A Review of The Causes, Pathophysiological Mechanisms and Clinical Consequences of Second-Trimester Breakthrough Bleeding (BTB)

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Editorial

Abstract: Bleeding during pregnancy is a major clinical challenge and can range from benign to life-threatening for both maternal and fetus. In the second trimester, breakthrough bleeding (abnormal vaginal bleeding in the presence of an ongoing normal pregnancy and in the absence of signs of labor or miscarriage) is a relatively rare but significant phenomenon.
Possible causes include hormonal changes, cervical abnormalities, early placental lesions, or damage to the decidua. Given the lack of scientific literature focused on BTB in this period of pregnancy, a comprehensive review and analysis of the available literature is necessary to clarify the underlying factors and clinical management.

Keywords: Second-Trimester Breakthrough Bleeding (BTB); Causes; Pathophysiological Mechanisms; Clinical Consequences; Review Article.

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Introduction

Vaginal bleeding in the second trimester of pregnancy (weeks 15 to 28) is a relatively rare phenomenon, affecting less than 1% of all pregnancies, but it is of great clinical importance due to its direct association with increased perinatal morbidity and mortality. The causes of this bleeding are often attributed to placental abnormalities such as placenta previa, placental abruption, low-lying placenta, and subchorionic hematomas [1,5]. However, in a significant proportion of cases (about 44%), despite sonographic investigations, the exact cause of the bleeding cannot be determined and the condition is therefore classified as idiopathic or unexplained bleeding [1,2]. Accurate diagnosis of the cause of bleeding by sonography is a key tool for predicting pregnancy outcomes and appropriate clinical management [3,5].

The pathophysiological mechanisms of unexplained bleeding are often associated with alterations in local decidual homeostasis and the presence of infection or inflammation in the choriodecidual space, which can lead to increased concentrations of inflammatory mediators such as interleukin-6 (IL-6) in the amniotic fluid [4]. This inflammatory response and activation of the coagulation cascade ultimately weaken the fetal membranes and stimulate uterine contractions. The clinical consequences of this condition include a significantly increased risk of preterm labor (PTB), premature rupture of membranes (PPROM), intrauterine fetal death, and an increased cesarean section rate [1,4]. Studies have shown that factors such as recurrent bleeding and its onset at a later gestational age (>22 weeks) are associated with a worse clinical prognosis [1].

Etiology

Vaginal bleeding in the second trimester of pregnancy (weeks 15–28) is a multifactorial phenomenon that affects less than 1% of all pregnancies, but is of great importance because of its direct association with increased perinatal complications [1,4]. The most common causes identified by ultrasound which are detected in approximately 56%–73% of cases, include placenta previa, abruption, low-lying placenta, and subchorionic or decidual hematomas [1,3,5].

Maternal causes such as inherited coagulation disorders (von Willebrand Disease, hemophilia, or coagulation factor deficiencies) account for less than 1% of pregnancy hemorrhages, but require specialized management to prevent severe postpartum hemorrhage [6].

However, in a significant proportion of cases (about 44%), despite imaging studies, no definitive cause for the bleeding is found, which is classified as idiopathic or unexplained bleeding. Rare factors such as trauma, sexual intercourse, and complications from cervical cerclage have also been reported in the literature [1,4].

Pathophysiology

From a pathophysiological perspective, the main mechanisms of unexplained bleeding are related to alterations in local decidual homeostasis due to infection or inflammation in the choriodecidual space[4]. This condition leads to intraamniotic inflammation and increased concentrations of inflammatory mediators such as interleukin-6 (IL-6) in the amniotic fluid. This inflammatory process, characterized by increased concentrations of inflammatory mediators in the amniotic fluid, activates the coagulation cascade and leads to the production of thrombin and plasmin[4]. These factors, by stimulating matrix metalloproteinases (MMPs), lead to collagen degradation, weakening of the fetal membranes, and induction of uterine contractions, which greatly increases the risk of preterm labor and premature rupture of membranes (PPROM) [1,4].

Studies show that microbial invasion of the amniotic cavity (MIAC), particularly by Ureaplasma spp., is observed in 25% to 36% of these cases [4]. Furthermore, pathological evidence suggests that 75% to 80% of idiopathic hemorrhage cases are associated with placental lesions due to maternal vascular perfusion defects (MVM), suggesting a role for vascular insufficiency in the development of this condition [4].

Differential Diagnosis

The differential diagnosis of bleeding in the second trimester of pregnancy (weeks 15 to 28) includes a wide range of placental disorders, maternal factors, and environmental factors, which are categorized as follows:

1) Placental Causes

The most common differential diagnoses in this period are related to disorders of the placental site and its attachment:

Placenta previa includes various types including complete, partial, marginal, and low placenta previa that that overlies the internal cervical os [1,4,5].

