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Placenta Accreta Spectrum

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The Society of Gynecologic Oncology endorses this document. This document was developed jointly by the American College of Obstetricians and Gynecologists and the Society for Maternal–Fetal Medicine with the assistance of Alison G. Cahill, MD, MSCI; Richard Beigi, MD, MSc; R. Phillips Heine, MD; Robert M. Silver, MD; and Joseph R. Wax, MD.

ABSTRACT: Placenta accreta spectrum, formerly known as morbidly adherent placenta, refers to the range of pathologic adherence of the placenta, including placenta increta, placenta percreta, and placenta accreta. The most favored hypothesis regarding the etiology of placenta accreta spectrum is that a defect of the endometrial–myometrial interface leads to a failure of normal decidualization in the area of a uterine scar, which allows abnormally deep placental anchoring villi and trophoblast infiltration. Maternal morbidity and mortality can occur because of severe and sometimes life-threatening hemorrhage, which often requires blood transfusion. Although ultrasound evaluation is important, the absence of ultrasound findings does not preclude a diagnosis of placenta accreta spectrum; thus, clinical risk factors remain equally important as predictors of placenta accreta spectrum by ultrasound findings. There are several risk factors for placenta accreta spectrum. The most common is a previous cesarean delivery, with the incidence of placenta accreta spectrum increasing with the number of prior cesarean deliveries. Antenatal diagnosis of placenta accreta spectrum is highly desirable because outcomes are optimized when delivery occurs at a level III or IV maternal care facility before the onset of labor or bleeding and with avoidance of placental disruption. The most generally accepted approach to placenta accreta spectrum is cesarean hysterectomy with the placenta left in situ after delivery of the fetus (attempts at placental removal are associated with significant risk of hemorrhage). Optimal management involves a standardized approach with a comprehensive multidisciplinary care team accustomed to management of placenta accreta spectrum. In addition, established infrastructure and strong nursing leadership accustomed to managing high-level postpartum hemorrhage should be in place, and access to a blood bank capable of employing massive transfusion protocols should help guide decisions about delivery location.

Introduction and Background

Placenta accreta is defined as abnormal trophoblast invasion of part or all of the placenta into the myometrium of the uterine wall (1). Placenta accreta spectrum, formerly known as morbidly adherent placenta, refers to the range of pathologic adherence of the placenta, including placenta increta, placenta percreta, and placenta accreta. Maternal morbidity and mortality can occur because of severe and sometimes life-threatening hemorrhage, which often requires blood transfusion. Rates of maternal death are increased for women with placenta accreta spectrum (1, 2). Additionally, patients with placenta accreta spectrum are more likely to require hysterectomy at the time of delivery or during the postpartum period and have longer hospital stays (2). In 2015, the American College of Obstetricians and Gynecologists (ACOG) and the Society for Maternal–Fetal Medicine developed a standardized risk-appropriate maternal idealized care system for facilities, based on region and expertise of the medical staff, to reduce overall maternal morbidity and mortality in the United States (3). This designation is referred to as "levels of maternal care," and exists for conditions such as placenta accreta spectrum. Placenta accreta spectrum is considered a high-risk condition with serious associated morbidities; therefore, ACOG and the Society for Maternal–Fetal Medicine recommend

these patients receive level III (subspecialty) or higher care. This level includes continuously available medical staff with appropriate training and experience in managing complex maternal and obstetric complications, including placenta accreta spectrum, as well as consistent access to interdisciplinary staff with expertise in critical care (ie, critical care subspecialists, hematologists, cardiologists, and neonatologists). The general resources needed to be able to attain improved health outcomes in the setting of a known or suspected placenta accreta include planning for delivery with appropriate subspecialists and having access to a blood bank with protocols in place for massive transfusion.

Incidence

Rates of placenta accreta spectrum are increasing. Observational studies from the 1970s and 1980s described the prevalence of placenta accreta as between 1 in 2,510 and 1 in 4,017 compared with a rate of 1 in 533 from 1982 to 2002 (4). A 2016 study conducted using the National Inpatient Sample found that the overall rate of placenta accreta in the United States was 1 in 272 for women who had a birth-related hospital discharge diagnosis, which is higher than any other published study (4–7). The increasing rate of placenta accreta over the past four decades is likely due to a change in risk factors, most notably the increased rate of cesarean delivery.

