

SECOND TRIMESTER BLEEDING OF UNKNOWN ORIGIN RISK FACTORS AND PREGNANCY OUTCOMES

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Abstract

Objective The purpose of our investigation was to evaluate factors associated with second trimester bleeding of unknown origin after 14 weeks of pregnancy and correlate this feature with maternal and pregnancy outcomes.

Methods This is a retrospective observational study, on a population of 821 singleton pregnancies monitored at Emergency University Hospital, Craiova, between January 2015 and September 2016. Inclusion criteria were: bleeding after 14 weeks of gestation without uterine contractions, with no apparent cause detected on vaginal examination or abdominal and vaginal ultrasound. Outcomes of these pregnancies were compared with those of pregnancies without bleeding. Main outcome parameters were: spontaneous abortion, oligoamnios and sludge association, preterm delivery at <28 weeks, <34 weeks, PROM; preterm PROM; admission to the neonatal intensive care unit (NICU); severe neonatal morbidity; neonatal death; ultrasound-to-delivery intervals.

Results The prevalence of second trimester bleeding of unknown origin in the study population was estimated at 3% (25/821). Pregnancies with persistent unexplained second trimester bleeding had a higher rate of spontaneous abortion (68% vs 4%, p test Fisher=0 <0.001 HS), oligoamnios (76% vs. 8%, p test Fisher=0 <0.001 HS), sludge association (60% vs 8%, p test Fisher=0.000105 <0.001 HS), preterm delivery at <28 weeks (20% vs 0.0%, p test Fisher=0 <0.001 HS), <34 weeks (16% vs 8%, p test Fisher=0.00073 <0.001 HS), PROM; preterm PROM (P <0.001). All cases that reached viability were admitted to the neonatal intensive care unit (NICU). Rates of severe neonatal morbidity and neonatal death were higher in this group. Ultrasound-to-delivery and ultrasound-to-preterm PROM intervals were shorter (3.1 weeks).

Conclusions Maternal outcome was not modified by the presence of second trimester persistent bleeding, but this is an independent risk factor for spontaneous abortion and spontaneous preterm delivery. The bleeding-sludge association shortens the ultrasound-to-delivery interval with 3.1 weeks in average. Furthermore, the combination of sludge and bleeding worsens the pregnancy outcome regardless to the cervical length.

Rezumat: Sângerarea antenatală de origine necunoscută. Factorii de risc și prognosticul sarcinii

Obiective. Scopul studiului nostru a fost de a evalua factorii asociați cu sângerarea antenatală de origine necunoscută în al doilea trimestru de sarcină începând cu vârsta gestațională de 14 săptămâni și de a corela acești parametri cu prognosticul matern și cel al sarcinii.

Material și metodă. Studiu retrospectiv observațional ce a inclus un lot de 821 de paciente monitorizate în Spitalul Clinic Județean de Urgență din Craiova în perioada ianuarie 2015 și septembrie 2016. Criteriile de includere au fost: sângerare antenatală după vârsta gestațională de 14 săptămâni de sarcină, fără contractilitate uterină asociată și fără o cauză evidentă clinic și ecografic. Evoluția acestor sarcini a fost comparată cu cea a sarcinilor fără sângerare. Parametrii finali de raportare au fost: avortul spontan, oligoamniotul și asocierea de "sludge", naștere prematură <28 de săptămâni respectiv <34 de săptămâni de sarcină, ruptură prematură de membrane amniocoriale (RPM); RPM înainte de termen; admiterea în unitatea de terapie intensivă neonatală; morbiditate neonatală severă; deces neonatal; intervalul de timp ecografie-naștere.

Rezultate. Prevalența sângerării antenatale de origine necunoscută (SAON) în populația de studiu a fost de 3% (25/821). Lotul cu SAON a înregistrat o rată mai crescută de avort spontan (68% vs 4%, p test Fisher=0 <0.001 HS), oligoamniot (76% vs. 8%, p test Fisher=0 <0.001 HS), asociere de "sludge" (60% vs 8%, p test Fisher=0.000105 <0.001 HS), naștere prematură înainte de 28 de săptămâni de sarcină (20% vs 0.0%, p test Fisher=0 <0.001 HS), și înainte de 34 de săptămâni de sarcină (16% vs 8%, p test Fisher=0.00073 <0.001 HS).

