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Abruption-associated prematurity

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SYNOPSIS

Chronic, subacute decidual hemorrhage (*i.e.*, abruptio placenta and retrochorionic hematoma formation) is an important contributor to preterm parturition. Such hemorrhage induces thrombin from decidual tissue factor, which play a pivotal role in the development of preterm premature rupture of membranes and preterm delivery by acting through protease-activated receptors to promote the production of pro-inflammatory cytokines, and matrix-degrading metalloproteinases. Severe, acute abruption can lead to maternal and fetal mortality. Current management of abruption is individualized based on severity of disease, underlying etiology, and gestational age.

Keywords

Decidua; hemorrhage; prematurity; abruption; inflammation; cytokines

Introduction

Despite intense investigations into its pathogenesis and prevention, preterm delivery (PTD) remains a major public health concern. In 2008, the preterm birth rate in United States was 12.3% with PTD a major world-wide contributor of perinatal morbidity and mortality.¹ Long-term sequelae of prematurity include pulmonary dysfunction, blindness, hearing loss, gastrointestinal malfunction, intraventricular hemorrhage, mental retardation, and cerebral palsy. Healthcare costs associated with these acute and chronic complications of prematurity exceed \$26 billion per year.²

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An increasing body of evidence now links decidual hemorrhage (DH) to PTD, with approximately 10% of all PTD attributed to bleeding-related events.³ While vaginal bleeding can rarely arise from cervical polyps, most cases originate from the decidua basalis (placental abruption) or the decidua parietalis (retrochorionic hematoma). The occurrence of vaginal bleeding in the first trimester and in more than one trimester is respectively associated with two- and seven-fold increased risks of PTD compared to no bleeding.^{4–8} The occurrence of a clinically evident abruption, together with occult DH and retrochorionic hematoma formation, complicates almost 40% of PTDs due to preterm labor with intact membrane and preterm premature rupture of the fetal membranes (PPROM) between 22–38 weeks, versus 0.8% after term delivery ($p < 0.01$).⁷

Beyond inducing prematurity, pregnancies complicated by placental abruption display an increase in perinatal mortality beginning at about 28 weeks of gestation (Fig. 1). The resulting neonates exhibit increased rates of perinatal asphyxia, intraventricular hemorrhage, periventricular leukomalacia, cerebral palsy and mortality, compared with age-matched controls.^{9,10} The demographic profile of DH-associated PTD differs from infection-associated PTD, with the former occurring more frequently in patients who are married, older, white, parous, college educated and tobacco users.¹¹ Other risk factors for DH include PPRM, thus DH is both a cause and consequence of this condition, as well as trauma, substance use, hypertensive disorders, renal disorders, multiple gestations, rapid uterine decompression, and history of abruption in a prior pregnancy.^{12–15} (Table 1)

Decidualization

Each menstrual cycle begins with hypoxia-induced angiogenesis and estradiol (E_2)-induced proliferation of epithelium and stromal cells, which had been sloughed off at the end of the previous infertile cycle. Coincident with the occurrence of ovulation is an elevation in plasma progesterone (P_4) levels which blocks further mitotic activity and initiates differentiation of the E_2 -primed cells. In the luteal phase of the human menstrual cycle, P_4 stimulates E_2 -primed human endometrial stromal cells to decidualize.^{16,17}

The process of decidualization begins around blood vessels and beneath the glands. It involves changes in differentiation that transform the interstitial extracellular matrix (ECM) of the follicular phase endometrium to an ECM enriched with basal laminar-type proteins and proteins that promote hemostasis. Under continued P_4 stimulation, decidualization spreads wave-like throughout the late luteal phase endometrium.¹⁸

