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Research Article

The Effect of Vaginal Bleeding in Early Pregnancy on First Trimester Screening Test, Uterine Artery Doppler Indices and Perinatal Outcomes

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Abstract

Aim: We aimed to prospectively investigate the effect of first trimester vaginal bleeding on first trimester screening test, uterine artery (UtA) Doppler results and perinatal outcomes.

Material and Methods: Fifty cases that presented with vaginal bleeding in the first trimester between 2019 and 2020 constituted the early vaginal bleeding (abortus imminens-threatened abortion) group and fifty cases without a history of vaginal bleeding in pregnancy constituted the control group. Demographic datas were noted at the first visit. Both groups were followed up until birth. First trimester screening test (double screening test) between 11-14 weeks and UtA Doppler examination between 20-24 weeks of gestation was performed. Perinatal outcomes and values of nuchal translucency (NT), free β human chorionic gonadotropin (f β-hCG), pregnancy-associated plasma protein A (PAPP-A), and UtA Doppler were compared between the two groups.

Results: There was no statistically significant difference was found between the two groups in terms of NT and PAPP-A among the first trimester screening test results (p=0.741 and p=0.937, respectively). In the group with threatened miscarriage, f β-hCG value was numerically higher, but there was no statistically significant difference (1.24±0.59 vs. 1.1±0.93, p=0.057). In the Doppler examination of the UtA, there was no statistically significant difference between the groups in terms of systolic/diastolic ratio, pulsatility index, resistive index and the presence of a notch (p=0.713, p=0.528, p=424, p=0.538, respectively). Perinatal complication rate was statistically significantly higher in the study group (p=0.013; Odds Ratio:3.2, 95% CI 1.2-8.3).

Conclusion: Contrary to some different studies, we believe that first trimester screening test parameters or uterine artery Doppler flow indices do not have a place in predicting perinatal outcomes of pregnant women with a history of vaginal bleeding in the first trimester. In addition, early vaginal bleeding does not significantly affect screening parameters. Perinatal complication rate was found to be statistically significantly higher in the group with a history of threatened miscarriage.

Keywords: Doppler, uterine artery, abortus imminens, threatened abortion, vaginal bleeding, first trimester

INTRODUCTION

Chromosomal major diseases cause serious health, sociological and economic problems. Early screening methods have been developed for these diseases, which do not have a specific treatment. The two main methods used today are first trimester screening test (double screening test) and fetal anomaly screening ultrasound. The first trimester screening test is performed in the first trimester between 11-14 weeks. In fetal trisomy screening in the first trimester, the rate of trisomy 21 detection reaches around 90% with 5% false positivity, with the double screening test performed by adding nuchal translucency (NT) measurement to maternal serum pregnancy-associated plasma protein A (PAPP-A) and free β human chorionic gonadotropin (f β-hCG) values (1–3). In our tertiary center, the first trimester screening test is performed in accordance with the recommendations of

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the American College of Obstetricians and Gynecologists (ACOG) (3).

Fetal anomaly screening ultrasound is the detailed examination of the organs, systems and tissue structures of the fetus. Fetal anomaly screening ultrasound is performed between 18-24 weeks (4). Fetal anomaly screening ultrasound is also performed in our tertiary care center in line with The International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) recommendations (4). One component of this screening ultrasound is uterine artery (UtA) Doppler indices. Compliance decreases with trophoblastic invasion to the spiral artery, which is a branch of the uterine artery. Placental insufficiency prevents the decrease in compliance and changes that would give findings in UtA Doppler measurement cause adverse perinatal outcomes (5). The specificity of the test (86-96%) in diagnosing perinatal complications (fetal growth restriction, preeclampsia, and prenatal death) is higher than its sensitivity (24-89%) (6).

