Abruptio Placentae and Disseminated Intravascular Coagulopathy

David R. Hall, MBChB, MMed, MD

Abruptio placentae is an important cause of vaginal bleeding in the latter half of pregnancy. The key factor in the pathophysiology is hemorrhage at the decidual–placental interface. Small episodes may escape clinical detection, but severe grades impact significantly on fetal and maternal morbidity and mortality, with the most frequent complications being fetal death, severe maternal shock, disseminated intravascular coagulopathy, and renal failure. Important risk factors for the development of abruptio placentae are previous abruption, hypertensive diseases, abdominal trauma, growth restriction, and smoking. The diagnosis is essentially made on the clinical picture that includes vaginal bleeding (usually dark blood), abdominal pain, and uterine contractions. The essence of management is restoration of circulating volume followed by delivery of the fetus and placenta, most often by cesarean section when the diagnosis is clear and the fetus alive and viable. Aggressive resuscitation and expeditious vaginal delivery are the goals when the fetus is dead.
Semin Perinatol 33:189-195 © 2009 Elsevier Inc. All rights reserved.

KEYWORDS abruptio placentae, antepartum hemorrhage, disseminated intravascular coagulopathy, fetal death, hemorrhagic shock, hypertension

Definition and Context

Abruptio placentae is defined as the partial or complete separation of a normally implanted placenta from the uterine wall, before delivery, after the 20th week of pregnancy. It is an important cause of maternal and perinatal mortality and morbidity. The incidence is quoted as 0.49-1.8%,[2] and evidence from the US and Norway indicate that the frequency is increasing.[1,2] Small episodes of placental abruption may escape clinical detection and only be diagnosed after routine examination of the placenta. In such cases, the reported incidence is higher. Unlike severe grades, minor, self-limited abruption may have few consequences.

The maternal mortality rate is approximately 1%. Severe hemorrhage may also cause severe morbidity, such as disseminated intravascular coagulation (DIC), renal failure, massive transfusions, and hysterectomy. Postpartum hemorrhage can result from DIC or from a Couvelaire uterus with an impaired ability to contract. In the 2000-2002 triennium in the UK,[3] 4 maternal deaths occurred; whereas in South Africa, 51/81 maternal deaths from antepartum hemorrhage (assigned a causal subcategory) were due to abruptio placentae during the 2002-2004 triennium.[4]

Most perinatal losses are due to intrauterine death before admission,[5,6] whereas neonatal deaths are chiefly related to prematurity. This is important as it has been shown that the peak rate of abruption occurs between 24 and 27 weeks' gestation.[7] The perinatal mortality rate varies widely (4.4-67%) depending on the accuracy of diagnosis and neonatal facilities. A large population-based study in the US noted a rate of 119/1000 for abruptio placentae, compared with 8.2/1000 for all other births.[8] Although not specifically divided into subcategories, antepartum hemorrhage was the most frequent cause (22%) of fresh stillborn babies >500 g in South Africa during the 2003-2005 triennium.[9] Although neonatal outcomes have improved in developed countries due to advances in neonatal care, the problems of perinatal deaths of severely preterm babies in developing countries remain problematic. Surviving babies also carry an increased risk of handicap, including cerebral palsy.[10] This is because abruptio placentae is believed to share a common cause with intrauterine growth restriction and preterm delivery (Fig. 1).[11,12]

Risk Factors

The causes of placental abruption vary. Conditions associated with ischemic placental disease, such as pre-eclampsia,