Placental abruption refers to the separation of the placenta from the uterine wall, which can lead to severe bleeding and adverse perinatal outcomes [1,3,4].

Uterine hematomas include subchorionic hematoma (bleeding behind the fetal membranes) or partially detached placenta, which are seen on ultrasound as intrauterine clots or separation of membranes [1,3,5].

2) Local and Genital Causes

These include lesions that do not originate directly from the placenta or uterus:

Cervical lesions such as ectropion (protrusion of cervical tissue), cervical polyps, and structural changes of the cervix are among these [1,4].

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Local trauma, such as injury to the vaginal entrance area (introitus) or vaginal walls, which may be caused by examination or external factors [4].

3) Systemic Causes and Coagulation Disorders

Although these account for less than 1% of all hemorrhages, their diagnosis is critical:

Maternal coagulopathies and coagulation disorders such as von Willebrand Disease (VWD), carrier hemophilia (with low factor levels), platelet function or count defects, and other coagulation factor deficiencies are among the most important of these [4,6]. Connective tissue disorders can also affect vascular health and hemostasis during pregnancy [6].

Pregnancy Complications and Induced Factors

Premature rupture of membranes (PPROM) and amniotic fluid leakage are sometimes associated with spotting or bleeding [1].

Preterm labor and the onset of regular uterine contractions can also cause hemorrhage [4].

Trauma and external factors, including physical trauma (such as a car accident), sexual activity (intercourse), and complications from cerclage (cerclage) in women, can cause bleeding [1].

Abortion and bleeding due to threatened abortion or spontaneous termination of pregnancy in the second trimester can also be considered as causative factors of BBT [6].

Idiopathic Bleeding

In about 44% of cases, despite careful sonographic examinations, none of the above causes (placental, local or systemic) is found and the bleeding is classified as idiopathic [1,4]. These cases are often associated with intra-amniotic inflammation or latent infections (such as Ureaplasma spp.) [4].

Maternal and fetal outcomes

Bleeding in the second trimester of pregnancy (weeks 15 to 28), although rare, is associated with a significant increase in maternal and fetal morbidity and mortality. The main outcomes are categorized as follows:

1) Maternal Outcomes

Bleeding during this period can lead to serious interventions and pregnancy complications for the mother:

The risk of preterm birth is increased by 3.9 to 6.5 times in women with second- trimester bleeding [1,5]. About 47% of these women will have a preterm birth[1].

These patients are at a 4.5 times higher risk of premature rupture of membranes (PPROM) [4]. Increased cesarean section rates due to placental complications or fetal distress, with the cesarean section rate in this group reported to be 41% to 42%, which is almost double that of the general population[1,3].

The risk of postpartum hemorrhage (PPH) is greatly increased in cases where the cause of bleeding is due to maternal coagulation disorders (such as von Willebrand Disease) [6]. Prolonged hospitalization (mean 18 days) and the risk of oligohydramnios (reduced amniotic fluid) are other maternal outcomes[3,4].

2) Fetal and Neonatal Outcomes

The impact of hemorrhage on the fetus is very serious and can lead to death or long-term disabilities.

The risk of fetal or neonatal death (Perinatal Mortality) is 5.4 to 8.8 times higher in these patients [1,5].

The perinatal mortality rate has been reported to be as high as 17% in some studies [3].

About 25% of cases of hemorrhage in the second trimester result in fetal loss (miscarriage or intrauterine death). 85% of deaths occur before 24 weeks of gestation [5].

These infants are at high risk of intrauterine growth restriction (FGR/SGA) and low birth weight (LBW)[4,5]. Infants born to these mothers are 3.2 times more likely to require NICU admission [5].

Complications such as respiratory distress syndrome (RDS), late-onset sepsis, bronchopulmonary dysplasia (BPD), and necrotizing enterocolitis (NEC) are more common in this group of infants [4]. In specific cases where the mother is a carrier of hemophilia, male infants are at risk of intracranial hemorrhage (ICH), especially if delivery is performed vaginally [6]. Based on statistical analyses, recurrent bleeding, onset of bleeding after 22 weeks of gestation, and the presence of placental abnormalities on ultrasound are the most important predictors of the worst outcomes for the mother and fetus [1,5].

Management of Second Trimester Bleeding

1) Initial Stabilization & Risk Stratification

Based on retrospective studies such as Chollet 2020, Koifman 2008, and Parant 2000; assessing maternal hemodynamics, determining the source of bleeding with ultrasound, and differentiating placental causes from idiopathic cases are important for choosing the appropriate treatment method. Steps such as monitoring vital signs, CBC and coagulation status assessment, determining blood type and crossmatch, ultrasound to check the location of the placenta and hematoma, and avoiding digital vaginal examination in case of suspicion of placenta previa have been proposed in all articles as the basic standard methods of BTB management.