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RPM; RPM înainte de termen ($P<0.001$). Toate cazurile care au atins vârsta de viabilitate au fost internate în Unitatea de Terapie Intensivă Neonatală. Rata de mortalitate neonatală a fost mult mai mare în acest grup. Intervalul de timp ecografie-naștere a fost semnificativ mai scurt pentru pacientele care au dezvoltat 'sludge', în medie cu 3.1 săptămâni.

Concluzii. Prezența sângerării persistente în trimestrul al doilea de sarcină reprezintă un factor independent de risc pentru avortul spontan și pentru nașterea înainte de termen. Prognosticul matern nu a fost influențat negativ. Asocierea sângerare- 'sludge' a scăzut intervalul dintre ecografie și avort/naștere, în medie cu 3.1 săptămâni. Se pare că secvența sângerare pe cale vaginală urmată de apariția oligoamniosului marchează momentul de alterare a prognosticului sarcinii.

Cuvinte cheie: sângerare antenatală de origine necunoscută, primul trimestru de sarcină, amniotic „sludge”.

Introduction

In our study, second trimester bleeding of unknown origin was defined as bleeding after 14 weeks of gestation but before the onset of labor with no cause detected on vaginal examination or abdominal ultrasound.

There are studies that have evaluated pregnancy outcomes related to antenatal bleeding of unknown origin (1). The researches included patients in both the first and second trimester of pregnancy (2,3) and were carried out on antepartum clinical assessments without the use of ultrasound. Some of them evaluated outcomes by comparing pregnancies with bleeding to pregnancies without bleeding. The gestational ages were different between studies with one <20 weeks (4), two studies at 13–26 weeks (5,6), two studies at >28 weeks (7) and one at <34 weeks (8). According to these researches, the frequency of congenital anomalies and growth-retarded infants was unaffected. Neonatal death and low Apgar scores were seen more often than expected, but stillbirth rates were not significantly increased. ABUO that occurs before 34 weeks is associated with a high risk of preterm delivery before 34 weeks (29.3%). The chance of delivery within the first week is 62.5% when there are coexisting uterine contractions. Even if contractions are absent, the risk is still high (13.6%) and persists beyond the first week.

The purpose of our investigation was to evaluate factors associated with second trimester

bleeding of unknown origin after 14 weeks of pregnancy and correlate this feature with maternal and pregnancy outcomes.

Outcomes of these pregnancies were collated and compared with pregnancies without second trimester bleeding of unknown origin.

Materials and methods

This is a retrospective observational study, on a population of unselected 821 singleton pregnancies evaluated consecutively at Emergency University Hospital, Craiova, between January 2015 and September 2016.

Patients were initially diagnosed with second trimester bleeding of unknown origin after abdominal and vaginal ultrasound examinations in our Antenatal Diagnostic Unit.

Second trimester bleeding of unknown origin after 14 weeks of pregnancy was defined as vaginal bleeding without evidence of a vaginal or cervical cause (polyps, cancer), trauma, placenta praevia, placenta accreta/increta/percreta or placental abruption. The abdominal ultrasound determined placental location and searched for ultrasound evidence of a placental abruption. Once an abnormal placenta has been ruled out, vaginal examination excluded a vaginal or a cervical cause of the bleeding. Uterine contractions were also excluded.

Maternal evaluation included information regarding maternal demographics, maternal age, smoking and caesarean section history.

Outcomes of these pregnancies were compared with those of pregnancies without bleeding. The main outcome parameters were: spontaneous abortion, oligoamnios and sludge association, preterm delivery at <28 weeks, <34 weeks, PROM; preterm PROM; admission to the neonatal intensive care unit (NICU); severe neonatal morbidity; neonatal death; ultrasound-to-delivery intervals.

We examined the factors associated with the prevalence of second trimester bleeding of unknown origin, and the effects of this feature on spontaneous abortion and pregnancy outcomes. Maternal age, caesarean section history, demographic characteristics and medical history were considered risk factors for second trimester bleeding of unknown origin.