After implantation, blastocyst-derived extravillous trophoblasts (EVTs) traverse the decidua and enter the inner third of the myometrium. This stepwise process begins with attachment of EVT-expressed adhesion molecules to specific basal laminar proteins in the decidual ECM.¹⁹ Trophoblasts then breach decidual capillaries to provide the embryo with a rich source of oxygen and nutrients, and eventually remodel maternal spiral arteries to form high-capacitance, low-resistance vessels that increase blood flow to the fetal-placental unit.²⁰ Invasion of decidual capillaries and arteries occurs within a matrix of decidual cells that express tissue factor (TF) under continued stimulation by P_4 . Elevated decidual cell expression of TF is temporally and spatially positioned to promote hemostasis during this invasive process.²¹

Role of Tissue Factor

TF is a transmembrane 45-kDa glycoprotein member of the class 2 cytokine receptor family.^{21–23} Unlike endothelial cells, which do not normally express TF, tissues that are highly vulnerable to bleeding such as the brain and placental villi constitutively express high levels of TF.^{24,25} Expression of TF may provide an evolutionary advantage in prevention of

fatal hemorrhage. In human endometrial stromal cells, P₄ uniquely induces high levels of TF to prevent hemorrhage during placentation, but in the absence of a conception, P₄ withdrawal promotes inhibition of TF expression to facilitate menstruation.²²

In response to vascular injury, the clotting cascade is initiated by binding of extravasated circulating factor VII to the hydrophilic extracellular domain of perivascular cell membrane-bound TF. Factor VII auto-activates upon binding to TF to form the TF/VIIa complex, and triggers a greater than 100-fold increase in catalytic activity.²⁶ The TF/VIIa complex cleaves pro-thrombin to thrombin, which then ultimately converts fibrinogen to fibrin. The final hemostatic plug is formed when fibrin monomers self-polymerize and are cross-linked by thrombin-activated factor XIIIa.^{27–28} Simultaneously, thrombin induces platelet plug formation. The clotting cascade (Fig. 2) meets maternal hemostatic demands, beginning at the initial breach of decidual capillaries by syncytiotrophoblast, through EVT remodeling of spiral arteries,^{20,29} and finally during physiologic placental detachment at the third stage of labor.²⁹

The maternal-fetal interface at term displays prominent immunostaining for TF in decidual cells while cytotrophoblasts are virtually devoid of TF immunostaining.³⁰ That abruptio-induced thrombin formation is promoted by decidual cell-expressed TF and linked to PTD is indicated by: a) the standard use of fibrinogen consumption to measure abruptio severity; b) enhanced fibrin deposition in the decidua; and c) the high sensitivity and specificity with which elevated circulating thrombin-antithrombin (TAT) complex levels predict the subsequent occurrence of PTD associated with PTL and/or PPROM.^{31–34}

Direct and Indirect Roles for Thrombin in PTD and PPROM

Through this protective cascade, abruptio results in an intense local generation of thrombin which paradoxically predisposes to PPROM and PTD. In addition to promoting hemostasis via its extracellular actions, thrombin induces several biological effects via decidual cell membrane-bound protease-activated receptors (PARs), a family of four distinct “seven membrane” G protein-coupled receptors. As is the case for thrombin, each PAR ligand is a serine protease that binds to and cleaves its receptor to expose an N-terminal tethered ligand domain that autoactivates the cleaved receptor.³⁴

Among its protean cellular effects, thrombin induces proliferation and chemotaxis of pro-inflammatory immune and mesenchymal cells and activates endothelial cells via PAR-1, 3 and 4. In contrast, PAR-2 is primarily a receptor for trypsin and trypsin-like enzymes, which includes the TF/VIIa complex.^{35–37} Binding to PARs can directly induce production of matrix metalloproteinases (MMPs) which degrade various ECM components.^{38–40}

Bioengineering measurements taken together with comprehensive histological and biochemical observations indicate that the fibrillar collagen-rich amnion and choriodecidua ECM provide greater than additive tensile strength and structural integrity that withstand disruptive forces derived from the human fetus and myometrium.⁴¹ The weakest membrane component, the choriodecidua, was observed to rupture first, followed by its amnion support structure. Proteases secreted by neighboring cell types degrade collagens I and IV in the ECM of choriodecidua and amnion, thereby impairing the integrity and strength of these ECMs.⁴²