Expectant /Conservative Management

This method is the most common approach in stable cases without fetal distress [1,2,5]. Mild to moderate bleeding, stable hemodynamics, and no extensive placental abruption are among the most important indications for this treatment method.

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Short-term hospitalization and monitoring, relative rest, serial sonographic monitoring, cervical length assessment, and monitoring for signs of preterm labor are important measures in this method. Most cases of low-lying placenta and small hematomas are managed with this approach [1,5].

2) Specific management based on placental cause

A) Placenta previa

Avoiding digital examination, limiting activity, planning for cesarean section in stable cases, hospitalization in cases of recurrent bleeding in cases of placenta previa is the most appropriate management method.

B) Placental Abruption

Immediate hospitalization, continuous fetal monitoring, termination of pregnancy in severe cases, and administration of blood products in DIC are the main treatment options in cases of premature placental abruption. Clinical severity determines this treatment course.

3) Management of Idiopathic/Inflammatory BTB

Based on the latest available studies, targeted antibiotic therapy aimed at reducing the severity of intra-amniotic inflammation, reducing IL-6 in amniotic fluid, and reducing the risk of preterm delivery in MIAC-positive cases is the most important treatment and management measures in cases of idiopathic bleeding. This is the first evidence of direct intervention in idiopathic BTB; however, there is still no definitive consensus on this issue and patient selection is important [4].

4) Prevention of preterm complications

Given the increased risk of PTB and PPROM in second trimester bleeding; in case of threatened preterm delivery, the use of fetal corticosteroids between 24–34 weeks and management with magnesium sulfate in case of threatened delivery before 32 weeks, and in cases of active contractions, the use of tocolytics is recognized as the first-line treatment methods. These measures are mostly used in the management of secondary bleeding complications[8,9].

5) Management of Maternal Coagulation Disorders

Evaluation of coagulation factor levels, desmopressin in mild VWD and specific factor injection in severe cases, careful delivery planning and prevention of PPH, which generally requires collaboration between hematologists and gynecologists, are among the management steps in maternal coagulation disorders[6].

6) Delivery / Termination

Indications such as hemodynamic instability, fetal distress, severe placental abruption and advanced intra-amniotic infection are recommended for termination of pregnancy. Cesarean section in cases of placenta previa or distress or vaginal delivery in selected cases are considered by the attending physician for termination of pregnancy.

Discussion

Bleeding in the middle of pregnancy (second trimester) is uncommon but may be a sign of a serious problem. There are several causes of bleeding in the middle of pregnancy, some of which are not serious and can be caused by a mild infection, benign cervical polyps, intercourse or a pelvic exam. This generally only results in light spotting that stops within a day or two. However, heavier, more persistent bleeding is more serious than light bleeding or spotting. Causes of heavier bleeding may be due to conditions related to problems with the cervix or placenta.

Bleeding in mid- and late pregnancy is more serious and may signal a complication in the mother or baby. Therefore, it should be taken seriously. Expectant mothers should have an emergency line of communication with their doctor and should identify the nearest hospital with high-quality facilities near where they live.

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Table 1. Differential diagnoses of vaginal bleeding in the second trimester of pregnancy

Category	Diagnosis	Main Mechanism	Clinical Findings	Ultrasound / Paraclinical Findings	Key Differential Points
Placental Causes	Placenta Previa	Placenta located over or near the internal cervical os	Painless, recurrent bleeding	Placenta covering the internal os	Digital vaginal examination is contraindicated
Placental Causes	Low-lying Placenta	Placental edge close to the internal os	Mild spotting	Short distance between placenta and os	May resolve with uterine growth
Placental Causes	Placental Abruption	Premature separation of placenta from uterine wall	Abdominal pain, uterine tenderness, dark bleeding	Retroplacental hematoma	Bleeding may be concealed
Placental Causes	Subchorionic Hematoma	Blood collection between chorion and decidua	Mild spotting or bleeding	Hypoechoic collection	Prognosis depends on size
Local Causes (Genital Tract)	Cervical Ectropion	Fragility of columnar epithelium	Postcoital bleeding	Speculum examination	Benign condition
Local Causes (Genital Tract)	Cervical Polyp	Vascular cervical lesion	Intermittent spotting	Direct visualization	Usually no fetal risk
Local Causes (Genital Tract)	Vaginal Trauma	Injury to vaginal mucosa	Bleeding after exam or intercourse	Physical examination	History is key
Systemic Causes	Von Willebrand Disease (VWD)	vWF factor deficiency	Prolonged bleeding, personal/family history	Abnormal coagulation tests	High risk of PPH
Systemic Causes	Hemophilia Carrier / Coagulation Factor Deficiency	Reduced factor VIII or IX levels	Disproportionate bleeding	Low factor levels	Hematology consultation required
Systemic Causes	Platelet Disorders	Platelet function or count defect	Petechiae / ecchymosis	CBC and platelet function tests	Rare but important
Pregnancy Complications	PPROM	Premature rupture of membranes	Fluid leakage + spotting	Decreased AFI	Nitrazine / ferning test
Pregnancy Complications	Preterm Labor	Regular uterine contractions	Crampy pain + bleeding	Short cervix	Fetal fibronectin testing
Pregnancy Complications	Second Trimester Miscarriage	Cervical dilation	Pain + bleeding	Open cervix	Evaluate retained products
Pregnancy Complications	Cerclage Complications	Irritation or infection	Spotting after procedure	Suture status	Surgical history important
Idiopathic (BTB)	Unexplained Bleeding	Intra-amniotic inflammation, MIAC, maternal vascular malperfusion	Bleeding without clear cause	Normal ultrasound	↑ IL-6, associated with PTB

