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Placental blood flow and pregnancy outcomes in women with abnormal placental localization and absence of placental “migration”

S. V. Barinova, Y. I. Tirskaya, I. V. Shamina, I. O. Ledovskikh and O. J. Atamanenko

Aim: We investigated the arcuate artery blood flow in the region of the abnormally localized placenta in women who had undergone insertion of an obstetric pessary and were receiving micronized progesterone.

Materials and methods: The study included 120 pregnant women with high perinatal risks and abnormal placental localization. The patients were randomized to receive the Arabin’s pessary and vaginal micronized progesterone (Group A, n = 60) or vaginal micronized progesterone only (Group B, n = 60). Randomization was carried based on the order of hospital admission: odd patient numbers were allocated to Group A and even numbers to Group B. Patients underwent a series of ultrasound scans to evaluate the placental migration and presence of abnormal placental attachment. Depending on the results of the scan, study participants were divided into the following groups: (1) patients without placental migration: A1 (n = 23) and B1 (n = 42); and (2) patients with placental migration: A2 (n = 37) and B2 (n = 18). Women in subgroups A1 and B1 were further divided into the subgroups based on the presence of abnormal placental attachment: A1x (n = 5) and B1x (n = 12) with abnormal placental attachment; and A1O (n = 18) and B1O (n = 30) without the abnormal placental attachment.

Conclusion: In patients with abnormal placental attachment, the resistance of blood flow in the arcuate arteries was significantly higher than in those with normal placental attachment. A significant increase in the blood flow resistance occurred between 24 and 28 weeks of gestation. The combined use of the obstetric pessary and vaginal micronized progesterone in women with abnormal placental localization helped maintain the resistivity index at low levels and reduce the rate of abnormal placental attachment by 1.3-fold (OR 0.694 (95% CI: 0.21–2.29)).

Introduction

Prevention of pregnancy and delivery complications in women with high perinatal risks is a central goal of obstetrics. Obstetric bleeding is one of the most dangerous pregnancy complications and is associated with high maternal and perinatal morbidity and mortality. Abnormal localization and attachment of the placenta are among the leading causes of bleeding during pregnancy and delivery [1–3].

The causes of abnormal placental attachment remain unclear to date. It is hypothesized that this condition may be associated with the underlying endometrial pathology or impaired implantation potential of the early-stage embryo. Risk factors for abnormal placental localization include abortions, history of endometritis, presence of the uterine scar after cesarean delivery or myomectomy, uterine fibroids, uterine hypoplasia, sexually transmitted infections (STIs), menstrual disorders, hypothyroidism and other extragenital diseases, as well as smoking and substance abuse during early pregnancy [4,5]. The presence of a uterine scar has been proven to increase the risk of abnormal placental attachment, and there is a direct association between the number of surgeries and the odds of this condition [1]. Abnormal placental localization has been reported in 0.04–0.2% of deliveries [6,7]. Interestingly, the rate of abnormal localization of the villous chorion in the first pregnancy trimester exceeds 10%, while complete placenta praevia is diagnosed only in approximately 0.5% of term pregnancies. This difference in the rates of abnormal chorionic and placental localization is...
caused by placental migration. This phenomenon of gradual placental movement away from the internal os is observed in some women as the lower uterine segment develops and the myometrium in this area stretches and proliferates.

The anatomical and functional condition of the isthmic-cervical uterine region impacts the presence and extent of placental migration. Infections and cervical insufficiency may increase the mechanical tension of the placenta, accelerate the migration, and result in lower abdominal pain and vaginal bleeding. Some authors have noted that placental migration is more pronounced in women with the anterior placenta, but also in patients who had been treated for cervical insufficiency using an obstetric pessary or stitches [8,9].

Current understanding of the functional state of the placenta during its migration and the mechanisms via which the cervical intervention promotes placental migration is limited. Furthermore, there is no consensus on the efficacy of the pessary in women with the abnormal placental location in facilitating placental migration.