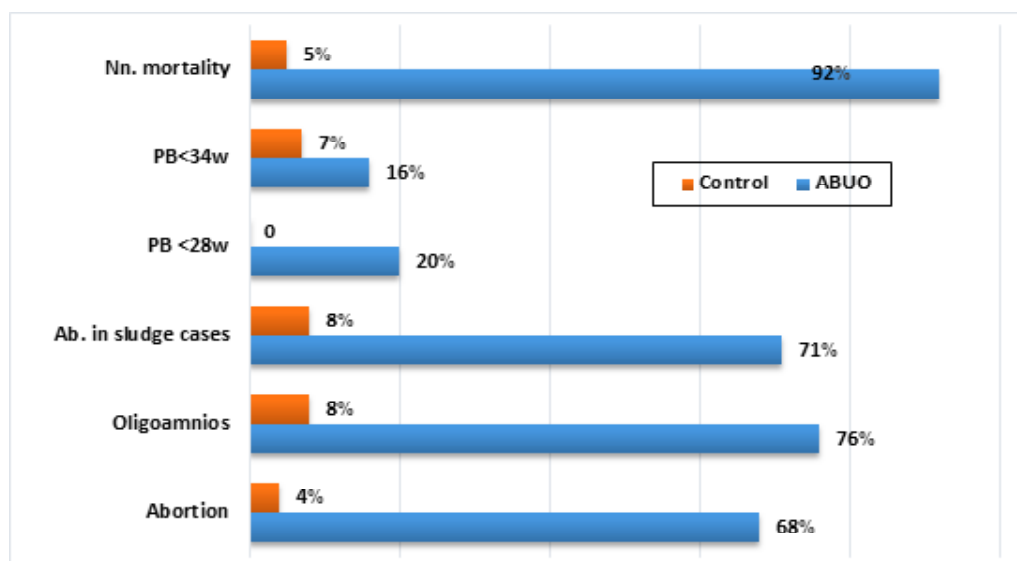
Statistical analysis was performed by the Biostatistics Department of the University of Medicine and Pharmacy of Craiova, Romania, using Microsoft Excel (Microsoft Corp., Redmond, WA, USA), together with the XLSTAT add-on for MS Excel (Addinsoft S.A.R.L., Paris, France) and IBM SPSS Statistics 20.0 (IBM Corporation, Armonk, NY, USA) for processing the data. The resulting contingency tables were analyzed using Fisher's exact test, suited for small groups, and $P < 0.001$ was considered statistically highly significant.

Results

Between January 2015 and September 2016, there were 821 singleton pregnancies available for analysis at the Antenatal Diagnostic Unit of Emergency University Hospital, Craiova, Romania. The prevalence of second trimester bleeding of unknown origin in the study population was 3% (25/821).

Most of the woman we evaluated were between 21 and 28 years old (21, 84%), and had no history of miscarriages (22, 88%) ($P < 0.001$). Some of them smoked at the beginning of the pregnancy (8, 32%), and were more likely to have second trimester bleeding of unknown origin, although this could not be quantified by the number of cigarettes smoked. There were no significant statistical differences in the ABUO group on maternal medical history, such as Cesarean section (p test Fisher=0.334 >0.05 NS). Women who had bleeding prior to 14 weeks, were more likely to have second trimester bleeding of unknown origin (72% vs. 12%, p test Fisher=0.0000172 <0.001 HS).

Several antepartum and intrapartum complications were significantly different between the groups with and without ABUO. We identified a higher rate of spontaneous abortion before 23 weeks (68% vs. 4%, p test Fisher=0 <0.001 HS) in the ABUO group compared with the non-ABUO group (Graph 1).



Graph 1. Comparative outcome between the group with antenatal bleeding of unknown origin and the control group.

Women with persistent bleeding in the second trimester of pregnancy, prior to 17 weeks, developed oligoamnios after 20 weeks (76% vs 8%, p test Fisher=0 <0.001 HS) and had a higher rate of abortion prior to 23 weeks. The origin of the oligoamnios remains uncertain, as we could not identify any cause (maternal or fetal cause).