Risk Factors

There are several risk factors for placenta accreta spectrum. The most common is a previous cesarean delivery, with the incidence of placenta accreta spectrum increasing with the number of prior cesarean deliveries (1, 8, 9). In a systematic review, the rate of placenta accreta spectrum increased from 0.3% in women with one previous cesarean delivery to 6.74% for women with five or more cesarean deliveries (10). Additional risk factors include advanced maternal age, multiparity, prior uterine surgeries or curettage, and Asherman syndrome (8, 11, 12).

Placenta previa is another significant risk factor. Placenta accreta spectrum occurs in 3% of women diagnosed with placenta previa and no prior cesarean deliveries. In the setting of a placenta previa and one or more previous cesarean deliveries, the risk of placenta accreta spectrum is dramatically increased. For women with placenta previa, the risk of placenta accreta is 3%, 11%, 40%, 61%, and 67%, for the first, second, third, fourth, and fifth or more cesarean, respectively (13).

Moreover, abnormal results of placental biomarkers increase the risk of placenta accreta spectrum. For example, unexplained elevation in maternal serum alpha fetoprotein is associated with an increased risk of placenta accreta spectrum (14–16). However, maternal serum alpha fetoprotein is a poor predictor of placenta accreta spectrum and is not accurate enough to be clinically useful. Other placental analytes linked to placenta accreta spectrum include pregnancy-associated plasma protein A, pro B-type natriuretic peptide, troponin, free β-hCG (mRNA), and human placental lactogen (cell-free mRNA) (16–20). In addition, other proposed markers of aberrant trophoblast invasion, such as total placental cell-free mRNA, may be associated with placenta accreta spectrum (21). As with alpha fetoprotein, they are too nonspecific for clinical use.

Etiology and Pathophysiology

The most favored hypothesis regarding the etiology of placenta accreta spectrum is that a defect of the endometrial–myometrial interface leads to a failure of normal decidualization in the area of a uterine scar, which allows abnormally deep placental anchoring villi and trophoblast infiltration (22). Several studies suggest that disruptions within the uterine cavity cause damage to the endometrial–myometrial interface, thereby affecting the development of scar tissue and increasing the likelihood of placenta accreta (22, 23). However, this explanation fails to explain the rare occurrence of placenta accreta spectrum in nulliparous women without any previous uterine surgery or instrumentation.

Diagnosis of Placenta Accreta Spectrum

Antenatal diagnosis of placenta accreta spectrum is highly desirable because outcomes are optimized when delivery occurs at a level III or IV maternal care facility before the onset of labor or bleeding and with avoidance of placental disruption (24–27). The primary diagnostic modality for antenatal diagnosis is obstetric ultrasonography. Features of accreta visible by ultrasonography may be present as early as the first trimester; however, most women are diagnosed in the second and third trimesters. Ideally, women with risk factors for placenta accreta spectrum, such as placenta previa and previous cesarean delivery, should be evaluated by obstetrician–gynecologists or other health care providers with experience and expertise in the diagnosis of placenta accreta spectrum by ultrasonography.

Perhaps the most important ultrasonographic association of placenta accreta spectrum in the second and third trimesters is the presence of placenta previa, which is present in more than 80% of accretas in most large series (25–27). Other gray-scale abnormalities that are associated with placenta accreta spectrum include multiple vascular lacunae within the placenta, loss of the normal hypoechoic zone between the placenta and myometrium, decreased retroplacental myometrial thickness (less than 1 mm), abnormalities of the uterine serosa–bladder interface, and extension of placenta into myometrium, serosa, or bladder (28, 29).

The use of color flow Doppler imaging may facilitate the diagnosis. Turbulent lacunar blood flow is the most common finding of placenta accreta spectrum on color flow Doppler imaging. Other Doppler findings of placenta accreta spectrum include increased subplacental

vascularity, gaps in myometrial blood flow, and vessels bridging the placenta to the uterine margin (9, 28, 29).