Department of Obstetrics and Gynaecology, Stellenbosch University, Tygerberg Hospital, Tygerberg, South Africa.
Address reprint requests to David R. Hall, MBChB, MMed, MD, Department of Obstetrics and Gynaecology, Stellenbosch University and Tygerberg Hospital, PO Box 19063, Tygerberg, 7505, South Africa. E-mail: drh@sun.ac.za
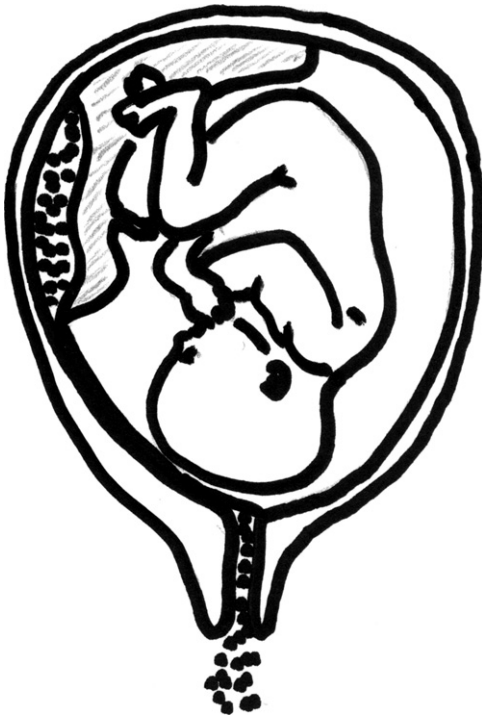
Figure 1 Abruptio placentae with blood tracking from retroplacental hemorrhage.

growth restriction, and placental abruption, have a substantially increased risk of recurrence alone or in combination in a subsequent pregnancy.[13] Ananth and coworkers[14] have postulated that there are acute and more often chronic disease processes reflected in the known associated risk factors. Disease patterns at term may differ from those occurring at preterm gestations. Conditions associated with chronic disease processes are present throughout pregnancy, but those associated with acute inflammation are more common at preterm gestations. Recent work by Nath and coworkers[15] has confirmed the association of histologic chorioamnionitis with abruptio placentae in both preterm and term gestations. Examples of associated risk factors are:

- Previous abruptio placentae. The recurrence rate is ±11% after one episode, rising to 25% after two episodes.[5] However a small, retrospective study from South Africa found that 16/45 (35%) of women with previous abruption had a repeat event.[16]
- Maternal hypertensive diseases. Early, severe pre-eclampsia and chronic hypertension carry significantly increased risks.[17,18]
- Cocaine and vasoconstrictive drugs affecting uteroplacental blood flow and decidual integrity.
- Cigarette smoking in a dose–response relationship.[19,20] Smoking is associated with decidual necrosis, chorionic villous hemorrhage, and intervillous thrombosis.
- Multiple pregnancy.
- Premature and prelabor rupture of membranes (PPROM) due to sudden decompression of the uterus or inflammation. Preterm labor and PPROM represent acute disease processes associated with abruption.

- Chorioamnionitis.
- Abdominal trauma[21] or uterine manipulation, such as external cephalic version.
- Others factors indicated below.

Other associated risks include an increase with parity, placental abnormalities (such as a circumvallate placenta), poly- or oligo-hydramnios, dietary deficiencies (such as folate deficiency), and hyperhomocysteinemia. The association between abruption and the common thrombophilias has been more difficult to define with studies showing mixed results.[7,22-24] Homocysteine can cause vascular damage. Gebhardt and coworkers[25] investigated the involvement of the methylenetetrahydrofolate reductase gene mutations C677T and A1289C implicated in abruptio placentae and growth restriction. They found that combined heterozygosity may represent a genetic marker for abruptio placentae. However, another South African study looking only at the C677T mutations in black patients found a very low frequency (1%) of the genotype,[26] emphasizing the importance of ethnicity. A recent, large, population-based Norwegian study demonstrated that folic acid supplementation significantly reduces the incidence of abruptio placentae, probably by lowering plasma homocysteine. The risk was further reduced by supplementation with other vitamins, especially in women who smoked (19-33% risk reduction).[27] Abnormalities in circulating angiogenic factors have been reported in diseases with abnormal placentation. Decreased levels of proangiogenic placental growth factor (PLGF) and increased levels of the antiangiogenic ratio soluble fms-like tyrosine kinase 1/PLGF were documented in nulliparous women who subsequently developed hypertension and placental abruption.[28]

