Vaginal bleeding during the first 20 weeks of pregnancy and its impact on adverse perinatal outcome

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Abstract

Bleeding during the first half of pregnancy, referred to as threatened abortion, is an emergency complication experienced by 14-26% of women. It is a source of justified maternal stress as it endangers physiological development of the pregnancy. Threatened abortion may result in complete or incomplete spontaneous abortion, but generally it does not put mothers life in danger. Major-league data confirms that even if the symptoms of threatened abortion pass, there is a risk of multiple complications in ongoing pregnancy. Some of those complications are life-threatening for both mother and the fetus. There is also evidence of worse neonatal outcomes and increased risk in subsequent pregnancy. There is also evidence of worsening outcomes and increased risk in subsequent pregnancy. This paper elaborately presents not only the theses assessing that influence, but also the etiology, diagnostics and potential treatment of threatened abortion. What's more, a frequent finding in early pregnancy – subchorionic hematoma and its possible consequences are discussed. The article introduces up-to-date blood and urine markers with suggested prognostic value in threatened abortion. Considering the increasing evidence that the placental damage caused by oxidative stress in early pregnancy is associated with threatened abortion, it is essential to mention the role of oxidative damage in placental functions impairment.

Key words: threatened abortion, miscarriage, bleeding in pregnancy, subchorionic hematoma, oxidative stress, blood markers in threatened abortion, progesterone, hCG

1. Introduction

Vaginal bleeding is a common phenomenon during pregnancy, threatening its proper development and successful outcome. Therefore, it is an evident source of major maternal stress and anxiety. Vaginal bleeding in gravidas may have different causes, but developing or already developed placental unit is believed to be the most dominant [1]. When bleeding occurs during the first 21 weeks of gestation and the examination reveals a viable intrauterine pregnancy and closed cervix, the diagnosis of threatened abortion is made. The incidence of this complication varies in different studies between 14-26% of all pregnancies [1, 9, 13, 32, 71-79]. Evidently, threatened abortion may progress to spontaneous abortion. If the pregnancy continues, substantial data prove a higher incidence of multiple complications, worsening perinatal outcomes. Some studies show it may even have a negative impact on subsequent pregnancy. Therefore, many authors suggest that a gestation complicated by bleeding should be treated as high-risk pregnancy [11, 65]. The prevalence of progressing to spontaneous abortion and complications in ongoing pregnancy is directly proportional to the heaviness of bleeding [1]. Furthermore, the stage of pregnancy when the bleeding occurs is significant [1, 44]. In this article, I list the potential causes of bleeding during first 20 weeks of gestation, focusing on threatened abortion and its consequences. The fact that predominantly the bleeding origins from disrupted decidual vessels suggests that a placental pathology beginning early in pregnancy underlies the complications responsible for adverse perinatal outcome [1, 66].

2. Impact of bleeding on perinatal outcome

As mentioned above, bleeding during pregnancy may progress to inevitable, incomplete or complete miscarriage. Wittels and colleagues analyzed 5.4 million emergency department visits for vaginal bleeding in early pregnancy over the course of 11 years. They reported this complication is a reason of nearly 500 000 emergency department visits per year. The authors calculated that 50% of patients experiencing vaginal bleeding in early pregnancy over the course of 11 years. They reported this complication is a reason of nearly 500 000 emergency department visits per year. The authors calculated that 50% of patients experiencing vaginal bleeding in early pregnancy over the course of 11 years. They reported this complication is a reason of nearly 500 000 emergency department visits per year. The authors calculated that 50% of patients experiencing vaginal bleeding in early pregnancy over the course of 11 years. They reported this complication is a reason of nearly 500 000 emergency department visits per year. The authors calculated that 50% of patients experiencing vaginal bleeding in early pregnancy over the course of 11 years. They reported this complication is a reason of nearly 500 000 emergency department visits per year. The authors calculated that 50% of patients experiencing vaginal bleeding in early pregnancy over the course of 11 years. They reported this complication is a reason of nearly 500 000 emergency department visits per year. The authors calculated that 50% of patients experiencing vaginal bleeding in early pregnancy over the course of 11 years. They reported this complication is a reason of nearly 500 000 emergency department visits per year.
edjing leads to miscarriage in 15% of cases, but the risk of spontaneous abortion after bleeding during the second trimester is nearly 3 fold lower and amounts to 5.6%. They emphasize that the symptoms of threatened abortion before 6th week of gestation carry the highest risk of miscarriage and average out at 29% [44].