Threatened abortion (abortus imminens) is vaginal bleeding in which the cervix is closed before 20 weeks of gestation (7). Early vaginal bleeding occurs in about a quarter of pregnant women (8). The etiology of vaginal bleeding has not been fully elucidated, but one of the most important causes is the separation of decidual vessels on the maternal-fetal face (9). It is well known that vaginal bleeding in early pregnancy affects the serum alpha-fetoprotein value (10,11), but its effect on other parameters is controversial. Some studies argue that early pregnancy bleeding affects serum PAPP-A and f β-hCG values (12,13), while some studies argue that there is no significant effect (14,15). Similarly, some studies have associated uterine artery resistance with early pregnancy bleeding, but all these studies were conducted at the time of bleeding in early pregnancy (16,17), long-term follow-up was not investigated. There are no suitable randomized prospective cohort studies on these parameters. Therefore, we aimed to prospectively investigate the effects of first trimester vaginal bleeding on NT, f β-hCG and PAPP-A values measured in first trimester screening, and UtA Doppler indices measured in second trimester fetal anomaly screening. We also evaluated the perinatal outcomes of these patients.

MATERIAL AND METHOD

This prospective cohort study was conducted with pregnant women selected between January 2019 and April 2019 in a tertiary referral center. Power analysis was performed with G-power for the number of samples. Accordingly, a minimum limit of 34 people was found for each group. A total of 100 pregnant women, 50 pregnant women who applied to the emergency service and pregnancy outpatient clinics with first trimester (before the 12th gestational week) vaginal bleeding (threatened abortion group), and 50 pregnant women who did not experience any vaginal bleeding during pregnancy (control group), were included in this study. Exclusion criteria were being younger than 18 and older than 40 years of age, previous diagnosis of habitual abortion and/or cervical insufficiency, and a history of conization. The cases were followed up until January 2020, when all of them already gave birth (Figure 1).