Pathophysiology

The key factor in the pathophysiology is hemorrhage at the decidual–placental interface. This hemorrhage separates the decidua, leaving a thin layer attached to the placenta. As the hematoma enlarges, there is further separation and compression of the overlying intervillous space, resulting in local destruction of placental tissue.[29] Macroscopically, this may appear as an organized clot lying on a depressed maternal surface of the placenta, but the process may develop so rapidly that an organized clot will not be found if delivery follows shortly thereafter (Fig. 2). A growing body of evidence suggests that abruptio placentae is often the final dramatic expression of a chronic placental disorder. Acute and chronic inflammatory processes are characterized by activated neutrophils and macrophages that secrete cytokines and tumor necrosis factor. These upregulate the production and activity of matrix metalloproteinases in the trophoblast. Matrix metalloproteinases are presumed to have important functions in normal placental detachment, but increased production may result in destruction of extracellular matrices and cellular connections that secure the placenta, ending in premature detachment.[14]

Damage to the fetus is caused by the clot forming a barrier between the placental bed and the villi, as well as the release

Figure 2 Maternal surface of placenta with large (±40%) clot. (Color version of figure is available online.)

of prostaglandins causing uterine spasm, both decreasing placental perfusion. The overall effect depends on fetal and placental reserve as well as the size of the affected area. Sometimes it is self-limited, but if bleeding is continuous, the entire placenta can separate with extravasation of blood into the myometrium reaching the peritoneal surface, causing pain and further uterine spasm. These blotchy blue areas denote the so-called Couvelaire uterus. The dissecting retroplacental hematoma may pass the edge of the placenta, between the decidua and fetal membranes, through the cervix and into the vagina, becoming visible as dark blood or clots.

Clinical Picture

The classic presentation includes vaginal bleeding (usually dark blood), abdominal pain, and uterine contractions. These may not all be present and may vary in degree. Vaginal bleeding may even be absent when hemorrhage is concealed in the uterus (20-30% of cases). Thus, the observed amount of bleeding is unreliable to estimate the loss from the maternal circulation. Abdominal pain may present as uterine irritability, intermittent contractions, persistent dull lower abdominal, or back pain (posterior placenta). Severe abruption causes a painful, distended, and hard uterus. In such cases, it is difficult to palpate the fetal parts. The pain may be due to extravasation of blood into the myometrium, overdistension of the uterus due to retroplacental bleeding, or the frequent contractions associated with the release of prostaglandins. This may be accompanied by nausea, vomiting, and reduced or absent fetal movements. The contractions characteristically have a high frequency but low amplitude (>5 per 10 minutes—"sawtooth" pattern) with an elevated baseline tone, but this may not be reliable when using an external contraction monitor. If the membranes are ruptured, blood-stained liquor may be seen (Figs. 3 and 4).