Substantial research prove that a history of bleeding significantly elevates the incidence of complications in ongoing pregnancy, exacerbating perinatal morbidity and mortality. Ananth and Savitz calculated that first trimester bleeding is followed by a twofold risk augmentation of other complications [13]. What’s more, some studies prove its negative impact on subsequent pregnancy as well [11]. The repeatedly reported consequences of bleeding include preterm delivery, PPROM, cesarean delivery and pathologies related to the placenta, such as placenta praevia, placental abruption, preeclampsia and IUGR. A prospective multicenter study by Weiss et al. confirm that first-trimester vaginal bleeding is a risk factor for poor perinatal outcome, proportionally to its heaviness. The authors postulate that not only spontaneous loss of pregnancy before 24 weeks, placental abruption, preterm premature rupture of membranes and preterm delivery, but also preeclampsia, IUGR and cesarean delivery are directly related to first-trimester bleeding [1]. Wijesiriwardana et al. compared almost 8000 patients with threatened abortion in the first trimester to nearly 32 000 controls. They proved that threatened abortion is not only a risk factor of abnormalities during pregnancy, such as antepartum haemorrhage, preterm delivery and malpresentation but it also increases the incidence of interventions such as cesarean sections (OR 1.3; 95% CI 1.14-1.48), and manual removal of the placenta (OR 1.40, 95% CI 1.21-1.62) [3]. In the study by Sipila et al. the incidence of bleeding during first and second trimester in Finland came out at 9.3% and was associated with preterm birth, LBW and fetal congenital malformations. Surprisingly, they reported no impact of bleeding on perinatal mortality [24].

2.1 Preterm delivery and preterm premature rupture of membranes (PPROM)

Preterm delivery (PTD) is the most frequently reported consequence of bleeding during pregnancy, regardless of gestational age. It may be a spontaneous preterm delivery, a result of PPROM or consequence of preterm cesarean section performed due to urgent indications such as placental abruption or preeclampsia. In the prospective cohort study on almost 3000 patients, Yang et al. proved that vaginal bleeding during 1st and 2nd trimester increases the overall risk of preterm delivery 1.3 fold. Nevertheless, bleeding in the first trimester elevated the relative risk of delivery at or before 34 1.6 fold, and the incidence of PTD caused by PPROM was nearly twofold higher. Bleeding in both 1st and 2nd trimester raised the incidence of preterm birth 3.6 fold (RR 3.6, 95% CI: 1.1, 1.6). The highest PTD rate was among women with significant, recurrent bleeding (especially occurring in both trimesters) that lasted longer than 1 day. Single episode of light bleeding limited to the one trimester, of only 1 day duration did not increase the risk of PTD [32]. Velez Edwards et al. investigated the impact of color, heaviness and duration of bleeding on the PTD prevalence. Among 26% from almost 4000 patients who bled in the first trimester, the highest risk of preterm delivery was reported among those who bled heavily (OR 2.4, 95% CI 1.18-4.88), with red color (OR 1.92, 95% CI, 1.32-2.82) and for a long time (OR 1.67, 95% CI 1.17-2.38) [71].