Our study aimed to assess and compare the efficacy of different approaches to the management of pregnancies associated with abnormal placental localization and attachment, and determine the ultrasound markers of favorable and unfavorable pregnancy course. To achieve this, we monitored the arcuate artery blood flow in the region of the abnormally localized placenta in women who had undergone insertion of an obstetric pessary and were receiving micronized progesterone and evaluated their pregnancy outcomes.

**Materials and methods**

The study was conducted in the Perinatal center of the Budget Healthcare Omsk Region Institution “Regional Clinical Hospital,” carrying out over 3500 deliveries annually. The proportion of deliveries complicated by the placenta praevia in the last 3 years (between 2015 and 2017) remained steadily at 1.7%.

The study included 120 pregnant women with high perinatal risks and abnormal placental localization. The patients were randomized to receive the Arabin’s pessary and vaginal micronized progesterone (Group A, \( n = 60 \)) or vaginal micronized progesterone only (Group B, \( n = 60 \)). Randomization was carried out by the order of admission: odd patient numbers were allocated to Group A and even numbers to Group B. We used the following inclusion criteria: abnormal placental localization combined with previous obstetric complications and gynecological conditions (late spontaneous abortions, recurrent miscarriage, history of preterm birth, scarring of the cervix). Exclusion criteria were: developmental abnormalities of the fetus, uterine fibroids (intramural or large subserous), multiple pregnancy, relapse of chronic extragenital conditions during pregnancy, cancer, acute infection, preeclampsia, diabetes, and hypertension.

All patients underwent a series of ultrasound scans using the Voluson TM8/EB Expert scanner (GE Healthcare Austria GmbH & Co OG, Austria). We assessed the condition of the fetus and cervix and measured the Pourcelot index in the arcuate arteries of the placental area. We also measured the anterior uterine-cervical angle between the anterior wall of the lower uterine segment and the cervical canal axis. Ultrasound scans were performed between 18 and 20 weeks of pregnancy (before the pessary insertion), between 23 and 24 weeks, at 28 weeks, and between 32 and 33 weeks. We also evaluated the ultrasound signs of placental migration.

Depending on the result of the scans, participants were divided into the following groups: women without placental migration: \( A_1 \) (\( n = 23 \)) and \( B_1 \) (\( n = 42 \)); and women with placental migration: \( A_2 \) (\( n = 37 \)) and \( B_2 \) (\( n = 18 \)). Women in subgroups \( A_1 \) and \( B_1 \) were further divided into subgroups depending on the presence of abnormal placental attachment: \( A_{1x} \) (\( n = 5 \)) and \( B_{1x} \) (\( n = 12 \)) with the abnormal attachment of the placenta; and \( A_{1O} \) (\( n = 18 \)) and \( B_{1O} \) (\( n = 30 \)) without the abnormal attachment of the placenta. The patient disposition is presented in the Supplementary Appendix.

At this phase of the study, we investigated the uterine-placental blood flow and changes in the uterine-cervical angle in groups \( A_1 \) and \( B_1 \). The results of the first phase of this study have been published in 2018 [10].

The ultrasound method enables to diagnose the abnormal placental localization from the first trimester; however, in 26–60% of these cases the placenta undergoes spontaneous migration by 20 weeks of pregnancy [11]. Our study included the patients who had not demonstrated spontaneous migration of abnormally localized placenta by that gestational age. We considered the gestational age of 18–20 weeks as a threshold for lower odds of subsequent spontaneous placental migration and proceeded with pessary insertion to patients in Group A at this stage of pregnancy.
The pessary was selected based on the cervical length [12]. Before the insertion of the pessary, we performed vaginal swab microscopy and endocervical culture, including antibiotic sensitivity tests, in all participants. In patients with vaginal dysbiosis, we administered a course of antimicrobial therapy based on the results of antibiotic sensitivity, followed by a course of vaginal ascorbic acid (250 mg; reg.No LSR-005889/08 from 23.07.08) to restore the microbiome. Vaginal swab microscopy was then performed monthly and, additionally, in the cases of bacterial vaginosis symptoms.