The diagnosis is essentially a clinical one. The symptoms and signs are clear in moderate and severe cases. In mild forms, however, the diagnosis is often only made after delivery of the placenta with the observation of a retroplacental clot. Ultrasound examination is helpful in certain cases and can be used to exclude placenta praevia. It is, however, not reliable enough to consistently diagnose or exclude abruptio placentae. Valuable time should not be lost performing an ultrasound examination in an unstable mother or in the pres-
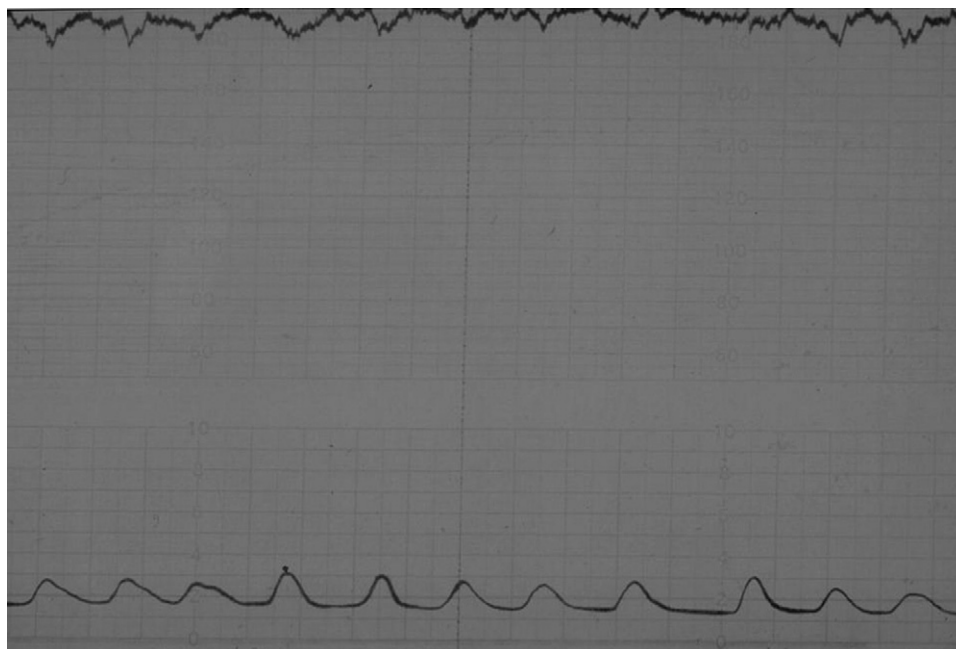
Figure 3 Cardiotocogram with internal monitoring in a case with abruptio placentae. The fetus has a tachycardia (±190 bpm) with repeated decelerations. The baseline intrauterine pressure is raised with frequent contractions of low amplitude (sawtooth pattern).

Figure 4 Cardiotocogram in abruptio placentae. The fetus is dead. The uterine contractions show a "sawtooth pattern." (Color version of figure is available online.)

ence of fetal distress when the placental site is already known. Neither is the Kleihauer-Betke test of value in the diagnostic work-up of these patients. The discrepancy between the rates of diagnosis by clinicians and pathologists is well known. When delivery occurs quickly after an acute catastrophic abruption, an organized retroplacental clot is unlikely to be found. Because abruptio placentae may be present as an incidental placental finding, obstetricians should probably reserve the term for cases diagnosed on clinical grounds or with adverse outcomes.

Early severe pre-eclampsia carries a high risk for abruptio placentae. Although expectant management of early severe pre-eclampsia is now more widely advocated,[30] placental abruption remains a concern. The rates range from 4.1% to 22.9%[31] and were 20% and 6% in the two largest reported studies.[32,33] These women were, however, managed in tertiary units by dedicated teams capable of rapid intervention. During the early stages of abruption, catecholamine-induced vasoconstriction may selectively maintain perfusion of the maternal heart and brain at the expense of uteroplacental blood flow. Thus, fetal distress is an important sign of hemodynamic compromise. In a case-control series (including 69 cases of abruptio placentae) of women managed expectantly for early severe pre-eclampsia, Odendaal and coworkers[34] showed that late decelerations detected by 6-hourly fetal heart rate monitoring were the only early warning of abruptio placentae. With rapid intervention, a good outcome for both the mother and her baby can be anticipated. Abruptio placentae may also present as idiopathic preterm labor without initial signs of fetal distress. Such cases require intensive fetal

monitoring, and suppression of labor should not be entertained.

Management

The management depends on the maternal and fetal conditions, associated complications, and the gestational age. When the fetus is still alive, the blood loss is less. In cases with moderate or severe abruptio placentae and where the diagnosis is clear, the principles of management are stabilization of the mother and delivery of the baby. When the diagnosis is uncertain (e.g., antepartum hemorrhage of uncertain origin) or when the retroplacental clot is small, self-limited, and asymptomatic, treatment may be individualized taking the gestational age into account.