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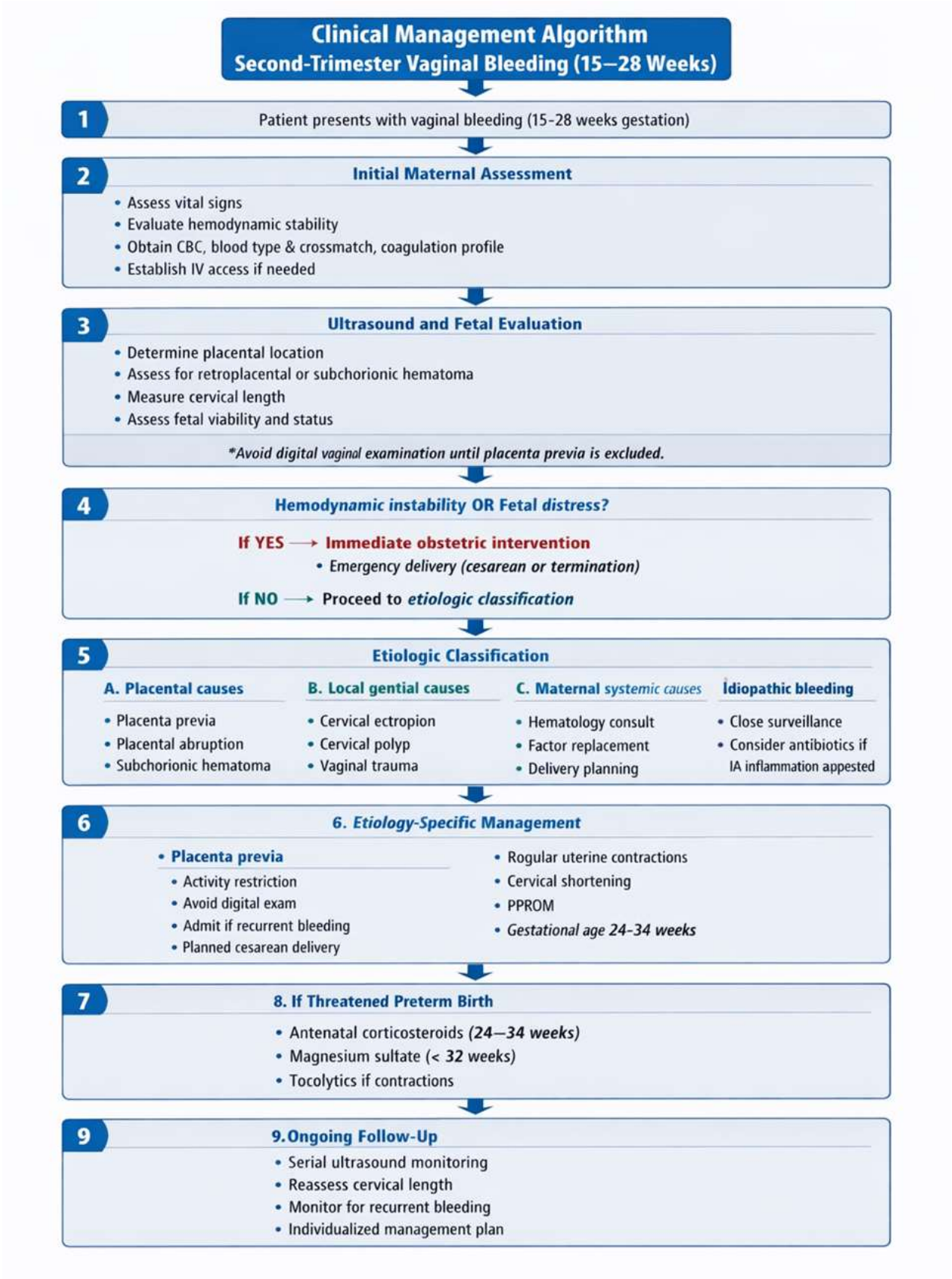

Figure 1. Management flowchart algorithm

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