The MMPs are the primary mediators of ECM degradation. Specifically, 1) the collagenases, exemplified by MMP-1, effectively degrade fibrillar collagens; 2) the stromelysins, exemplified by MMP-3, degrade a broad array of ECM components, as well as activate the secreted zymogenic forms of pro-MMP-1 and pro-MMP-9 to promote an ECM-degrading cascade; and 3) the gelatinases, exemplified by MMP-9 and MMP-2, preferentially degrade basal laminar proteins such as collagen IV.^{38–43} In cultured human term decidual cell s,

thrombin markedly augments MMP-1 and MMP-3.^{46,47} Third trimester human decidua contains abundant, constitutively expressed MMP-2, as well as the key regulators of MMP activity, tissue inhibitor of MMPs (TIMP-1 and TIMP-2).¹⁹ A rich decidual infiltrate of neutrophils, which express high levels of such ECM-degrading proteases as elastase, collagenase and MMP-9, accompanies abruption-induced PPROM even in the absence of infection.^{48–50}

The association between PPROM and intra-amniotic infections is well-established and strong evidence now links PPROM with placental abruption in the absence of infection.⁵ In the amniotic fluid of women with PTD and coexisting chorioamnionitis, levels of interleukin-8 (IL-8), the primary neutrophil chemoattractant and activator^{51–52}, and IL-6, a decisive mediator of chronic inflammation, are elevated.^{53–54} Similarly, we observed that thrombin elicited a dose-dependent elevation in IL-8 secretion by decidual cells compared to untreated cultures ($P<0.05$), with 2.5 U/mL of thrombin increasing IL-8 levels by greater than 14-fold.⁵⁵ The decidua of placental sections of abruption-induced PPROM in the absence of infection showed co-localization of the immunoreactive IL-8 with fibrin deposits consistent with thrombin-induction of IL-8 production by decidual cells. Furthermore, immunostaining for the neutrophil marker CD15 in placentas after overt abruption, with or without PPROM, showed marked decidual neutrophil infiltration that peaked after PPROM, whereas decidua from gestational age-matched controls were virtually devoid of neutrophils. Neutrophil infiltrates also co-localized with fibrin deposition. As a rich source of proteases, neutrophils contribute to degradation of ECM and abruption-mediated PPROM.⁵²

Additionally, thrombin has been shown to be a potent direct uterotonic agent both *in vitro* and *in vivo*.⁵⁶ Using a rat model, thrombin was shown to increase frequency, intensity and tone of myometrial contractions in a dose-dependent manner. Pre-treatment of thrombin with hirudin, a thrombin inactivator, or heparin suppressed the uterotonic effects of thrombin.

Therefore, during DH, thrombin generated from TF localized on the cell membranes of decidual cells is positioned to induce PPROM and PTD directly via enhanced decidual cell expressed MMP expression, and indirectly by promoting neutrophil trafficking and uterine contractility, as summarized in Fig. 3. These pathologic mechanisms together contribute to a 7-fold increase in risk of PPROM when vaginal bleeding is seen in more than one trimester.^{6–8}

Clinical manifestations of Decidual Hemorrhage

Abruptions associated with preterm labor and PPROM usually reflect sub-acute, chronic processes. However, acute, clinically evident abruptions can lead to both maternal and fetal death. Abruptions are defined as the partial or complete separation of a normally implanted placenta from the placental implantation site prior to delivery. Abruption occurs in 0.48% to 1.8% of pregnancies, and its incidence may be increasing.^{57,58} In recent decades, a disproportionate increase has been seen in African-American women.⁵⁹ The incidence of abruption is highest between 24–28 weeks of gestation and decreases as gestation advances.^{9,10} (Fig. 4)