Active Management

A rapid evaluation of the maternal condition should be done. The vital signs must be monitored frequently with particular attention to the maternal heart rate, as underlying hypertension can mask concealed blood loss. Fetal death indicates a larger blood loss with a high chance of associated complications, such as shock, DIC, and renal failure. A retrospective study of 96 cases of abruption with fetal death found that 53% developed major complications, but that with careful tertiary management, the impact could be reduced.[35] In severe cases, two large-bore infusion lines should be placed and a bladder catheter inserted. Initial resuscitation is with crystalloid solution if there are any signs of hypovolemia, after which blood components (usually packed red cells and

Table 1 Special Investigations

- Hemoglobin level and platelet count
- Cross match blood
- Serum electrolytes
- Blood gas and acid–base status (shock)
- Coagulation tests (as indicated in text)
- Cardiotocogram and ultrasonography (as indicated in text)

plasma) are used as required. Baseline blood investigations are shown in Table 1. Coagulation studies are carried out if the patient is clinically shocked or has a low hematocrit or thrombocytopenia. Once the mother has been quickly assessed and stabilization begun, the fetal status is evaluated. If the position of the placenta is unknown, an ultrasound examination can exclude placenta previa, and fetal heart rate monitoring can be commenced as appropriate.

When the fetus is alive and viable, and the diagnosis of moderate or severe abruptio placentae is clear, delivery should be expedited. The clinician must decide whether vaginal delivery is achievable without severe maternal or fetal morbidity or death. When signs of fetal distress are present, delivery by cesarean section is required; however, if the heart rate tracing is normal and the uterus relaxes between contractions, vaginal delivery may be attempted. No specific time limit need be applied as long as continuous fetal and intensive maternal surveillance reveals no deterioration and labor progresses normally. However, when placental abruption is progressive, most women will require delivery by cesarean section unless labor is far advanced. Although clinicians and anesthetists may be concerned about DIC, this condition is uncommon with a living fetus and should not interfere with decisions regarding operative delivery. It is important to remember that both the maternal and fetal conditions can deteriorate rapidly and indecision may lead to fetal death. In a small case-control study in patients with severe abruption and fetal bradycardia, longer-decision delivery intervals were associated with poorer perinatal outcomes.[36]

Fetal death and maternal coagulopathy are common in severe placental abruption. Vaginal delivery is the route of choice in such cases, but cesarean section is occasionally necessary for maternal indications alone. The fetal membranes should be ruptured as soon as possible to decrease the intrauterine pressure, which causes dissemination of thromboplastins into the maternal circulation, and to hasten labor. With fetal death, the risks of complications increase significantly due to continuous hemorrhage from the placental bed. Therefore, blood and coagulation factors (usually packed red cells and fresh frozen plasma) should be replaced aggressively. Only once the fetus and placenta are expelled can the uterus contract properly to accomplish hemostasis. The shearing effect of blood between the membranes and decidua causes a significant release of prostaglandins, thus labor usually proceeds rapidly in the active phase. Oxytocin should only be used after careful consideration due to the risk of overstimulation and uterine rupture. Operative delivery should be avoided, but when necessary, DIC must first be reversed if

present. A particular problem is the presence of a cesarean scar. It can be difficult to distinguish between the painful, hard abdomen of abruption with fetal death and scar rupture. In such cases, management should be individualized, but where there is reasonable concern, abdominal delivery after evaluation of coagulation status may be prudent. Once delivery has been accomplished, the concealed blood loss in the form of retroplacental clots will become evident. An oxytocin infusion will help keep the uterus well contracted, thereby avoiding postpartum hemorrhage.

Expectant Management

This approach is for mild (self-limited) abruption or when the diagnosis is uncertain. In such cases, the vaginal bleeding is slight, the pain mild or absent, and the mother and fetus are completely stable. It is not always possible to distinguish between idiopathic preterm labor and mild abruption. In these stable cases, tocolysis may be cautiously prescribed, particularly when the pregnancy is remote from term. In a review of 236 cases of bleeding in the third trimester that included 131 cases of abruptio placentae, Towers and coworkers noted that tocolysis had been used in 73% of the abruption cases. All cases of mortality were related to prematurity, and no adverse maternal or fetal effects could be ascribed to the tocolysis.[37] If the underlying condition is abruption that deteriorates, it will manifest with signs of fetal distress first and later with maternal signs and symptoms within 12-24 hours. Other associated conditions, such as trauma, hypertension, and substance abuse, should be excluded.