In all study groups (A and B), patients received 200 mg of vaginal micronized progesterone daily from 7–9 weeks until 32 weeks of pregnancy. Intrapartum and postpartum blood loss were measured gravimetrically.

Statistical data analysis was performed using Statistica 12.0. Data are presented as a median (lower quartile; upper quartile). Quantitative and order variables were compared using the nonparametric Mann–Whitney (U), Wilcoxon, and Kolmogorov–Smirnov tests; the \( \chi^2 \)-square with Yates’ correction was used as appropriate. When testing statistical hypotheses, the level of critical significance \( p < 0.05 \) was utilized.

### Results

Our study included 120 pregnant women with placenta praevia, of which 65 patients (subgroups A1 and B1) did not demonstrate placental migration. The average age of participants was 31 (27–35) years. There were no significant differences in the age, number of previous pregnancies, deliveries, and abortions, and rates of somatic and gynecological conditions.

Placental migration was more common in multiparous compared with primiparous women (87.7% [57/65] versus 12.3% [8/65], respectively). All patients included in our study had previous obstetric complications or a history of gynecological conditions. History of infertility was present in 23% (15/65) of women, uterine fibroids in 13.8% (9/65), and second-trimester spontaneous pregnancy loss in 46.1% (30/65). The rate of preterm birth in Group A was 24.6% (16/65). Genital inflammation had occurred in 36.9% (24/65). More than a third of the study participants had undergone cesarean delivery (35% [23/65]). Postpartum endometritis had been previously diagnosed in 13.8% (9/65) of women. Incomplete placenta praevia was the most common type of abnormal placental localization (69.6% [16/23] in Group A1 and 64.3% [27/42] in Group B1; \( p = .6453 \)). The low placenta was present in 17.4% (4/23) of patients in Group A1 and 21.4% (9/42) in Group B1 (\( p = .0512 \)). Complete placenta previa was present in 14% (3/23) of patients in Group A1 and 14.3% (6/42) in Group B1 (\( p = .8534 \)).

In subgroup B1, vaginal spotting was reported in 64.3% (27/42) of women versus 17.4% (4/23) in Group A1 (\( \chi^2 = 4.195; p = .04 \)). Intrapartum bleeding developed 30.4% (7/23) of women in Group A1 compared with 85.7% (36/42) in Group B1 (\( \chi^2 = 3.805; p = .05 \)).

Ultrasound scans were performed at 18–20, 24, 28 and 32–33 weeks of pregnancy. We measured the cervical length using a vaginal scan as we deemed this technique more accurate compared with the transabdominal scan. In Group A1, cervical length did not change significantly over the course of pregnancy (\( p = .075 \)). In contrast, in Group B1, the cervix shortened significantly, by 7.5 mm (\( p < .05 \)). We did not, however, view this cervical shortening as clinically meaningful, since the median cervical length at 33 weeks of pregnancy still reached 30.5 mm (29.0; 32.5). Nevertheless, our findings show that the use of obstetric pessary in addition to vaginal progesterone may prevent cervical shortening in high-risk pregnancies. Detailed measurements of the cervical length in study participants are presented in Table 1.

In the first phase of our study, we observed that the insertion of obstetric pessary in subgroups A2 and B2 altered the uterine-cervical angle and promoted placental migration [10]. In this study, there were no significant changes in the uterine-cervical angle in subgroups A1 and B1 without placental migration.

The uterine-cervical angle in subgroup A1 was 98° (90; 99) at 18 weeks, 105° (95; 102) at 24 weeks, 102° (96; 103) at 28 weeks and 100° (97; 102) at 33 weeks. These values were not significantly different from subgroup B1, in which the uterine-cervical angle was 96° (92; 98) at 18 weeks, 97.5° (93; 99) at 24 weeks, 98.5° (93; 100) at 28 weeks and 98° (93; 99) at 33 weeks.