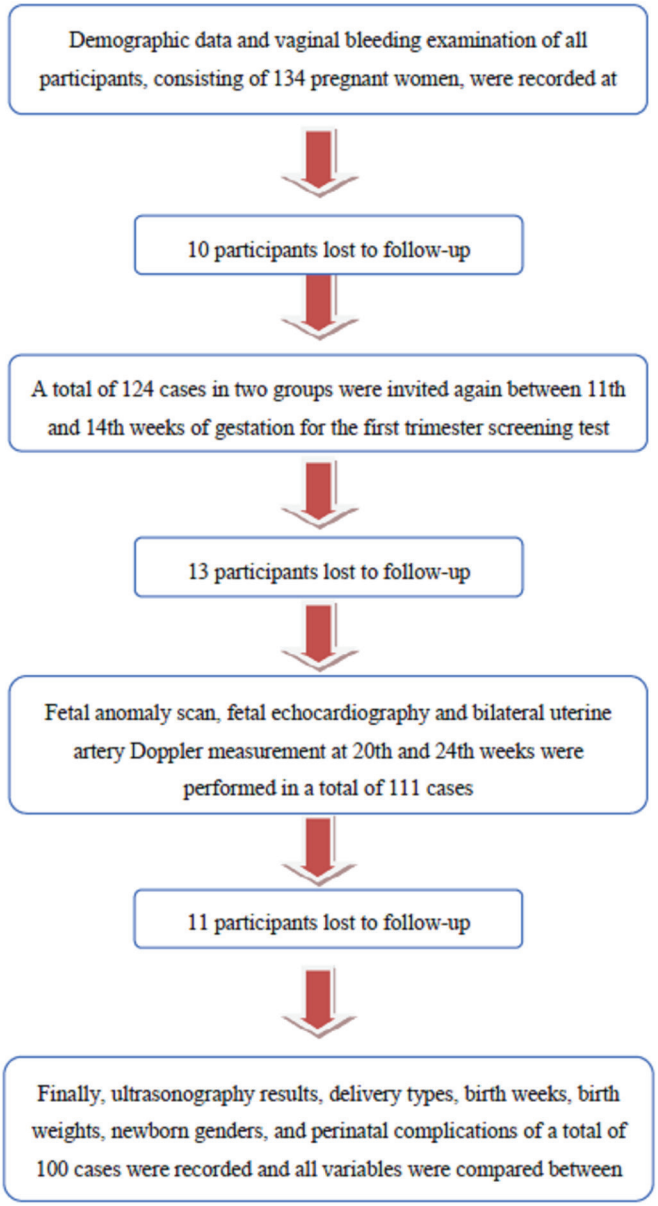

Figure 1. Flow chart of participants

This study was conducted following the Helsinki Declaration Ethical Standards. The ethics committee approval for this study was obtained from the University of Health Sciences Tepecik Training and Research Hospital Local Ethics Committee (approval number: 2018/ 16-9). The nature and aims of the study were fully explained to all the participants, and consent forms were signed by all participants.

Age, body mass index (BMI), parity, blood pressure and heart rate values of the cases were recorded at the first visit. The threatened abortion group was given 400 mg natural micronized progesterone (Progestan ®, Kocak Pharma, Tekirdag, Turkey) daily treatment during the period

of bleeding. The bleeding was classified as mild/severe according to its amount. Spotting and bleedings up to 1 pad/day were considered mild and bleedings of 2 pads/day and above were considered severe. Control group cases were enrolled consecutively in similar pregnancy weeks. A total of 100 cases in two groups were invited again between 11-14 weeks of gestation (within the range of 45mm≤ crown-rump length (CRL) <84mm) for the first trimester screening test. Fetal imaging was performed abdominally with Toshiba Aplio 500 (Toshiba Medical Systems, Tokyo, Japan) ultrasound device. Following the CRL and NT MoM measurements in the first trimester ultrasound examination, f β-hCG MoM and PAPP-A MoM values in maternal blood detected in the laboratory were recorded. The results obtained were combined with maternal age and weight, diabetes and smoking history, as well as a history of having a baby with Down Syndrome and evaluated with Prisca 5.0 Software (Prenatal Risk Calculator, Typolog Software GmBH, Hamburg, Germany) in terms of trisomy 21, 13, and 18, and risk scores were established.

UtA Doppler measurements were made between 20-24 weeks of pregnancy in all these cases. All UtA Doppler measurements were performed by the same individual to prevent inter-practitioner variability. The practitioner (M.B.) with the Doppler certificate of The Fetal Medicine Foundation made an abdominal evaluation in the supine position by using Toshiba Aplio 500 (Toshiba Medical Systems, Tokyo, Japan). First, the uterine artery was defined with color Doppler by slightly bending the probe in the sagittal plane at the same level as internal cervical os and a regular flow wave form was created with pulsed wave Doppler. UtA systolic/diastolic ratio (S/D), resistive index (RI), pulsatility index (PI) and the presence of notch were evaluated bilaterally in the wave form image. Presence/absence of bilateral notch, presence/absence of notch on any side, presence/absence of an increase in bilateral RI resistance, presence/absence of an increase in RI resistance on any side, presence/absence of an increase in resistance in the mean RI value of the two uterine arteries and the mean RI, PI, S/D values of two UtA were compared between the two groups. It was considered that an increase was present when RI was >0.58.

Finally, ultrasonography results, delivery type, delivery weeks, birth weights, newborn genders, and perinatal complications of for all cases were recorded. Preterm birth threat, preterm labor, minor fetal anomaly, premature rupture of membranes, placenta accreta, fetal growth restriction, gestational hypertension, preeclampsia, oligohydramnios, gestational diabetes, cholestasis, postpartum atony, placenta abruption were defined as perinatal complications.

Statistical Analysis

Before starting the statistical analysis, all parametric variables were evaluated in terms of normality and homogeneity assumptions. Independent variables conforming to the assumption were evaluated with the Independent Samples T Test, and those not conforming to the assumption with Mann Whitney U test. Categorical variables were evaluated by using the Chi Square and Fisher's Exact Tests. Descriptive statistics were given as mean ± SD, median (minimum-maximum) and n (%). p <0.05 was considered significant. SPSS 22.0 (SPSS Inc., Chicago, Illinois) software was used in statistical analysis.