Complications

Two complications will be briefly expanded upon.

Hemorrhagic Shock

Abruptio placenta is often associated with significant loss of blood volume, either vaginally or concealed within the uterus. This is particularly so when there is fetal death. Shock, which is a clinical condition characterized by tissue hypoperfusion, then ensues; although underlying hypertension may initially mask true hypovolemia. During pregnancy, the enhanced blood volume and increased levels of coagulation factors, such as fibrinogen and factors VII, VIII, and X, provide physiological protection against hemorrhage, but when blood loss exceeds 25% of total volume, rapid hemodynamic deterioration occurs.[38] Ongoing hemorrhage and the development of anaerobic metabolism with acidosis lead to left ventricular failure and thereafter irreversible shock.

The prudent approach is to restore effective circulating blood volume to improve tissue perfusion and avoid ischemic necrosis of target organs. Initial crystalloid infusion before blood and plasma are available should be two to three times that of estimated blood loss, as shock is associated with significant fluid shifts from the intravascular to the extravascular compartments. Thereafter, red cell replacement may be guided by the hematocrit. When a vaginal delivery is antici-

pated, replacement of platelets is only necessary if the platelet count falls below 30×10^9/L, or there is oozing from puncture sites after adequate replacement of fibrinogen using fresh frozen plasma. When surgery is necessary, the platelet count must be elevated to 50×10^9/L. Because platelets are quickly consumed, they should be administered in theater shortly before the surgery. The response to volume replacement can be monitored by urine output (>0.5 mL/kg/hour) or central monitoring, particularly when renal damage is present. Pulse and blood pressure monitoring remain important but may be misleading in pre-eclampsia. With massive transfusion (6-8 U of blood), the serum potassium levels must be monitored to avoid hyperkalemia from banked blood.

Disseminated Intravascular Coagulation

As with hemorrhagic shock, DIC is more common in severe abruption with fetal death. Normal hemostasis depends on a delicate balance between the coagulation and fibrinolytic systems. Changes in the coagulation system depend on the extent of blood loss and, in abruptio placentae specifically, the release of procoagulant substances (tissue thromboplastins from placental injury) into the maternal circulation. Hypovolemia and hypoxia lead to an endothelial response with activated white cells and production of pro-inflammatory cytokines and oxygen free radicals. These augment oxidative stress and promote lipid peroxidation once antioxidant mechanisms are saturated, with resultant loss of vascular integrity and increased vascular permeability. Endothelial damage and infused thromboplastins lead to widespread activation of the clotting cascade. If unchecked, there is rapid consumption of coagulation factors and platelets, with fibrin deposition in the microcirculation and in the thrombus formation on the maternal surface of the placenta, leading to defibrination, thrombocytopenia, and hemostatic failure. However, a significant coagulation disorder can be present for some time without obvious clinical signs. Fibrinolysis is stimulated by DIC and the resultant fibrin degradation products (FDPs) interfere with fibrin clot formation exacerbating hemorrhage and negatively affecting cardiac and myometrial function.

The diagnosis of DIC is a combination of the clinical picture (abruptio placentae and bleeding tendency) together with laboratory test results (platelet count, INR, aPTT, FDPs, thromboelastogram). The bleeding can occur at surgical wounds, venipuncture sites, gums, nose, urogenital tract, or rectum. Decreasing platelet counts and abnormal coagulation tests (INR and aPTT) will be present. However, these are insensitive indicators as $>50\%$ of clotting factors must be consumed before the coagulation tests become abnormal. The thromboelastogram is a qualitative measure of clot formation. It is important to remember that fibrinogen levels are elevated in normal pregnancy, and therefore even low "normal levels" should raise concern. Fibrin degradation products, including D-dimer, are measurable in the peripheral circulation, and abnormal levels confirm the presence of a coagulopathy. In summary, early diagnosis is helpful in that blood component therapy can be anticipated and a trend

toward abnormal laboratory values with serial measurements recognized as an indicator of a developing coagulopathy.