Diagnosis of placental abruption is based on classical clinical findings of vaginal bleeding, abdominal pain and increased uterine contractions. Differential diagnoses include placenta previa, vasa previa, cervical lesions, infection (cervicitis), trauma, urinary source, and others.⁶⁰ Approximately, 10–35% of abruptions may be concealed within the uterus, and therefore result in clinical underestimation of blood loss.^{61–62}

Physical examination may reveal a rigid abdomen secondary to tetanic contractions or Couvelaire uterus, vaginal bleeding, and evidence of maternal hypoperfusion or fetal distress. Cardiotocography may display uterine tachysystole with or without a NICHD Category III fetal heart rate tracing. Although ultrasound evaluation of the placenta can sometimes show presence of a retroplacental or retrochorionic hematoma, approximately 50% of placental abruptions produce no distinct ultrasound findings.¹⁰ Clinical sequelae include 1) fetal manifestations of uteroplacental insufficiency, 2) maternal complications of hemorrhage, or 3) as previously described, premature birth.

The severity of DH ranges from subclinical separation of the placenta, incidentally detected on ultrasound or on gross examination of placenta after delivery, to major abruption with associated clinical sequelae. The grading of placental abruptions is seen in Table 2. Grade 3 placental abruption occurs in approximately 0.2% of pregnancies.⁶¹ Formation of a hematoma in the decidua may result in compression of the overlying intervillous space, local destruction of the placental parenchyma, and fetal hypoxia. Therefore, chronic placental abruption often manifest as uteroplacental insufficiency, fetal growth restriction, or oligohydramnios. Most pregnancies complicated by abruption result in the delivery of an infant weighing less than the 10th percentile for gestational age.⁶²

In severe case, placental abruption involving greater than 50% separation can result in intrauterine fetal demise.¹⁰ With a perinatal mortality rate of approximately 12%, placental abruption carries a 15-fold increase in risk of intrauterine and neonatal demise compared to controls. At the optimal gestational age of 40 weeks (when overall perinatal mortality normally nadirs), perinatal mortality was 19-fold greater for abruption complicated than for non-abruption associated births (34.6 vs. 1.8 per 1,000 births, respectively). Mortality with abruption was more likely to occur antepartum than after delivery (relative risk for stillbirth was 18 compared with 10 for neonatal death).⁶³

Maternal sequelae of placental abruption include complications of severe hemorrhage, such as hypotension, hysterectomy, disseminated intravascular coagulation (DIC), massive transfusions, intensive care unit admission, and multisystem organ failure. Maternal mortality rate ranges from 0.04% to 1%.^{64–65} Approximately 10% of patients with placental abruption show significant coagulopathy, with the incidence increasing to 20–30% in cases of massive abruption. The robust thrombin production in severe placental abruption is the pathophysiology behind DIC with consumptive hypofibrinogenemia.¹⁰

Women who have experienced an abruption have increased long term health risks. Placental abruption with fetal compromise has been associated with maternal cardiovascular sequelae later in life in a large population-based study of over a million women, with an adjusted hazard ratio of 2.0 (95% CI: 1.7–2.2).⁶⁶ These future cardiovascular events, such as ischemic heart disease, cerebrovascular accident, and peripheral artery disease, may be a delayed manifestation of the underlying maternal vascular pathology that predisposed to adverse pregnancy outcomes.

Management of Placental Abruption

Management of suspected placental abruption should include prompt assessment of maternal and fetal status, and a subsequent individualized management algorithm based on severity of disease, underlying etiology, and gestational age. In severe cases of placental abruption with life-threatening hemorrhage, maternal hemodynamic stabilization is the priority. As previously mentioned, the majority of maternal complications result from hypovolemic shock secondary to massive blood loss, whether concealed or clinically visible. Maternal vital signs, including blood pressure, heart rate, and urine output should be closely

monitored. Hypovolemia may be masked in cases of abruption in which severe hypertension is the etiology.