Retrospective study carried out in Denmark on over a million gravidas prove that bleeding before 12 weeks of gestation doubles the risk of delivery between 32 and 36 weeks and triples the risk of delivery at 28-30 weeks of gestation. They also discovered that bleeding in the first pregnancy leads to a nearly twofold risk augmentation (2.7% vs. 4.8%) of PTD in the second pregnancy [11]. Dadkhah et al., after comparing 500 women with threatened abortion to 500 controls, reported the 25,2% incidence of preterm delivery among bleeding group vs. 9,4% in controls. The prevalence of PROM was 10,2% vs. 4,8%, respectively [65]. Saraswat et al. reported that the risk of PPROM rises 1.78 fold after first-trimester bleeding and the rate of preterm delivery is twice higher [2]. The proportion of preterm deliveries after threatened abortion in the first-trimester is 1.56 fold higher (95% CI 1.43-1.71) according to Wijesiriwardana et al. [3]. As reported by Johns et al., there is a 2.29 fold relative risk growth of preterm delivery and 3.72 fold of PPROM after threatened abortion. The authors found neither an influence of threatened abortion on other obstetrical complications nor on neonatal mean birth weight [54]. As stated by Hossain et al., the risk of PPROM and preterm delivery rises substantially if a woman bleeds during both 1st and 2nd trimester and it’s 3.0 and 6.24 fold higher, respectively [8]. Weiss et al. emphasize the meaning of the heaviness of bleeding. In their study, the preterm delivery incidence was 1.3 fold higher among women with light bleeding and 3.0 fold higher for heavy-bleeders [1].
2.2 Antepartum haemorrhage and placental abruption

Significant bleeding results in thrombin generation and proteolytic cascade activation that is proven to trigger PPROM [28,30] and preterm contractions of the uterus [28,30]. The connection between early pregnancy bleeding and placental complications later in pregnancy suggests underlying impaired placentation. It is important to emphasize that vaginal haemorrhage during pregnancy, especially related to placental abruption, is a life-threatening complication for both mother and the fetus. As established by Wijesiriwardana et al., bleeding in the first trimester leads to 1.83 fold higher risk of antepartum haemorrhage [3]. Saraswat and colleagues established that first-trimester bleeding increases the incidence of vaginal haemorrhage in subsequent trimesters, especially caused by placenta praevia (OR 1.62, 95% CI 1.19, 2.22) or of unknown origin (OR 2.47, 95% CI 1.52, 4.02) [2]. Dadkhah and colleagues report 4% incidence of placental abruption among patients with a history of threatened abortion versus 1.4% among controls [65]. According to both Saraswat and Dadkhah, placental abruption incidence has no impact on the route of delivery [2, 65]. Lykke and colleagues, after assessing over 1 million cases, reported 1.4% placental abruption rate in the group of first-trimester bleeders versus 1.0% in controls. The risk of bleeding recurrence in subsequent pregnancy was 8.2% [11].

2.3 Preeclampsia and IUGR

Hypertension during pregnancy, preeclampsia and IUGR are directly related to each other as they share a common etiology – impaired placentation early in pregnancy. Saraswat reports that the incidence of intrauterine growth restriction among women who experienced bleeding during the first trimester is 1.54 higher than in the control group. The overall risk of delivering a low birth weight infant rises 1.83 fold for women who experienced symptoms of threatened abortion [2]. Assessing the group of 11444 non-diabetic gravidas, amongst whom 1174 (9.7%) bled in the first-trimester, Williams and colleagues report 1.6 fold risk augmentation of neonatal low birth weight at term [7]. In turn, Nagy et al. compared pregnancies with intrauterine hematoma to controls. They found significantly increased prevalence of pregnancy-induced hypertension (15.5% vs. 7.5%), preeclampsia (8% vs. 2%) and IUGR (7% vs. 3%) in the investigated group compared to controls [17]. On the contrary, on the basis of their study, Dadkhah et al. claim that threatened abortion does not change preeclampsia, fetal growth restriction or cesarean sections ratio [65].

2.4 Neonatal outcome

Worse neonatal outcome is an obvious consequence of all listed pregnancy complications, most notably of prematurity. Concerning neonatal outcome, infants delivered by women with a history of early pregnancy bleeding have lower Apgar score (less than 7 points in 5th minute) and more frequent require an admission to the neonatal intensive care unit (NICU). Perinatal mortality is 2.15 times higher in pregnancies complicated by bleeding [2, 4-6]. Williams and colleagues reported a double risk of prematurity (RR 2.0; 95% CI 1.6-2.5), and higher incidence of neonatal death among patients with a history of bleeding in current gestation [7]. According to Nagy et al., fetuses from gestations diagnosed with intrauterine hematomata are at higher risk intrauterine death (1.1% vs. 0.7%). There is also significantly higher rate of neonatal complications such as fetal distress (19.2% vs. 7.5%) and a necessity of NICU admission (20.9% vs. 3.7%). They reported 2.1% perinatal mortality rate among the group with intrauterine hematomata vs. 1.2% in controls [17]. Some reports suggest a correlation between vaginal bleeding during pregnancy and congenital anomalies, mental retardation and epilepsy [33, 34].