We also measured the Pourcelot (resistivity) index in the arcuate arteries in the region of the abnormally localized placenta. Over the course of pregnancy, the

<table>
<thead>
<tr>
<th>Table 1. Cervical length throughout pregnancy.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age</td>
</tr>
<tr>
<td>-----------------</td>
</tr>
<tr>
<td>Group A1</td>
</tr>
<tr>
<td>Group B1</td>
</tr>
</tbody>
</table>

Data presented as median (25%; 75%).

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[10]: The Journal of Maternal-Fetal & Neonatal Medicine, [Volume Issue], [Page Numbers].
resistivity index in subgroups A1 and B1 gradually increased (Table 2). In patients who had undergone the pessary insertion, blood flow resistance increased by 1.12-fold between 18 and 33 weeks of pregnancy ($p = .0004$). In subgroup B1, the increase was 1.22-fold ($p = .024$). In subgroup B1 receiving micronized progesterone only, the blood flow between 18 and 24 weeks increased by 1.15-fold ($p = .0005$). In subgroup A1, the blood flow remained unchanged. There were no further resistivity index changes in the arcuate arteries between 24 and 33 weeks of pregnancy in both subgroups. At the same time, women who used only micronized progesterone had significantly higher resistivity index at 24 and 33 weeks of pregnancy versus subgroup A1 ($p = .08; p = .0028$, respectively).

Thus, the use of pessary in addition to vaginal micronized progesterone in patients with abnormal placental localization prevented the increase in arcuate artery resistivity index in the placental area.

The resistivity index at the placental site did not differ in groups A1x and A1O (combined use of the pessary and vaginal micronised progesterone) at 18 weeks ($p = .7942$), the start of the treatment and 24 weeks ($p = .1921$) (Figure 1(A)). The Pourcelot index differed significantly between the groups only at 28 weeks of pregnancy. In the subgroup A1O, the arcuate artery blood flow was significantly lower (resistivity index 0.61 (0.57; 0.69) than in subgroup A1x (resistivity index 0.70 (0.70; 0.77); $p = .0073$). Similarly, the resistivity index at 33 weeks of pregnancy in subgroup A1O was significantly lower (0.66 (0.58; 0.70)) than in subgroup A1x (0.70 (0.70; 0.77); $p = .0482$). Therefore, in women with abnormal placental attachment (subgroup A1x), there was an increase in blood flow resistance at the placental site between 24–28 weeks, and the high resistivity index subsequently did not change.

In subgroup A1O without placental attachment abnormalities, the resistance of blood flow at 28 and 33 weeks of pregnancy was lower ($p < .05$) than in women in subgroup A1x.

There was a similar pattern of changes in the arcuate artery blood flow at the placental site in subgroups B1x and B1O (Figure 1(B)). Patients in subgroup B1x with placenta accreta had an increase in the resistivity index between 24 weeks (0.7 (0.68; 0.72)) and 28 weeks (0.74 (0.72; 0.81)) of pregnancy ($p = .0179$) with a further slight increase to 0.78 (0.78; 0.74) at 33 weeks of pregnancy. These values differed significantly compared with women with the normal attachment of the placenta. Specifically, the resistivity index at 28 weeks of pregnancy in subgroup B1O was 0.68 (0.66; 0.72), significantly lower than in subgroup B1x ($p = .0006$). At 33 weeks, the resistivity index in women in subgroup B1O was significantly lower (0.72 (0.76; 0.74); $p = .0149$) than in subgroup B1x. In summary, in women with abnormal placental attachment (subgroup B1x), there was an increase in the resistance of arcuate artery blood flow between 24–28 weeks of pregnancy, followed by a further increase in the resistivity index by 33 weeks.