Sludge association worsens pregnancy outcome in the ABUO group. There has been a higher rate of miscarriages before 23 weeks (60% vs 8%, p test Fisher=0.000105 <0.001 HS) in pregnancies with ABUO and sludge association prior to 18 weeks and after 20 weeks.

Both, oligoamnios and sludge association are independent risk factors for spontaneous abortion and preterm delivery, but the ultrasound-to-delivery interval shortens at 3.1 weeks in average.

In pregnancies with ABUO, we noted a high incidence of spontaneous preterm delivery prior to 28 weeks (20% vs 0.0%, p test Fisher=0 <0.001 HS) and 34 weeks (16% vs 8%, p test Fisher=0.00073 <0.001 HS).

The mode of delivery was not significantly different in the ABUO group, as most deliveries were <28 weeks. Neonates were required admission to the neonatal intensive care unit. The neonates whose mother had second trimester bleeding of unknown origin, and delivered <28 weeks and <34 weeks, had higher rates of severe neonatal morbidity and neonatal death ($P<0.001$) (Graph 1).

Discussion

In our study, the rate of ABUO was approximately 3%. This feature was linked to several poor outcome parameters.

In the literature, the rates reported by other investigators, were estimated at 2% of the pregnancies after reviewing the research in this field (1). However, many of the studies were undertaken 5 to 35 years ago. Our study is a pilot study made on a small number of patients, and therefore the true rate in our settings may have been under-reported or the rate may be increasing.

The maternal outcome was not modified by the presence of second trimester persistent bleeding,

but this is an independent risk factor for spontaneous abortion and spontaneous preterm delivery. Preterm delivery was significantly increased in pregnancies with persistent second trimester bleeding of unknown origin, prior to 28 and 34 weeks. Women with ABUO had significantly smaller babies and the neonates in those pregnancies complicated by ABUO were more likely to have low Apgar scores and higher admission to NICU. ABUO increased the risk of preterm delivery and this finding is consistent with other studies.

Smoking during pregnancy at some time is also an independent risk factor, and women who smoked during pregnancy are more likely to have ABUO (9), although this could not be quantified by the number of cigarettes smoked or if the women stopped smoking during pregnancy.

In the ABUO group, we noted a similar Cesarean delivery rate, not significantly higher than pregnancies without second trimester bleeding of unknown origin.

The management of pregnancies complicated by second trimester bleeding of unknown origin, as we know, is uncertain, as the reason for the bleeding is unsure. In this study, we discovered an increased number of spontaneous abortion in pregnancies with normal cervical length and sludge association, preterm deliveries, smaller neonates and increased NICU admission rate.

We hereby present a case of a 35 years old patient, previously diagnosed with primary infertility that obtained a twin pregnancy after induced ovulation. We evidenced a continuous vaginal bleeding from the early first trimester that persisted in the second trimester with persistent over the "cut-off" cervical length and sludge association (figure 2). Both fetuses had normal anatomy at the morphologic first trimester scan (figure 3) but one of the fetuses presented severe oligoamnios. After 3 weeks of persistent vaginal bleeding with unknown origin, the respective fetus was spontaneously aborted (figure 4). The outcome of the second twin was favorable.

These pregnancies with ABUO are at higher risk for spontaneous abortion and preterm deliveries (10, 11, 12) and their neonates are at risk for NICU admissions, severe neonatal morbidity and neonatal