3. Etiology and risk factors

Regarding the fact that in 50% cases of bleeding the cause remains unknown [25-27], very often it is difficult to establish its origin. It is crucial to exclude the life-threatening conditions, such as placental abruption and eliminate non-obstetrical causes. Patients’ ultrasound documentation of intrauterine pregnancy diagnosed prior to the episode of bleeding narrows the diagnosis. There are multiple potential causes of bleeding in early gestation. Bleeding or spotting at the very early stage of gestation is frequently a reaction to the implantation of the embryo to the decidual layer of the uterus, usually occurring 14 days after fertilization. Bleeding may also be the sign of the onset of miscarriage or ectopic or heterotopic pregnancy, which is a life-threatening condition and must be excluded in every patient presenting with this complaints. Another rare but severe pathology that may manifest in bleeding and positive urine and blood pregnancy test is a trophoblastic disease. Nevertheless, threatened, inevitable or complete miscarriage is the most common cause of vaginal bleeding in the first half of pregnancy.

Bleeding during 1st and 2nd trimester is more frequent among ≥35 years old gravidas, patients with fertility problems, women who had an intrauterine contraceptive device (IUCD) before pregnancy or those who
miscarried before [24]. Patients’ history of 2 or more consecutive miscarriages, genetic condition, thrombophilia, uterine anomalies and poorly controlled systemic disease, such as diabetes mellitus [45] and endocrinopathies (principally thyroid disease) increase the risk of threatened and inevitable miscarriage [46]. Basama and Crossfile assessed the influence of age on the rate of miscarriage. The highest rate of miscarriage (27.1%) regarded the group of 31-40-year olds. Also young maternal age appears to be a risk factor, considering that in the group of 16-20-year olds the reported incidence of spontaneous abortion was 18.2%. The lowest risk of 7.1% was noted among patients between 21 and 30 years old. On the basis of their research, the authors claim that parity, history of miscarriage, the amount and number of episodes of vaginal bleeding seem to have no influence on miscarriage prevalence [44]. Uerpairojkit and colleagues prove the influence of age on pregnancy outcome as well. They compared sonographic findings in women who presented with bleeding during the first half of pregnancy. The rate of a viable intrauterine pregnancy among patients between 25-29th year of life was 49% comparing to 0% in the group of women older than 40 [64]. Also Bennett et al. mention the association between advancing age and spontaneous abortion incidence. They calculated a double risk of miscarriage among women who bled and had a subchorionic hemorrhage after they turned 35 years old (13.8% vs. 7.3%) [50].

4. Diagnosis

Detailed patients anamnesis is often a clue to a quick and proper diagnosis. Beside patients last menstrual period (LMP), parity and general medical history, it is important to establish the extent of bleeding, its colour and presence of blood clots or tissues. Patients general well-being and additional symptoms such as abdominal cramping are also meaningful. Assessing patients general condition should be the first step of medical examination. A presence of tachycardia, low blood pressure, attenuation or pallor suggest severe bleeding that requires quick treatment. Any tissue passed by the patient should be assessed by histopathologist to confirm the presence of products of conception or other pathologies. Observation of the perineal and anal area may reveal some non-obstetrical causes of bleeding such as haemorrhoids or genital warts. Speculum examination is necessary to diagnose other non-obstetrical pathologies that manifest in bleeding e.g. vaginal or cervical polyps, cervical ectropion, vaginal or cervical trauma, infection or neoplasm [28]. Speculum examination is also useful to visualize presumptive PPROM, significant cervical dilation or embryonic/fetal tissues coming out of cervical canal during inevitable abortion [43]. The bimanual obstetrical examination enables establishing the size and position of the uterus, cervical dilation or the presence of any adnexal mass or tenderness.

