2. The incidence of PA in the studied population was 0,1%. In the case of PA, an increase in incidence was also demonstrated in the group with a previous Cesarean Section, respectively 0,4%, and again the highest incidence was registered in the high risk group – 1,3%.

3. In our study, the following were established as risk factors for PP: maternal age, mode of conception, gravidity, previous Cesarean Section, previous myomectomy and previous uterine surgery. In the PA group: maternal age, ethnic origin, gravidity, parity, previous Cesarean Section and previous uterine surgery, proved to be risk factors.

   Association between fetal gender and maternal smoking as risk factors was not found in both placental pathologies.

   After analysis, the previous Cesarean Section was determined as a risk factor in both - PP and PA groups, and in the PA group, a correlation between the number of previous Cesarean Sections and the incidence of this placental pathology was proven.

   A statistically significant difference was found for PAPP-A, with higher deviations of this hormone, expected to be observed, in women with PA, in the first trimester of pregnancy.

4. After analyzing the results of our study, we came to the conclusion that the diagnosis of PP can be made at 28-32 weeks' gestation, but it is strongly recommended to follow up all cases with remaining low-lying placenta again at 34-36 weeks' gestation, because a significant part of them undergo placenta migration. The primary method for the diagnosis of PP is the ultrasound examination, and more precisely, the transvaginal ultrasound examination, with an empty bladder and absence of uterine contraction.

The analysis of our study proved that the use of a screening method for stratification patients at high risk for placenta accreta spectrum abnormalities, in the first trimester of pregnancy, combining data from the anamnesis and ultrasound examination, has high diagnostic accuracy. In our study, all cases of PA were found in the thus defined high risk group. Ultrasound marker, used to diagnose PA in our study were: non-visible cesarean section scar, bladder wall interruption, thin retroplacental myometrial thickness, intraplacental lacunar spaces, retroplacental arterial-trophoblastic blood flow and pathology on the 3D images of the placental vascularization with Power Doppler. The diagnosis of PA was made if there were abnormalities in at least three of the above features.

5. Our study results, proved the high sensitivity and specificity of the ultrasound method for the diagnose of PP and PA.

   The sensitivity and specificity of the ultrasound method in diagnosis in PP group at 28-32 weeks' gestation was found to be high 1,0000 and 0,9914, respectively.

   In the PA group, based on the ultrasound markers used and the prenatal diagnosis in the first trimester, the accuracy of the ultrasound method as a screening method in this early period of pregnancy was calculated. Again, the sensitivity and specificity were rated high at 0,92857 and 1,00000.

6. The created score system, with the use of logistic regression, gave the opportunity to study the effect of each of the ultrasound markers used in our study, on the presence or absence of PA. The severity of each of the markers was established. After calculating the points obtained for each case and assigning it to the corresponding probability group, a complete overlap was found in women with "very high" and "high" probability of PA with the results after delivery, which proves the accuracy of the scoring system and the applicability also in practice.

7. In the studied population, the lowest average gestational week at birth was found in cases with PA (35,7 weeks' gestation), followed by PP (37,6 weeks' gestation). The recommended gestational age for delivery, adopted for the purpose of the study, for PA 35+0 up to 36+0 weeks 'gestation and for PP 37+0 to 37+6 weeks' gestation, proved to be optimal after analyzing the results.

8. Our study found a statistically significant difference in the average blood lost in women with PP who delivered between 37+0 and 37+6 weeks'gestation, compared to those who delivered before and after that period. The lowest average blood loss (0,54 l.) was recorded in those who delivered between 37+0-37+6 weeks' gestation. This is the group where we have the lowest percentage of emergency deliveries and majority of deliveries were planned, after preliminary preparation and discussion of the case. After analysis, in the PA group we made conclusion, that the average blood loss is mostly determined by the operative approach during delivery, with a prior diagnosis.

9. The obstetric protocols used in our study are characterized by relatively high sensitivity and specificity in the diagnosis of PP and PA. The proposed way of follow-up in the PP group, would not increase the cost or prolong a routine ultrasound examination. From the study and its analysis, it can be seen that the application of a screening method in the first trimester of pregnancy, including parameters from the anamnesis and ultrasound examination, will define with great accuracy the high risk group for placenta accreta spectrum. This group will be follow-up. Our study demonstrated that the use of this approach has high sensitivity and specificity in the diagnosis of PA.

8. CONTRIBUTIONS OF THE DISSERTATION WORK

Original scientific and applied contributions:

1. Development of a screening method in the first trimester of pregnancy, for early prediction and correct obstetric managment in PA cases.

2. Development of clinical protocols for follow up and obstetric management in pregnancies complicated with PP and PA.

3. Development of a score system for the diagnosis of PA cases.

Contributions of a confirmatory nature:

1. A prospective study was done including 21,474 cases, of which 158 cases had placenta previa and 13 cases had placenta accreta spectrum abnormalities.

2. Demographic and clinical parameters from this study are presented and analyzed.

3. The results in the group with PP and PA and the control group were compared.

4. The incidence of both placental pathologies in the general population and in the high-risk group for placenta accreta was determined.

5. The risk factors for PP and PA have been established.

6. The specificity and sensitivity of the ultrasound method in the diagnosis of PP and PA were investigated.

7. The optimal gestational period of delivery in PP and PA was examined.

8. The average blood lost at delivery was analyzed in the PP group, and in the PA group, and in the PP group this blood lost was analyzed in relation to the gestational period of delivery. In the PA group, the analysis was performed in relation to the method of operative approach.

9. The applicability and effectiveness of the designed clinical model follow-up of cases with PP and PA was analyzed, with the aim of creating clinical protocols for correct obstetric managment.

9. DISSERTATION RELATED PUBLICATIONS

1. Panaiotova J. Ultrasound of the placenta. Normal findings and placenta abnormalities: a review. *Obstetrics and Gynecology* 2016; **55(5):** 41-52.

2. Panaiotova J. Placenta previa: diagnosis and management. Review article. *Obstetrics and Gynecology* 2017; **56(3):**12-20.

3. Zosmer N, Jauniaux E, Bunce C, Panaiotova J, Shaikh H, Nicholaides K. Interobserver agreement on standardized ultrasound and histopathologic signs for the prenatal diagnosis of placenta accreta spectrum disorders. *Int J Gynaecol Obstet* 2018; 326-331.

4. Panaiotova J, Tokunaka M, Krajewska K, Zosmer N, Nicolaides K H. Screening for morbidly adherent placenta in early pregnancy. *Ultrasound Obstet Gynecol* 2019; **53(1):**101-106.

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