RESULTS

Our prospective cohort study was completed with the data of 100 patients including a case group that experienced threatened miscarriage (n=50) and a control group (n=50). In the study group, 40 (80%) of the patients had mild vaginal bleeding and 10 (20%) had severe vaginal bleeding. Demographic and clinical data of participants are summarized in Table 1. Both groups were similar in terms of maternal age, BMI, and parity. The pulses (79±8 vs. 77±8, p=0.546), systolic blood pressures (110±13 vs. 110±13, p=0.866), and diastolic blood pressures (64±19 vs. 67±11, p=0.536) of both groups were statistically similar.

Table 1. Demographic and clinical data of participants

	Threatened miscarriage n=50	Control n=50	P Value
Age (mean±SD)	29.1±5.8	27.7±5.4	0.195*
Body mass index (mean±SD)	26.1±5.0	26.5±5.1	0.712*
Parity (n,%)			0.689[a]
Nulliparous	23 (46%)	25 (50%)	
Multiparous	27 (54%)	25 (50%)	
Pulse (bpm) (mean±SD)	79±8	77±8	0.546*
Blood pressure (mmHg) (mean±SD)			
Systolic	110±13	110±13	0.866*
Diastolic	64±19	67±11	0.536*

*Independent Sample T Test, [a]Pearson Chi Square Test

First trimester screening test results are summarized in Table 2. No statistically significant difference was found between the threatened miscarriage and control groups in terms of CRL sizes on ultrasound (61.66±8.30 vs. 61.83±9.25, p=0.922), NT MoM values (0.90±0.36 vs. 0.88±0.21, p=0.741) and maternal serum PAPP-A MoM values (0.99±0.51 vs. 0.97±0.52, p=0.937). Although the f β-hCG MoM values were numerically higher in the threatened miscarriage group, the result could not reach a significant level (1.24±0.59 vs. 1.10±0.93, p=0.057).

Table 2. First trimester screening test results

	Threatened miscarriage n=50	Control n=50	P Value
CRL (mm) (mean±SD)	61.66±8.30	61.83±9.25	0.922*
NT (MoM) (mean±SD)	0.90±0.36	0.88±0.21	0.741*
f β-hCG (MoM) (mean±SD)	1.24±0.59	1.10±0.93	0.057*
PAPP-A (MoM) (mean±SD)	0.99±0.51	0.97±0.52	0.937*

Abbrevations: CRL: Crown-rump length, NT: Nuchal translucency, f β-hCG: Free beta human chorionic gonadotropin, PAPP-A: Pregnancy-associated plasma protein A, MoM: Multiple of the median
*Independent Sample T Test

Comparison of uterine artery Doppler measurement results is summarized in Table 3. Accordingly, bilateral (6% vs. 6%, N/A) and any side (11.1% vs. 14%, p=0.538) uterine notch was observed at a statistically similar rate in both groups. Bilateral S/D (0.62±0.09 vs. 0.62±0.10, p=0.713), RI (1.25±0.43 vs. 1.27±0.35, p=0.432) and PI (3.02±1.18 vs. 3.05±1.09, p=0.528) arithmetic mean was similar between the groups. Bilateral (20% vs. 14%, p=0.424), any side (58% vs. 46%, p=0.230) and arithmetic mean (68% vs. 76%, p=0.373) RI increases were observed to be similar in both groups.