Transvaginal ultrasonography is a golden standard in diagnosing patients who bleed during pregnancy. It enables localizing the pregnancy and determining its viability. The TV ultrasound intrauterine localization of the embryo or fetus, correct CRL measurement and visualization or Doppler auscultation (after 11 weeks of pregnancy) of fetal heart rate is a good pregnancy outcome predictor. TV ultrasound enables the obstetrician not only to assess the fetus, but also the chorion or placenta, possible presence of free fluid in Douglas’ cavity or adnexal pathology. On the basis of the CRL measurement, it is possible to determine the gestational age and potential variance between the date of the last menstrual period (LMP) and ultrasound gestational age.

During the 5th week of pregnancy, a gestational sac made of double ring of echogenic chorionic villi and the decidua with a central blastocyst inside should be visualized. When the CRL reaches 5 mm, fetal heart activity should be detected in properly developing pregnancy [43]. Visible fetal heart activity of the embryo is a good predictive factor of its survival. Nearly 19 out of 20 intrauterine pregnancies with a normal fetus continue at least to 20 weeks if a fetal heart movement is present at the initial ultrasound, with the sensitivity of 97% and specificity of 98% [64]. Visualizing a gestational sac inside the uterine cavity is nearly 100% sensitive in diagnosing intrauterine pregnancy at levels of hCG between 1500 and 2000 mIU/ml [12]. Too small CRL not corresponding with LMP, empty sac and fetal bradycardia are predictive factors of adverse outcome of the pregnancy among women with threatened abortion [43]. Women bleeding during 2nd trimester, prior to 20 weeks should be suspected of cervical insufficiency, spontaneous miscarriage or placental pathologies such as abruption. Also in the 2nd trimester, the TV ultrasonography is a cornerstone in establishing the diagnosis allowing the obstetrician to assess if the placenta covers the internal ostium of the cervix, placental separation, abruption or measure cervical length and dilation.
Regrettfully, in many cases it’s impossible to establish the cause and origin of bleeding on the ultrasound examination. Uerpairokit et al. studied the sonographic findings in a group of 268 patients who bled in the first 20 weeks of pregnancy. They reported that only 100 of them (37.3%) had a viable pregnancy. Embryonic demise rate was 27.3% and 17.2% of patients presented anembryonic pregnancy. The complete miscarriage rate amounted to 5.2%. The rarest ultrasound findings among those patients were molar and ectopic pregnancy, diagnosed in 2.2% and 1.1%, respectively. Nearly 10% of gravidas had no evident findings on the ultrasound. Those patients were followed-up weekly in order to establish the final diagnosis. Among the followed-up group, the same incidence of 3.3% concerned anembryonic pregnancy and incomplete miscarriage. There was only 0.4% rate of viable fetus [64].

Assessment of serum hCG levels may help in differential diagnosis between physiologically developing, anembryonic and failing intrauterine gestation, ectopic pregnancy and gestational trophoblastic disease. Proper rise of serum hCG levels suggests a viable intrauterine pregnancy, since 99.9% of viable gestations are consistent with hCG rise of more than 35% by 48 hours [10]. Slower (less than 35%) rise or plateau of hCG levels over time imply abnormal development of intrauterine gestation or ectopic pregnancy. Falling levels of hCG have the worst prognostic value for intrauterine pregnancy, since they suggest a non-viable intrauterine or involuting ectopic pregnancy. Combination of transvaginal ultrasound and repeated hCG serum levels are proven to be the most important diagnostic tools in assessing the first-trimester bleeding [14, 15]. Morphology and coagulation should be considered and performed in every woman who bleeds in the course of pregnancy.

5. Subchorionic hematoma

Subchorionic hematoma, also called intrauterine hematoma or subchorionic hemorrhage is a common ultrasound finding in gravidas who bleed in the first half of pregnancy. It is frequently detected among asymptomatic patients as well. A subchorionic hematoma is described as a crescent-shaped, sonolucent fluid (blood) collection behind the fetal membranes or the placenta that may disrupt the placental bed. According to Nagy et al., intrauterine hematoma (IUH) is diagnosed in 3.1% of patients during the first trimester of pregnancy. The authors ran a prospective, population-based study assessing the influence of IUH on continuation of gestation. In the group of patients with IUH, 71% had symptoms of threatened abortion and 18.7% experienced spontaneous abortion. The spontaneous abortion rate in the group of controls was only 9.5%. They report that, comparing to controls, pregnancies with IUH are at much higher risk of both fetal and maternal complications, such as the necessity of operative delivery, PIH, IUGR, placental abruption (4.8 vs. 0.9%) and preterm delivery (16% vs 7.1%).