The management is aimed at treating the underlying condition itself by delivering the fetus and placenta. Maintenance of effective circulation works against the negative effects of ischemia and aids clearance of FDPs from the blood by the liver. Fibrinogen is the specific procoagulant most often needed and is administered in fresh frozen plasma. The use of heparin or antifibrinolytic agents is generally not indicated in DIC induced by abruptio placentae. Once delivery is accomplished, the process usually resolves fairly rapidly, and it is uncommon for clinically evident coagulopathy to persist beyond 12 hours after delivery.[29] However, the platelet count may only return to normal levels 2-3 days after delivery, as time is necessary for maturation and release of platelets from the bone marrow.

Rhesus Isoimmunization

The amount of fetomaternal hemorrhage can be significant. Therefore, all rhesus-negative women with abruptio placentae should undergo a Kleihauer-Betke test to determine the appropriate dose of anti-D immunoglobulin to prevent immunization.

References

1. Ananth CV, Oyelese Y, Yeo L, et al: Placental abruption in the United States, 1979 through 2001: Temporal trends and potential determinants. Am J Obstet Gynecol 192:191-198, 2005
2. Rasmussen S, Irgens LM, Bergsjo P, et al: The occurrence of placental abruption in Norway. Acta Obstet Gynecol Scand 75:222-228, 1996
3. Department of Health: Why Mothers Die: A Report on Confidential Enquiries into Maternal Deaths in the United Kingdom 2000-2002. London, Stationary Office, 2004
4. Saving Mothers: Third Report on Confidential Enquiries into Maternal Deaths in South Africa 2002-2004. Pretoria, Department of Health
5. Konje JC, Taylor DJ: Bleeding in late pregnancy, in James DK, Steer PJ, Weiner CP, et al. (eds): High Risk Pregnancy: Management Options (ed 3). Philadelphia, Saunders, 2006, pp 1259-1275
6. Fretts RC: Etiology and prevention of stillbirth. Am J Obstet Gynecol 193:1923-1935, 2005
7. Oyelese Y, Ananth CV: Placental abruption. Obstet Gynecol 108:1005-1016, 2006
8. Ananth CV, Wilcox AJ: Placental abruption and perinatal mortality in the United States. Am J Epidemiol 153:332-337, 2001
9. Saving Babies V: Fifth Perinatal Care Survey of South Africa (2003-2005). Pretoria, Department of Health
10. Matsuda Y, Maeda T, Kouno S: Comparison of neonatal outcome including cerebral palsy between abruptio placentae and placenta previa. Eur J Obstet Gynecol Reprod Biol 106:125-129, 2003
11. Sheiner E, Shoham-Vardi I, Hallak M, et al: Placental abruption in term pregnancies: Clinical significance and obstetric risk factors. J Matern Fetal Med 13:45-49, 2003
12. Odendaal ES, Steyn DW, Odendaal HJ: Obstetric causes for delivery of very low birth weight babies at Tygerberg Hospital. S Afr Med J 93:61-64, 2003
13. Ananth CV, Peltier MR, Chavez MR: Recurrence of ischemic placental disease. Obstet Gynecol 110:128-133, 2007
14. Ananth CV, Getahun D, Peltier MR, et al: Placental abruption in term and preterm gestations: Evidence for heterogeneity in clinical pathways. Obstet Gynecol 107:785-792, 2006
15. Nath CA, Ananth CV, Simulian JC, et al: Histologic evidence of inflammation and risk of placental abruption. Am J Obstet Gynecol 197:319.e1-319.e6, 2007

16. Matsaseng T, Bagratee JS, Moodley J: Pregnancy outcomes in patients with previous history of abruptio placentae. Int J Gynecol Obstet 92: 253-254, 2006

17. Hall DR, Grové D, Carstens E: Early pre-eclampsia: What proportion of women qualify for expectant management and if not, why not? Eur J Obstet Gynecol Reprod Biol 128:169-174, 2006