Crystalloid, colloid, and blood product resuscitation may be initiated through two wide-bore intravenous lines, if necessary. Identification and correction of underlying risk factors, such as trauma, or a hypertensive crisis also play an important role in the management of placental abruption. A multidisciplinary approach should be undertaken, if available, with appropriate consultations with perinatologists, neonatologists, anesthesiologists, operating room staff, blood bank, and intensive care specialists.

Laboratory evaluation should include blood type and Rhesus-D status, complete blood counts, coagulation studies, and cross-matching of blood products. Hypofibrinogenemia is a result of the intense thrombin response and is the most sensitive indicator of coagulopathy. Prothrombin time and partial thromboplastin time may be elevated in cases of severe abruption. Kleihauer-Betke, an acid elution test employed to assess the presence of fetal hemoglobin in maternal circulation, may be useful in calculation of Rhesus-D immunoglobulin dosage in patients who are Rhesus-D negative.

If the fetus is at a gestational age deemed to be potentially viable, continuous fetal cardiotocography should be initiated to determine fetal well-being. Antenatal corticosteroids may be administered between 24 + 0/7 to 33 + 6/7 weeks of gestation for promotion of fetal lung maturity and prevention of prematurity-associated complications. If fetal decompensation unresponsive to intrauterine resuscitation occurs or the fetus is above 34 + 0/7 weeks of gestation, delivery should be expeditiously effected. Vaginal delivery can be attempted if the fetal heart rate tracing remains reassuring and the maternal status remains stable. Given the intense uterotonic effects of thrombin, patients may often undergo spontaneous labor without need for induction or augmentation. Cesarean delivery should be performed if the patient is remote from delivery with evidence of fetal distress, intolerance of labor, or for routine obstetrical indications.

In the case of an intrauterine fetal demise secondary to a massive abruption, the mode of delivery is dependent on maternal status, severity of hemorrhage, and other obstetrical complicating factors, such as prior classical hysterotomy incision. Vaginal delivery is the preferred modality in most cases, unless urgent delivery is necessary for maternal stabilization.

If the mother and fetus are both stable, such as in a mild, subacute, or chronic abruption, ultrasound evaluation of the intrauterine environment may be undertaken, including assessment of the placental location, placental appearance, amniotic fluid index, and fetal growth. Placenta previa may be present in 10% of placental abruptions.

Ultrasonographic appearance of a hematoma evolves over time. In the acute phase, the blood is hyperechoic to isoechoic when compared to the placenta. (Figs. 5 and 6) As the hematoma organizes and resolves, the insult appears hypoechoic within a week and may be anechoic within two weeks.⁶⁷ (Figs. 7 and 8) Exclusion of a retroplacental hematoma, however, does not exclude the presence of placental abruption.

The use of tocolytics in placental abruption has classically been discouraged, however, a few small non-randomized studies have shown possible benefit to administration of tocolytic agents to prolong gestation.⁶⁸⁻⁶⁹ Further studies are needed to elucidate the risks and benefits of tocolysis.

Careful management of a patient with placental abruption should continue into the postpartum period, given the risks of DIC and postpartum uterine atony. Uterotonic agents,

such as oxytocin, carboprost, misoprostol, and methyl-ergonovine, should be readily available.

Placental evaluation

Gross examination of a placenta may reveal a fresh clot attached to the maternal surface of the placenta in cases of recent placental abruption. Chronic or remote abruption may be seen as fibrin deposition at the site of abruption with infarcts or depression of the overlying placental parenchyma. Microscopic examination reveals hemosiderin-laden macrophages and evidence of villous hemorrhage.⁷⁰

Histological etiologies for DH include ischemic placental diseases, poor spiral artery remodeling, spiral artery thrombosis and sclerotic lesions in myometrial arteries.^{6,8,57} It is important to note, however, that evidence of abruption can be seen in up to 4.5% of placentas examined routinely, suggesting that small episodes of placental abruption are more common than those diagnosed clinically.⁷¹