What’s interesting, the research by Nagy and colleagues suggests that the symptoms of threatened abortion (spotting, bleeding or cramping), in contrast to the presence of IUH, had no influence on perinatal outcomes. They convince that IUH could be an early marker predicting adverse perinatal outcomes [17]. Pedersen et al. revealed that 18% of patients with threatened abortion between 9 and 20 weeks of pregnancy and a viable fetus inside the uterine cavity had a subchorionic hematoma. Comparing patients with and without a hematoma, neither there was a difference in abortion nor in premature delivery rate. The frequency of those complications amounted to 10% and 11%, respectively. They also reported no connection between hematomas size and spontaneous abortion or preterm labor incidence [16].

On the other hand, a retrospective review of 516 first-trimester viable pregnancies diagnosed with vaginal bleeding and a hematoma by Bennett et al. reported a 9.3% spontaneous miscarriage incidence. The risk was around double in patients with large (18.8% spontaneous abortion rate) compared to medium (9.2%) and small (7.7%) hematomas [50]. According to Johns et al., the presence of subchorionic hematoma does not change the incidence of adverse perinatal outcome [5]. There are conflict data on the significance of intrauterine hematomas size. Some studies suggest its significant impact on adverse perinatal outcome [18, 19, 50]. But most of studies show no correlation between its size and perinatal outcomes [17, 20, 21]. Instead, there are reports that hematomas retroplacental location is a strong risk factor of adverse perinatal outcome [17].

Some authors convince that a subchorionic hematoma is an early proof of abnormal trophoblast invasion and impaired placental function resulting in PIH, IUGR and higher risk of placental abruption. What’s more, not only the placental abruption incidence is higher among patients with IUH, but also the necessity of manual placental removal, suggesting abnormal placentation with liability to pathological attachment to the myometrium that may result in placenta accreta [17, 22, 23]. Despite the fact that most of IUH resolve over time, in some cases IUH persists throughout pregnancy. Those cases are at high risk of preterm delivery and intrauterine infection. The postulated mechanisms include hemato-
ma pressing the uterine wall, that could provoke uterine contractions and the bacteria accumulating in the hematoma leading to inflammatory factors release inducing preterm labor. In the research by Seki et al., the incidence of preterm labor and chorioamnionitis among patients with persistent IUH were 77% and 27.3%, respectively.

6. Blood markers predicting the outcome

There are two well-investigated markers useful in assessing the risk of miscarriage – beta-hCG and progesterone. Low levels of those hormones may predict spontaneous abortion. As reported by Al-Sebai et al., serum progesterone concentrations appear to be significantly lower among patients whose pregnancy terminates or is ectopic, than among women with threatened abortion who continue gestation. A cut-off level of 45 nmol/1 is suggested to differentiate between the viable and abnormal pregnancies, with estimated 87.6% sensitivity and 87.5% specificity. In the group of patients with 5 nmol/1 or lower progesterone concentration, 86% experienced miscarriage [47].

Low levels of beta-hCG directly predict the risk of miscarriage. Al-Sebai et al. propose 20 ng/ml as a cut-off to distinguish between viable continuing and unviable pregnancy. They reported 88% sensitivity and 83% positive predictive value for this value [48]. In turn, La Marca et al., who also report significantly lower levels of hCG in patients who miscarried, suggest a threshold of 25 IU/ml to predict the risk of miscarriage. What’s more, they found that low free thyroxin, high TSH levels and alterations in maternal IgG and IgM plasma levels are common in patients with negative pregnancy outcome. This suggests a correlation between maternal immune system, trophoblast and thyroid function [49].