Although clinical risk assessment may be the most important tool to assess for placenta accreta spectrum, many studies report very high sensitivity and specificity for obstetric ultrasonography in the diagnosis of placenta accreta spectrum. For example, a systematic review, including 23 studies and 3,707 pregnancies, noted an average sensitivity of 90.72% (95% CI, 87.2–93.6) and specificity of 96.94% (95% CI, 96.3–97.5%) (30). Some of the findings most strongly associated with placenta accreta spectrum are multiple lacunae and turbulent flow (9, 28–30). Although visualization of such findings on ultrasonography can be useful in diagnosis, none of the features (or combinations of features) associated with placenta accreta spectrum reliably predicts depth of invasion or type of placenta accreta spectrum (22).

These reports may overestimate the accuracy of ultrasonography for the diagnosis of placenta accreta spectrum. First, there is considerable bias inherent in patient selection for studies of placenta accreta spectrum. Most women in these studies had major risk factors for placenta accreta spectrum such as previa and previous cesarean delivery. Clinicians interpreting the images knew the high a priori risk. However, many of the abnormalities associated with placenta accreta spectrum are common in normal placentas in pregnancies without placenta accreta spectrum. A recent study with a large number of women with placenta previas without placenta accreta spectrum noted considerably lower sensitivities and specificities (9). Although ultrasound evaluation is important, the absence of ultrasound findings does not preclude a diagnosis of placenta accreta spectrum; thus, clinical risk factors remain equally important as predictors of placenta accreta spectrum by ultrasound findings (Table 1). This is particularly true in regions where ultrasonography expertise in identifying features of placenta accreta spectrum may be limited.

Second, there is sizeable interobserver variation in the interpretation of ultrasound findings of placenta accreta spectrum. Six experts blinded to clinical status

Table 1. Recommendations Regarding Management of Placenta Accreta Spectrum

Recommendation	Grade of Recommendation
Diagnosis of Placenta Accreta Spectrum	
Although ultrasound evaluation is important, the absence of ultrasound findings does not preclude a diagnosis of PAS; thus, clinical risk factors remain equally important as predictors of PAS by ultrasound findings.	1A Strong recommendation, high-quality evidence
It is unclear whether MRI improves diagnosis of PAS beyond that achieved with ultrasonography alone. Accordingly, MRI is not the preferred recommended modality for the initial evaluation of possible PAS.	1B Strong recommendation, moderate-quality evidence
Women with suspected PAS diagnosed in the antenatal period based on imaging or by clinical acumen should be delivered at a level III or IV center with considerable experience whenever possible to improve outcomes.	1B Strong recommendation, moderate-quality evidence
Management	
Optimal management involves a standardized approach with a comprehensive multidisciplinary care team accustomed to management of PAS.	1B Strong recommendation, moderate-quality evidence
Delivery at 34 0/7–35 6/7 weeks of gestation is suggested as the preferred gestational age for scheduled cesarean delivery or hysterectomy absent extenuating circumstances in a stable patient. Earlier delivery may be required in cases of persistent bleeding, preeclampsia, labor, rupture of membranes, fetal compromise, or developing maternal comorbidities.	1A Strong recommendation, high-quality evidence
In the setting of hemorrhage, data from other surgical disciplines support the use of a range of 1:1:1 to 1:2:4 strategy of packed red blood cells: fresh frozen plasma: platelets.	1A Strong recommendation, high-quality evidence
Conservative management or expectant management should be considered only for carefully selected cases of PAS after detailed counseling about the risks, uncertain benefits, and efficacy and should be considered investigational.	2C Week recommendation, low-quality evidence

Abbreviations: MRI, magnetic resonance imaging; PAS, placenta accreta spectrum.

varied substantially in their prediction of placenta accreta spectrum based on ultrasound findings with an overall kappa of 0.47 (±0.12), which reflects moderate agreement (31). Sensitivities ranged from 53.4% to 74.4% and specificities from 70.8% to 94.8% (31). These data illustrate the need to standardize the definitions of ultrasound abnormalities associated with placenta accreta spectrum. A group of European experts published a standardized description of ultrasonography features of placenta accreta spectrum (32), and an international group developed a pro forma for standardized reporting of ultrasound findings of placenta accreta spectrum (33). However, these guidelines are not yet in widespread use in the United States.