Recurrence, Prediction, and Prevention

The recurrence rate of placental abruption ranges from 6% to 17% after a first episode, similar to the recurrence risk of PTD and increases to 25% after two episodes. Approximately 7–15% of massive abruptions resulting in intrauterine fetal demise have the same outcome in a subsequent pregnancy.^{10,72} Thirty percent of all future pregnancies in women who have had a prior placental abruption do not carry to viability.⁷²

Although multiple trials exist for various treatments in the prevention of preeclampsia, no randomized-controlled trials exist for prevention of placental abruption. Prevention of recurrent abruption begins with correction of underlying modifiable risk factors. Consideration should be given to interval resection of a uterine septum or submucous myoma. Other established risk factors for placental abruption, such as cigarette smoking, drug use, chronic hypertension, pregnancy-induced hypertension, and preeclampsia, should be addressed. Preconceptional and prenatal counseling on the harmful effects of smoking and drug abuse during pregnancy can help to reduce the incidence of placental abruption and other adverse outcomes of pregnancy.³

Summary

Decidual hemorrhage is an important contributor to PTD and associated healthcare costs. Management of abruption should be individualized, and the patient should be counseled on risks of recurrence. Recent translational investigations on the role of TF and thrombin have helped to shed light on the complex disease process. Additional future research is imperative to development of targeted therapies in the treatment and prevention of placental abruption and PTD.

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Figure 1. Perinatal mortality in pregnancies with and without abruption across gestation, 2000–2002.⁹ Circles, pregnancies with abruption. Diamonds, pregnancies without abruption. (From Oyelese Y, Ananth CV. Placental abruption. *Obstet Gynecol* 2006;108(4):1005-16, with permission.)

Figure 2. Hemostatic, thrombotic, and fibrinolytic pathways⁶⁰

Ø, inhibitory effect; (+), stimulatory effect.

(From Han CS, Paidas MJ, Lockwood CJ. *Clotting Disorders. In: High Risk Pregnancy: Management Options*. Eds: James DK, Steer PJ, Weiner CP et al. New York, NY: Saunders; 2010, with permission.)

Figure 3. Pathway to prematurity from Decidual Hemorrhage

FVIIa: activated factor VII; TF: tissue factor; PAR: protease-activated receptors; MMP: matrix metalloproteinases; ECM: extracellular matrix.

(Courtesy of Charles J. Lockwood, MD, New Haven, Connecticut)

Figure 4.
Rates of abruption across gestation, United States, 2000–2002⁹
(From Oyelese Y, Ananth CV. Placental abruption. *Obstet Gynecol* 2006;108(4):1005-16,
with permission.)

Figures 5 and 6.
Retroplacental hematoma

Figure 7 and 8.
Resolving hematoma with hypoechoic appearance

Table 1Risk factors for Decidual Hemorrhage^{12–14}

Risk factor	OR or RR
Trauma	4.3–15.0
Cocaine use	5.0–10.0
Oligohydramnios	2.5–10
Chorioamnionitis	2.0–2.5
Maternal age and parity	1.1–3.7
Hypertensive disorders	
Eclampsia	3.3–3.9
Chronic hypertension with preeclampsia	7.8
Chronic hypertension	1.8–5.1
Mild and severe preeclampsia	0.4–4.5
PPROM	1.8–5.1
Multiple gestations	1.5–3.0
Alcohol use	1.5–1.7
Renal disorders	1.4–1.8
Tobacco use	1.4–2.5
Dietary or nutritional deficiency	0.9–2.0
Male fetus	0.9–1.3

Table 2Grading of placental abruption⁷⁰

Grade	Vaginal bleeding	Uterine tetany	Fetal distress	Maternal shock	Ultrasound finding
0	–	–	–	–	Small retroplacental clot
1	+	+/-	–	–	+/-
2	+/-	+/-	+	–	+/-
3	+/-	+	Fetal demise	+ with possible coagulopathy	+/-