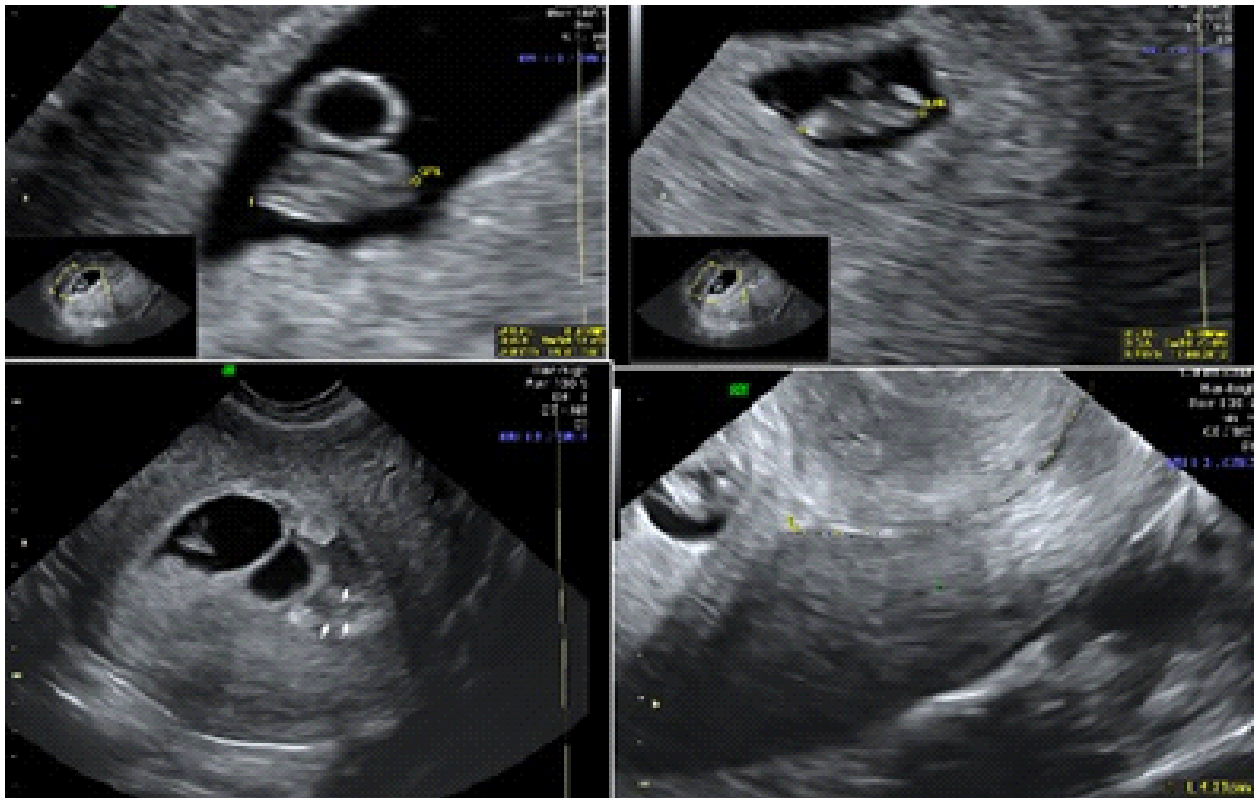


Figure 2. Biamniotic bichorionic pregnancy with spontaneous vaginal bleeding, in both first and second trimester of pregnancy, with a persistent over the “cut-off” cervical length and sludge association.