Table 3. Comparison of uterine artery doppler measurement results

	Threatened miscarriage n=50	Control n=50	P Value
Bilateral Notch (n,%)			N/A
Yes	3 (6%)	3 (6%)	
No	47 (94%)	47 (94%)	
Notch (Any Side) (n,%)			0.538[α]
With	5 (11.1%)	7 (14%)	
Without	45 (88.9%)	43 (86%)	
Bilateral S/D Arithmetic Mean (mean±SD)	0.62±0.09	0.62±0.10	0.713[*]
Bilateral RI Arithmetic Mean (mean±SD)	1.25±0.43	1.27±0.35	0.432[*]
Bilateral PI Arithmetic Mean (mean±SD)	3.02±1.18	3.05±1.09	0.528[*]
Bilateral RI Increased Resistance (n,%)			0.424[α]
With	10 (20%)	7 (14%)	
Without	40 (80%)	43 (86%)	
RI Increased Resistance (Any Side) (n,%)			0.230[α]
With	29 (58%)	23 (46%)	
Without	21 (42%)	27 (54%)	
RI Arithmetic Mean Increased (n,%)			0.373[α]
With	34 (68%)	38 (76%)	
Without	16 (32%)	12 (24%)	

Abbrevations: S/D: systolic/diastolic ratio, RI: resistance index, PI: pulsatility index
[*]Independent Sample T Test, [α]Pearson Chi-Square Test

Perinatal outcomes are showed in Table 4. In the light of all data obtained, the perinatal complication rate was found to be statistically significantly higher in the group with a history of threatened miscarriage (p=0.013; Odds Ratio: 3.2, 95% CI 1.2 - 8.3). These complications were threatened preterm labor in 5 (26.3%) cases, preterm labor in 3 (15.8%) cases, minor fetal anomaly in 3 (15.8%) cases, premature rupture of membranes in 1 (5.3%) case, placental invasion abnormality in 1 (5.3%) case, fetal growth restriction in 1 (5.3%) case, gestational hypertension in 1 (5.3%) case, preeclampsia in 1 (5.3%) case, gestational diabetes in 1 (5.3%) case, cholestasis in 1 (5.3%) case, and postpartum atony in 1 (5.3%) case, respectively in the cohort group. Uneventful pregnancy rate in threatened miscarriage group was 42% (n=31), control group was 84% (n=42). Delivery week and birth weight are statistically similar between the groups (p=0.108 and p=0.495, respectively). In addition, there was no statistically significant difference in the mode of delivery and primary cesarean rates between the two groups (p=0.422 and p=0.389, respectively).

Table 4. Perinatal outcomes

	Threatened miscarriage n=50	Control n=50	P Value
Perinatal complication (n,%)			0.013[α]
With	19 (38%)	8 (16%)	
Preterm Birth Threat	5 (26.3%)	1 (12.5%)	
Preterm Labor	3 (15.8%)	0	
Minor Fetal Anomaly	3 (15.8%)	1 (12.5%)	
Premature rupture of membranes	1 (5.3%)	0	
Placenta Accreta	1 (5.3%)	0	
Fetal Growth Restriction	1 (5.3%)	1 (12.5%)	
Gestational Hypertension	1 (5.3%)	1 (12.5%)	
Preeclampsia	1 (5.3%)	1 (12.5%)	
Oligohydramnios	0	1 (12.5%)	
Gestational Diabetes	1 (5.3%)	1 (12.5%)	
Cholestasis	1 (5.3%)	0	
Postpartum Atony	1 (5.3%)	0	
Placental Abruption	0	1 (12.5%)	
Without	31 (42%)	42 (84%)	
Birth type (n,%)			0.422[β]
Vaginal	21 (42%)	25 (50%)	
C- Section	29 (58%)	25 (50%)	
C- Section type (n,%)			0.389[α]
Primer	14 (48.3%)	15 (60%)	
Seconder	15 (51.7%)	10 (40%)	
Birth time (week) median (min,max)	38 (23-41)	39 (26-41)	0.108[x]
Birth weight (g) (mean±SD)	2980±704	3140±591	0.495*
Newborn gender (n,%)			0.420[α]
Female	30 (60%)	26 (52%)	
Male	20 (40%)	24 (48%)	

[*]Independent Sample T Test, [x]Mann Whitney U Test [α]Pearson Chi-Square Test, [β]Fisher's Exact Test

DISCUSSION

In this study, it was found that vaginal bleeding in early pregnancy did not significantly affect first trimester screening test (double screening) parameters as NT, f β-hCG and PAPP-A. Also, contrary to expectations, UtA Doppler indices and RI resistance were not affected by first trimester bleeding. However, threatened miscarriage was associated with 3.2 times more perinatal complications.