In subgroup B1O, the resistivity index did not show a significant change between 18 and 24 weeks ($p = .0000$). The blood flow stabilized between 24 and 28 weeks ($p = .4331$) and further increased by 33 weeks ($p = .0038$). However, in subgroup B1O with normal placental attachment, blood flow resistance at 28 and 33 weeks of pregnancy was lower ($p < .05$), than in subgroup B1x.

We have identified a correlation between the resistivity index at 28 weeks and abnormal placental attachment ($r = .51$). There was a moderate correlation between the resistivity index at 33 weeks and abnormal placental attachment ($r = .36$).

In subgroups A1O and B1O, the resistance of blood flow at 18 weeks (at the time of therapy initiation) was not significantly different ($p = .1699$) (Figure 1(C)). Subsequently, there blood flow resistance was lower in subgroup A1O. The resistivity index at 24 weeks of pregnancy in the pessary group was 0.62 (0.58; 0.66) and was significantly lower ($p = .0132$) compared with the micronized progesterone-only group (0.67 (0.65; 0.70)). The resistivity index was significantly different between groups A1O and B1O at 28 weeks ($p = .0147$) and 33 weeks ($p = .0073$).

In subgroups A1x and B1x with abnormal placental attachment, there were no significant differences in the resistivity index at all gestational ages when the follow-up Doppler scan was performed (Figure 1(D)).

### Table 2. Arcuate artery resistivity index in subgroups A1 and B1.

<table>
<thead>
<tr>
<th>Group</th>
<th>18–20 weeks</th>
<th>24 weeks</th>
<th>28 weeks</th>
<th>33 weeks</th>
<th>Wilcoxon p-value 18/24</th>
<th>Wilcoxon p-value 28/33</th>
<th>Wilcoxon p-value 18/33</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1</td>
<td>0.59 (0.55; 0.64)</td>
<td>0.62 (0.58; 0.66)</td>
<td>0.64 (0.57; 0.69)</td>
<td>0.66 (0.6; 0.7)</td>
<td>.053</td>
<td>.322</td>
<td>.0004</td>
</tr>
<tr>
<td>B1</td>
<td>0.58 (0.52; 0.61)</td>
<td>0.67 (0.65; 0.7)</td>
<td>0.67 (0.66; 0.72)</td>
<td>0.71 (0.67; 0.8)</td>
<td>.0005</td>
<td>.18</td>
<td>.024</td>
</tr>
<tr>
<td>Mann–Whitney p-level A1/B1</td>
<td>.2</td>
<td>.008</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Data presented as a median (25%; 75%).*
It is worth noting that all patients in these subgroups had a history of either cesarean delivery (88.2% [15/17]) or myomectomy (17.6% [3/17]). Additionally, all women had a history of surgical abortion or missed miscarriage associated with retention of the products of conception, or postpartum endometritis.

There was a trend towards higher odds of abnormal placental attachment in subgroup B1 versus group A1; however, the difference was not significant (0.694 [0.21; 2.29], $F$ risk ratio $= 0.7687$).

All patients with abnormal placental arrangement had cesarean delivery at 37 weeks of pregnancy. A third of the women (30.4% [7/23]) in Group A1 and 85.7% (36/42) in Group B1 developed intrapartum bleeding ($\chi^2 = 3.805; p = .05$). In subgroups $A_{1x}$ and $B_{1x}$, invasion of the placenta into the retrovesical pouch was observed in 23.5% (4/17) of cases. In one case, this included the penetration of blood vessels, and in two cases penetration of the infundibulopelvic and sacrouterine ligaments. Cesarean delivery in these patients was complicated by severe bleeding of 2000–5000 ml. The median intrapartum blood loss was 1800 ml (1000; 2000) and was not significantly different between Groups $A_{1x}$ and $B_{1x}$ ($p = .27$).
Due to a high risk of bleeding, we inserted a vaginal Zhukovsky catheter in all patients with abnormal placental localization prior to the surgery and expanded the catheter with saline immediately after the fetus had been delivered. All subsequent steps of the surgery were carried out with the expanded vaginal catheter present. We also performed ligation of the descending branches of uterine arteries immediately after the delivery.