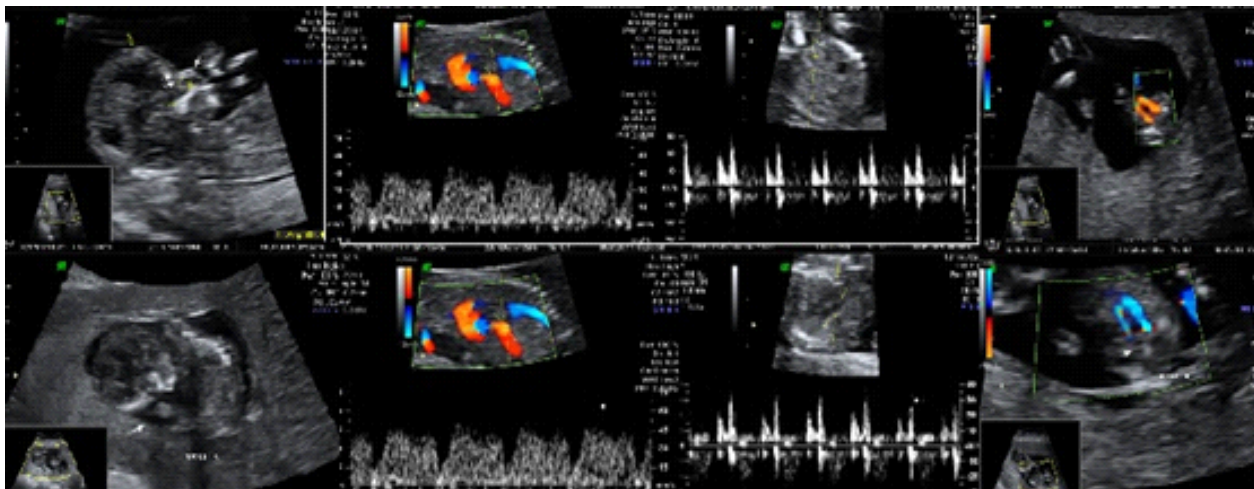


Figure 3. Same case. Morphological first trimester scan showed normal structures. The fetus B presented in the in the lower row developed oligoamnios.

death. According to other research (13), women with ABUO were more likely to have smaller babies (2940 versus 3325 g), and required admission to an intermediate level 2 nursery (23 versus 16%) or NICU (level 3 nursery, 20 versus 6%). The neonates whose mother had ABUO were more likely to have a hospital course complicated by hyperbilirubinaemia (6 versus 5%), early neonatal death (<28 days, 1.3 versus 0.3%), late neonatal deaths (0.14 versus 0.02%), and perinatal deaths. The bleeding-sludge association shortens the ultrasound-to-delivery

interval, as the termination of pregnancy was noted at 3.1 weeks in average. Furthermore, the combination of sludge and bleeding worsens the pregnancy outcome independent to the cervical length.

This study observational pilot study is made on a small population of patients (25) and these could be considered as limitations of the study. The limitations are balanced by the validity and consistency of the information for each woman. Many questions remain to be answered including the

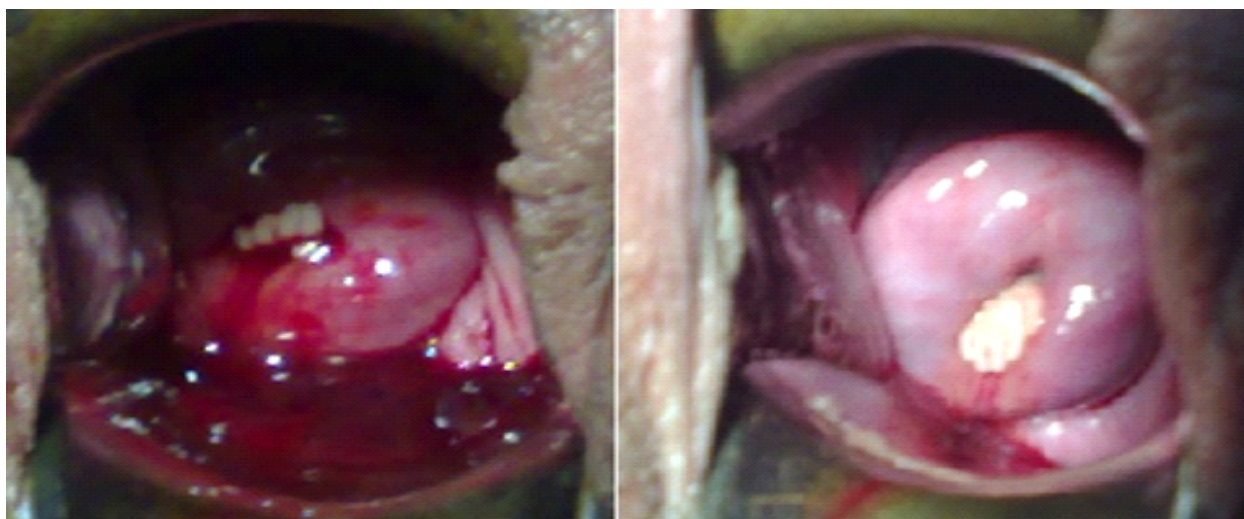


Figure 4. Same case. Spontaneous abortion of fetus B.

benefits of tocolysis and/or antibiotherapy with bleeding, but these can only be answered through larger retrospective and prospective randomized trials

Competing interests

The authors declare that they have no competing interests.

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