18. Sibai BM: Chronic hypertension in pregnancy. Obstet Gynecol 100: 369-377, 2002

19. Ananth CV, Savitz DA, Bowes WA Jr, et al: Influence of hypertensive disorders and cigarette smoking on placental abruption and uterine bleeding during pregnancy. Br J Obstet Gynaecol 104:572-578, 1997

20. Kaminsky LM, Ananth CV, Prasad V, et al: The influence of maternal cigarette smoking on placental pathology in pregnancies complicated by abruption. Am J Obstet Gynecol 197:275.e1-275.e5, 2007

21. Grossman NB: Blunt trauma in pregnancy. Am Fam Physician 70: 1303-1310, 1313, 2004

22. Paidas MJ, Ku D-HW, Arkel YS: Screening and management of inherited thrombophilias in the setting of adverse pregnancy outcome. Clin Perinatol 31:783-805, 2004

23. Dizon-Townson D, Miller C, Sibai B, et al: The relationship of the factor V Leiden mutation and pregnancy outcomes for mother and fetus. Obstet Gynecol 106:517-524, 2005

24. Ananth CV, Peltier MR, De Marco C, et al: Associations between 2 polymorphisms in the methylenetetrahydrofolate reductase gene and placental abruption. Am J Obstet Gynecol 197:385.e1-385.e7, 2007

25. Gebhardt GS, Scholtz CL, Hillermann R, et al: Combined heterozygosity for methylenetetrahydrofolate reductase (MTHFR) mutations C677T and A1298C is associated with abruptio placentae but not with intrauterine growth restriction. Eur J Obstet Gynecol Reprod Biol 97: 174-177, 2001

26. Naidu CA: Methylenetetrahydrofolate (MTHFR) reductase gene polymorphism in African women with abruptio placentae. Eur J Obstet Gynecol Reprod Biol 132:237-244, 2007

27. Nilsen RM, Vollset SE, Rasmussen SA, et al: Folic acid and multivitamin supplement use and risk of placental abruption: A population-based registry study. Am J Epidemiol 167:867-874, 2008

28. Signore C, Mills JL, Qian C, et al: Circulating angiogenic factors and placental abruption. Obstet Gynecol 108:338-344, 2006

29. Clark SL: Placenta previa and abruption placentae, in Creasy RK and Resnik R (eds): Maternal-Fetal Medicine, Principles and Practice (ed 5). Philadelphia, Saunders, 2004, pp 707-722

30. Frias AE, Belfort MA: Post Magpie: How should we be managing severe preeclampsia? Curr Opin Obstet Gynecol 15:489-495, 2003

31. Sibai BM, Barton JR: Expectant management of severe preeclampsia remote from term: Patient selection, treatment, and delivery indications. Am J Obstet Gynecol 196:514e.1-514.e9, 2007

32. Hall DR, Odendaal HJ, Steyn DW, et al: Expectant management of early onset, severe pre-eclampsia: Maternal outcome. Br J Obstet Gynaecol 107:1252-1257, 2000

33. Haddad B, Deis S, Goffinet F, et al: Maternal and perinatal outcomes during expectant management of 239 severe preeclamptic women between 24 and 33 weeks' gestation. Am J Obstet Gynecol 190:1590-1597, 2004

34. Odendaal HJ, Hall DR, Grové D: Risk factors for and perinatal mortality of abruptio placentae in patients hospitalized for early onset, severe pre-eclampsia: A case controlled study. J Obstet Gynaecol 20:358-364, 2000

35. Leunen K, Hall DR, Odendaal HJ, et al: The profile and complications of women with placental abruption and intra-uterine death. J Trop Pediatr 49:231-234, 2003

36. Kayani SI, Walkinshaw SA, Preston C: Pregnancy outcome in severe placental abruption. Br J Obstet Gynaecol 110:679-683, 2003

37. Towers CV, Pircon RA, Heppard M: Is tocolysis safe in the management of third-trimester bleeding? Am J Obstet Gynecol 180:1572-1578, 1999

38. Bonnar J: Massive obstetric haemorrhage. Bailliéres Clin Obstet Gynecol 14:1-18, 2000