In patients with placental invasion of up to one-third of myometrial thickness, the affected section of the myometrium was excised, and a ∞-shaped stitch placed in the placental bed area. If the cases of invasion of over two-thirds of myometrial thickness, we also excised the affected section [13–15]. We then inserted an intrauterine Zhukovsky catheter and completed the procedure. The duration of the balloon tamponade was between 10 and 14 h. In three patients, we performed hysterectomy due to severe bleeding and inefficiency of hemostatic measures and metroplasty.

Discussion

Current research into the placental pathology aims to identify the signs of abnormal placental attachment and use medical imaging such as magnetic resonance imaging (MRI) and ultrasound to detect it [16–18]. Some publications also compared the diagnostic accuracy of MRI and ultrasound [19,20].

Several authors evaluated the correlation between various ultrasound signs of abnormal placental attachment, according to the system proposed by the International Federation of Gynecology and Obstetrics (FIGO), and the delivery outcomes. The authors evaluated the placental bed vascularization index as a marker of abnormal placental attachment.

One of the studies assessed the index of placental bed vascularization as a marker of placenta accreta [21]. A study by De Vita confirmed that irregularly shaped placental lacunae with turbulent blood flow are a marker of this condition [22]. Other authors stated that measuring the myometrial thickness at the placental site is the most accurate diagnostic tool for the detection of placenta accreta [23]. Another research group looked into the degree of placental invasion by evaluating the retroplacental hypoechoic zone between the placenta and the serous membrane of the uterus, and between the placenta and the myometrium [24]. Other studies have investigated the ultrasound signs of abnormal placental attachment at 11–14 weeks of pregnancy in patients after cesarean delivery.

Today’s consensus is that the assessment of placental bed vascularization is a prerequisite for the diagnosis of abnormal placental attachment. The main risk factor for this placental pathology is past uterine surgeries, particularly cesarean delivery, and the risk is further increased in patients with a combination of placenta previa and a uterine scar. The timing of the deep invasion of chorionic villae into the myometrium remains unknown.

In our study, we evaluated pregnant women diagnosed with placenta previa in the second trimester using four ultrasound scans, including Doppler scans of the placental region. We measured the Pourcelot index in the arcuate arteries in the region of the abnormally localized placenta. We chose this test as it reflects the resistance towards the blood flow in the distal direction from the point of measurement. We believe the arcuate artery resistivity index represents a proxy for the blood flow in the immediate proximity of the placenta.

We found that in patients with abnormal placental attachment the resistivity index in the arcuate arteries was higher than in those with normal attachment. Furthermore, the resistivity index significantly increased between 24 and 28 weeks of pregnancy. We hypothesize that the altered blood flow dynamics promote the invasion of the anchoring villae into the myometrium, to locate more efficient sources of blood supply. Our data on the increased rate of abnormal placental attachment in women after cesarean delivery are in line with other reports [25].

The use of the pessary in women with abnormal placental localization was associated with a reduction in the resistivity index versus controls and a decrease in the rate of abnormal placental attachment by 1.3-fold (odds ratio (OR) 0.694; 95% confidence interval (CI): 0.21–2.29). We believe that the lack of statistical significance of our results in women with the abnormal placental attachment was caused by the alteration of endo- and myometrial anatomy and function due to past obstetric and gynecological pathology.

Conclusions

In this study, we showed that the resistance of uterine blood flow in women with abnormal placental localization increases by 1.1–1.2 fold between 18 and 33 week of pregnancy. In women with abnormal placental attachment, the resistivity index at the placental site is higher than in those with normal placental attachment. The combined use of the obstetric pessary and vaginal micronized progesterone in women with abnormal placental localization helped maintain
the resistivity index at low levels and reduce the rate of abnormal placental attachment by 1.3-fold (OR 0.694 (95% CI: 0.21–2.29)).

Disclosure statement
No potential conflict of interest was reported by the authors.

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