In the literature, the effect of vaginal bleeding in early pregnancy on especially f β-hCG MoM, which is one of the first trimester tests, is controversial. Spencer et al. investigated the first trimester screening test results of 42183 pregnant women with a history of threatened miscarriage and 7470 pregnant women with a normal pregnancy in two groups. As in the present study, there was no statistically significant difference between the f β-hCG MoM and PAPP-A MoM values of the patients who had vaginal bleeding in the early gestational weeks (14). In another study, 253 pregnant women with vaginal bleeding in early gestational weeks were compared with 2077 pregnant women with a normal pregnancy in terms of first trimester screening test parameters, and there was a statistically significant increase in the f β-hCG MoM value, contrary to our study result; however, no difference was found in PAPP-A MoM and NT values (12). In a similar smaller-scale study, although there was a statistically significant increase in f β-hCG MoM and PAPP-A MoM values, no increase was observed in the risk of Down Syndrome of above 1/250 in the first trimester screening test (18). However, all these studies are retrospective. Our results are based on prospective, long-term follow-up.

Heinig et al. reported that first trimester screening test parameters would not be affected by bleedings in the form of spotting. However, when there was an increased amount of bleeding they found a statistically significant increase in f β-hCG MoM (13). In the present study, in the analyses of subgroups according to the amount of bleeding, there was no statistically significant difference in β-hCG, PAPP-A, NT, and UtA Doppler values. We did not find a significant difference in these values according to the amount of bleeding. This may be due to the relatively different evaluation of the amount of bleeding. Heinig et al. classified the amount of bleeding according to the amount in the menstrual cycle of women. On the other hand, we tried to classify more objectively by performing prospective pad follow-up.

Histological examinations showed that insufficient trophoblastic invasion into the spiral arteries caused the miscarriages (19). Therefore, we considered that early evaluation of placentation with Doppler measurement could give us information about pregnancy outcomes in cases with threatened miscarriage. In our study, the limit value for the increased resistance in UtA Doppler measurement was determined as RI=0.58, which is used to predict preeclampsia, fetal growth restriction, and fetal death (20). In the statistical analysis, based on the results of the unilateral and bilateral variations of the increased UtA resistance and notch presence, maternal-placental bleeding in the first trimester was not significantly associated with placental vascularization, contrary to the expectations. In this study, although there was no statistically significant difference in first trimester screening test parameters and second trimester UtA Doppler flow results of patients with a history of threat of miscarriage, a statistically significant increase was found in perinatal complication rates.

In a prospective study by Alcázar et al. in 49 patients with a history of threatened miscarriage and 129 patients with a normal pregnancy, pregnant woment with vaginal bleeding between gestational weeks 6 and 12 were examined with Doppler for UtA and spiral artery by transvaginal ultrasound and compared with the pregnant women in the control group who were in a similar gestational week. Similar to our study, no statistically significant difference was found between the two groups in terms of peak systolic velocity and PI. In the same study, cases that developed spontaneous abortion were compared with normal pregnancies, but once again, no statistically significant difference was found (17). Stabile et al. compared 38 cases of threatened miscarriage with 73 uncomplicated pregnancies and did not observe a statistical difference in RI values in the Doppler measurement performed on sub-placental vessels (21). In a similar study conducted by Kurjak et al., although the control groups were not homogeneously distributed, the UtA Doppler results of 20 cases with a history of threatened miscarriage and 130 pregnant women with a normal pregnancy were compared. There was a statistically significant difference between radial artery and spiral artery Doppler results. However, when the results were examined, the radial artery PI was high in the group with threatened miscarriage, while the spiral artery PI was found to be significantly lower in the group with threatened miscarriage (22). In another larger-scale study of the author, no statistically significant difference was found in the Doppler indices (23). In that study, in 9 cases with retroplacental hematoma on ultrasound, the UtA RI value was statistically significantly lower in the contra-lateral of the hematoma side, and this difference was attributed to the possible pressure of the hematoma (23). In a study by Pellizzari et al., pregnancies complicated by vaginal bleeding during gestational week 6-12 were compared with unproblematic pregnancies, and no difference was observed in the Doppler parameters between incomplete abortion, missed abortion, imminent abortion, and normal pregnancies (16). Behery et al. conducted a study with 90 cases diagnosed with threatened miscarriage in the first trimester and 50 controls and found that patients who developed missed abortion during their follow-up showed a statistically significant increase in unilateral PI in their UtA Doppler results (24). However, all these studies were generally done in the first trimester, when there is vaginal bleeding. We wanted to see the long-term consequences of bleeding and performed the UtA Doppler examination between 20-24 weeks of gestation and did not observe any interaction between UtA and threat of miscarriage.