Finally, it is advisable, whenever possible, to refer women with clinical risk factors for placenta accreta spectrum to centers with experience and expertise in imaging and diagnosis of the condition. It is noteworthy that available data are from centers with considerable expertise with the condition and results may not be generalizable to facilities without experience managing placenta accreta spectrum. Also, given the reported accuracy of ultrasonography for the diagnosis of placenta accreta spectrum, the high frequency of undiagnosed placenta accreta spectrum suggests that referral to experts may increase the rate of antenatal diagnosis (34). However, there are no data that compare the diagnostic accuracy of experienced versus inexperienced clinicians.

Although rare, cesarean scar pregnancy may be diagnosed in the first trimester and is strongly associated with subsequent placenta accreta spectrum if untreated (35, 36). This occurs when the gestational sac is embedded in the uterine window at the site of a cesarean scar. The risk of placenta accreta spectrum approaches 100% if the pregnancy is allowed to continue (35, 36). Other first trimester features of placenta accreta spectrum visible on ultrasonograpy include a gestational sac that is located in the lower uterine segment and the presence of multiple irregular vascular spaces within the placental bed (28, 29).

Magnetic resonance imaging (MRI) is the other major tool used for the antenatal diagnosis of placenta accreta spectrum. Magnetic resonance imaging features associated with placenta accreta spectrum include dark intraplacental bands on T2-weighted imaging, abnormal bulging of the placenta or uterus, disruption of the zone between the uterus and the placenta, and abnormal or disorganized placental blood vessels (30). The accuracy of MRI for the prediction of placenta accreta spectrum is reasonably good, with a systematic review reporting sensitivities of 75–100% and specificities of 65–100% (30). Taken in total, the overall sensitivity of MRI was 94.4% (95% CI, 86.0–97.9) and the specificity was 84.0% (95% CI, 76.0–89.8), which is comparable to ultrasonography (30). These data should be interpreted with caution because studies of MRI are even more prone to selection bias than those of ultrasonography because generally only patients with an indeterminate ultrasound examination or at very high risk of placenta accreta spectrum undergo MRI.

It is unclear whether MRI improves diagnosis of placenta accreta spectrum beyond that achieved with ultrasonography (28, 30). Magnetic resonance imaging may be useful for diagnosis of difficult cases, such as posterior placenta previa, and to assess depth of invasion in suspected percreta (30, 37, 38). However, proof of clear value is lacking and there are downsides to MRI worthy of consideration. Magnetic resonance imaging is more expensive than ultrasonography and is less widely available; the expertise required to interpret these studies is currently limited. In addition, a recent study of 78 women with suspected placenta accreta spectrum noted MRI confirmed an incorrect diagnosis or incorrectly changed a diagnosis based on ultrasonography in 38% of cases (39). Accordingly, MRI is not the preferred recommended modality for the initial evaluation of possible placenta accreta spectrum (40).

The optimal timing and number of ultrasound examinations in suspected placenta accreta spectrum are unclear. Although many clinicians perform monthly ultrasound examinations, such a protocol has not been proved to improve maternal or neonatal outcomes. Early ultrasound examination for at-risk patients is important to consider to ensure accurate dating and enable early diagnosis. A reasonable approach is to perform ultrasound examinations at approximately 18–20, 28–30, and 32–34 weeks of gestation in asymptomatic patients. This allows for the assessment of previa resolution, placental location to optimize timing of delivery, and possible bladder invasion. There is some correlation with cervical length and the risk of preterm birth with previa (less likely with a longer cervix) (41–43), but cervical length has not been extensively evaluated in placenta accreta spectrum. One small study noted no increase in the risk of preterm birth with short cervix and accreta (44). Placenta previa is not a contraindication to transvaginal ultrasonography, and ultrasound examination may provide important information about placenta accreta spectrum and previa in addition to cervical length (35).