Other substances obtained by blood sample collection with a potential value to predict the outcome of pregnancy complicated by threatened abortion are: inhibin A, Ca-125, PIBF, anandamide, placental lactogen, estradiol and AFP. High level of Ca-125 is suggested to be a marker of decidual injury and may indicate upcoming spontaneous abortion. Comparing gravidas between 5 and 12 weeks of pregnancy, those who miscarried had a higher Ca-125 level. Authors suggest that even a single measurement of its level, in cases of 1st trimester bleeding, abdominal pain or both, Ca-125 concentrations may predict the outcome [52]. Low inhibin A, activin A and hCG are also reported to be markers of miscarriage, particularly inhibin A, which indicates placental dysfunction [53]. Johns et al. studied the impact of threatened abortion on the levels of 2nd trimester maternal serum AFP (MSAFP) and the pregnancy outcome. They report that MSAFP concentration rise implies the damage of the placenta during 2nd trimester. They established that the relative risk of AFP levels exceeding 2.5 MoM increases 6.25 fold in patients with history of threatened miscarriage [50]. Vitoratos and colleagues studied the profile of pro-inflammatory factors in patients with bleeding during 1st trimester and the obstetric outcome. They proved that IL-1β and TNF-α levels in maternal serum are higher among women with threatened abortion who miscarry comparing to those who continue a normal pregnancy. This suggests that spontaneous abortion is a result of maternal immune response [51]. Calleja-Agius et al. investigated maternal pro- and anti-inflammatory response in threatened abortion as well. They reported higher serum levels of Th1 (TNFα, INFγ, IL-10, IL-6, TNF-R1) and lower concentration of Th2 cytokines among patients who miscarried. Considering the fact that Th2 cytokines are proven to be associated with successful pregnancy, the imbalance between Th1 and Th2 response, promoting Th1 type cytokines, is a good predictor of miscarriage. On the basis of their investigation, TNF-R1 appears to be the best marker of miscarriage. The etiology of cytokine and hormone level modification in bleeding patients sera is not yet established [66].

7. The role of oxidative stress

During early development of the pregnancy, on the onset of fetomaternal circulation, the placental villi cover the entire choric sac. Those associated with the decidua capsularis degenerate and create a chorion laeve and the villi associated with decidua basalis form the placenta. Physiologically, at the early stage of pregnancy, the maternal blood flow through the placenta is limited in order to preserve differentiating cells from oxidative damage caused by free radicals. In order to develop properly, fetomaternal blood flow should begin at the marginal area, slowly reaching the center of the developing placenta. Janniaux et al. discovered differences in maternal blood flow through the placenta, especially its marginal zone, between successful and miscarried pregnancies. They prove that premature intervillous bloodflow, especially touching the whole placenta or its central region, has a negative influence on pregnancy. Early widespread onset of maternal blood flow, containing high oxygen levels, damage the trophoblast. The authors suggest that this oxidative damage may be a key cause of first trimester miscarriages [67]. In another study ran by Janniaux et al., they established that
oxygen tension in the intervillous space amounts to < 20 mm Hg at 8 weeks and that the placental tissue, especially syncytiotrophoblast, is very susceptible to oxidative damage. It is due to the low activity of antioxidants characterizing placental tissue until 8-9th week of pregnancy. After the precocious maternal arterial blood flow entry, before the completion of embryogenesis and development of the placenta, the oxygen tension exceeds 50 mm Hg leading to irreversible morphological and immuno-histochemical changes and syncytiotrophoblast degeneration [68]. Altered placentation has not only immediate effects, such as spontaneous miscarriage, but may also demonstrate in 2nd and 3rd trimester. It is widely investigated that hypertension in pregnancy, preeclampsia and intrauterine growth restriction, manifesting in different stages of pregnancy originate in early gestation and share common etiology [69]. Oxidative stress has a negative impact not only on the placenta. Gupta et al. suggest its influence on spontaneous abortion and recurrent pregnancy loss due to oxidative modification of phospholipids leading to antiphospholipid antibodies formation [70].