Another reason for the insufficiency of uterine artery Doppler results in predicting perinatal complications is that it varies with the gestational week. During the first trimester, the blood flow rate in the uteroplacental arteries increases and pulsatility index values decrease as the pregnancy progresses (25). In a study conducted to predict the results of preeclampsia, fetal growth restriction, intrauterine death, and placental abruption,

specificity and sensitivity results were determined by referencing RI> 0.58 or RI> 0.7 and the presence of bilateral notch or notch on either side. All reference values were evaluated separately for each disease. Sensitivity and specificity were not observed to be above 80% at the same time based on a single reference value for any of these diseases (26). Since the current diagnostic value of Doppler examination is as mentioned, it is clear that it cannot be a guide alone in forecasting perinatal outcomes in patients with threatened miscarriage. In the literature, uterine artery Doppler examination has usually been performed in the first trimester in case of pregnancies complicated by vaginal bleeding, and no study has been found investigating its effect on Doppler findings with abdominal USG between gestational weeks 20 and 24 as in the present study. According to the results obtained from our current findings, it has been determined that UtA Doppler use is not statistically significant in predicting adverse perinatal outcomes in pregnant women with bleeding in early gestational weeks.

In the literature, the probability of occurrence of adverse perinatal outcomes in patients with threatened miscarriage is high, similar to the present study. Preterm delivery, premature rupture of membranes, and placenta abruption have been observed more commonly in these cases (27). In a large-scale review by Tuuli et al., the incidence of placenta abruption was increased by 5.7 times, preterm birth by 1.4 times, and premature rupture of membranes by 1.6 times (28). In a multi-center large-scale prospective study, the cases were divided into three groups as those with no bleeding, those with mild bleeding, and those with severe bleeding, and their perinatal outcomes were examined (29). It was observed that the probability of miscarriage before the 24th week of pregnancy increased by 2-4 times in pregnant women with vaginal bleeding, but no statistically significant increase was observed in the cesarean rates. Mild vaginal bleeding was mostly associated with preeclampsia, preterm birth, and abruptio placentae; on the other hand, severe vaginal bleeding was associated with preterm birth, abruptio placentae, fetal growth restriction, and preterm rupture of membranes. According to these results, we believe that it would be appropriate to follow up the cases with threatened miscarriage more frequently in especially 3rd trimester due to the increased rate of perinatal complications.

The strength of our study is that it is prospective and ensures the continuity of the patients in the study. We followed patients long-term until delivery and increased the reliability of our results. Our limitation was that our follow-up was long, but we could not get continuous measurements, so we may not have been able to analyze the change graphs of the parameters.

CONCLUSION

In conclusion; contrary to some different studies, we believe that first trimester screening test parameters or uterine artery Doppler flow indices do not have a place in predicting perinatal outcomes of pregnant women with a history of vaginal bleeding in the first trimester. In addition, bleeding does not significantly affect screening parameters. Perinatal complication rate was found to be statistically significantly higher in the group with a history of threatened miscarriage.

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