8. Treatment

Commonly advised treatment of threatened abortion include bed rest and supplementation of progestins (progesterone, dydrogesterone) and hCG. The efficacy of all the treatment options including progestins is controversial. Progesterone, produced by the corpus luteum, supports the development of early pregnancy. By its antiprostaglandin effect it reduces uterine contractility. What’s more, progesterone plays a role in modulating immune response of the gravida. Progesterone-induced blocking factor (PIBF) decreases maternal inflammatory and thrombotic response through pregnancy. It enhances the promotion of protective Th-2 cytokines (IL-4 and IL-10) and suppresses Th-1 cytokine reactivity (IL12 and INF-γ) and NK-cells cytotoxicity by inhibiting their degranulation. It increases the level of non-cytotoxic blocking antibodies [59-61]. Properly, the level of PIBF continuously rises during the first 37 weeks of pregnancy and falls significantly after 41 weeks. Its adequate increase suggest a physiological pregnancy, whereas in pathological situations it doesn’t show a proper increase. Considering the fact that PIBF is not rising in patients who miscarry, it may be another marker of spontaneous abortion. What’s interesting, PIBF level is also lower among patients with preeclampsia and corresponds with the severity of the symptoms. Another study proves that PIBF concentration decreases shortly before labor, independently if it’s preterm or term. Therefore, urine PIBF test may be useful in predicting not only the risk of miscarriage and preeclampsia, but also risk of PTD and foreseeing the time of labor at or after term [62].

Concerning the efficacy of progestin treatment, the two big meta-analyses proved that the incidence of miscarriage was significantly lower after their supplementation. In the first one, which analyzed a group of 421 women, the noted spontaneous abortion rate was 14% in the group of progestin supplementation and 26% in non-treated or placebo group [35]. Analysis of 660 patients with threatened miscarriage performed by Carp, comparing placebo or bed rest with oral progestin treatment revealed a lower risk of miscarriage in progestin group – 13% vs. 24%, respectively [36]. Some studies report no positive effects of progesterone treatment. A large retrospective research conducted by Duan et al. assessed the effect of the progesterone course on 532 bleeding patients in comparison with 21 054 controls. A course of 14-day treatment with 20 mg intramuscular progesterone daily was administered to patients with threatened abortion, followed by individual treatment depending on the presence of bleeding. Then, they advised 20 mg of progesterone i.m. every other day for 2 weeks, and subsequently again 20 mg i.m. twice a week for 2 weeks. The authors reported no significant differences in the rate of preterm birth, live births, LBW, neonatal RDS, complications such as placenta previa, placental abruption, hypertension in pregnancy, gestational diabetes, intrahepatic cholestasis between the treated and control group. On the other hand, they claim that progesterone is effective in threatened abortions caused by immunological, luteinic or neuroendocrine factors and hypercontractility of the uterus [41].

Another medication widely prescribed in threatened abortion is hCG, that has an ability to stimulate the corpus luteum and fetoplacental unit to produce progesterone. The opinions on its effectiveness in preventing spontaneous abortions are questionable. In one study, women with a viable pregnancy who bled in the 1st trimester were prescribed 5000 IU of hCG i.m. once a week beginning at 14 weeks of gestation. A control group was treated with intramuscular placebo. Patients taking hCG had a higher progesterone blood concentration, but the miscarriage incidence was 12% in hCG group and 11% in placebo group. The study reports no effect of hCG in preventing miscarriage, but also neither adverse impact on continuing pregnancies, nor infant health [63].

Avoiding physical effort and vaginal intercourses is strongly advised for women who bleed during pregnan-
Recent Cochrane review stands for the opinion that bed rest or hospitalizing patients with threatened abortion does not prevent miscarriage and may be a cause of back pain, thromboembolic complications, muscle atrophy and bone mass loss [37, 55-57]. What’s more, it’s a cause of an emotional stress mainly caused by separation from the family [55-57]. Few studies report the efficacy of bed rest. Ben-Haroush et al. noted a lower rate of spontaneous abortions and higher incidence of term pregnancies among women with subchorionic hematoma who underwent bed rest [58].

It is very important to remember that Rh(D)-negative women with threatened abortion who demonstrate significant bleeding are at risk of alloimmunisation. Therefore, all of them should undergo immunoprophylaxis. Other causes of vaginal bleeding that require administering anti-D immune globulin are: spontaneous or induced abortion, ectopic pregnancy, hydatidiform mole, fetal death and every case of bleeding in the 2nd and 3rd trimester [38-40]. According to ACOG guidelines, before the onset of 12th week of pregnancy, the risk of alloimmunisation is low, so the 50 microgram dose of anti-D immune globulin is enough [39]. SOGC in turn stands for pre-risk of fetomaternal hemorrhage in the first half of pregnancy is low due to small volume of fetal blood [38-40].

References


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