Ideally, women with suspected placenta accreta spectrum diagnosed in the antenatal period based on imaging or clinical acumen should be delivered at a level III or IV center with considerable experience whenever possible to improve outcomes (Box 1). Suggested indications for predelivery referrals to placenta accreta spectrum Centers of Excellence are listed in a related publication and offer guidance (45). Resources available at centers with experience and expertise caring for women with placenta accreta spectrum may improve outcomes (45). Referral soon after placenta accreta spectrum is suspected may facilitate counseling and planning and may enhance the patient's emotional comfort with

Box 1. Relevant Considerations for Case Optimization in Planned Placenta Accreta Spectrum

Preoperative

- Maximization of preoperative hemoglobin values
- Verification of specific timing of planned delivery
- Identification of exact location of delivery (surgical suite and its associated capabilities)
- Verification that necessary preoperative consultations have occurred
- Consideration of patient and family needs given temporary relocation to placenta accreta spectrum center of excellence

Intraoperative

- Verification of appropriate complement of surgical expertise involved or available, or both
- Intraoperative availability of resources to optimize each case
  - eg, Cell-saver, intraoperative point of care testing, adequate surgical trays, and necessary urologic equipment
- Verification of availability of related services as necessary (eg, interventional radiology)
- Coordination of blood bank with scheduling or timing of case

Postoperative

- Assurance that critical care services are engaged and available for postoperative care
- Identification of the need for identification of primary service responsible for postoperative care

the referral facility and clinicians. Most cases of placenta accreta spectrum can be co-managed by local physicians in consultation with a level III or IV care facility, so that travel and time away from family can be minimized.

Management

The antenatal diagnosis of placenta accreta spectrum is critical because it provides an opportunity to optimize management and outcomes. Optimal management involves a standardized approach with a comprehensive multidisciplinary care team accustomed to management of placenta accreta spectrum (27, 46). Such an approach most frequently includes having an identified team available for early collaboration. This team will likely include, but is not limited to, experienced obstetricians and maternal–fetal medicine subspecialists, pelvic surgeons with advanced expertise (often, but not exclusively, gynecologic oncologists or female pelvic medicine and reconstructive surgeons), urologists, interventional radiologists, obstetric anesthesiologists, critical care experts, general surgeons, trauma surgeons, and neonatologists. In addition, established infrastructure and strong nursing leadership accustomed to managing high-level postpartum hemorrhage should be in place, and access to a blood bank capable of employing massive transfusion protocols should help guide decisions about delivery location.

Delivery in highly experienced maternity centers that have this type of coordinated care team and the ability to garner additional expertise and resources in cases of severe hemorrhage appears to improve outcomes (25, 46, 47). Again, this becomes most relevant for women in whom an antenatal diagnosis is apparent and the model of levels of maternal care applies (3). Similar to neonatal levels of care (3), regional coordination of care for those women at highest risk of severe morbidity or mortality has the potential to improve outcomes. When possible, recognition of the need for such care, coordinated antenatal transfer or co-management up until time of delivery, combined with delivery at large regional maternity centers, holds promise to minimize adverse outcomes (3). Perhaps no condition fits this conceptual framework more than antenatally diagnosed placenta accreta spectrum (46). Certainly, stabilization and transfer at the time of delivery with a newly recognized accreta is also a potential strategy in selected cases (maternal hemodynamic stability and local facility lacks expertise to manage potential complications). It is worth noting that even in the most optimal setting, substantial maternal morbidity and, occasionally, mortality occur. Management of "expected" and "unexpected" placenta accreta spectrum are discussed in greater detail in the following sections.

"Expected" or Antenatally Diagnosed Placenta Accreta Spectrum

Diagnosis Made in the Previable Period

When the diagnosis of placenta accreta spectrum is made in the previable period, it is important to include counseling about the possibility of pregnancy termination for maternal indications given the significant risks of maternal morbidity and mortality (48). However, there are currently no data to support the magnitude of risk reduction, if any. Further, pregnancy termination in the setting of suspected placenta accreta spectrum also carries risk, and the complexities of counseling should be undertaken by health care providers

who are experienced in these procedures. Readers are referred to ACOG's Practice Bulletin No. 135, *Second Trimester Abortion,* for more information on medical and surgical considerations if termination is pursued.

Preoperative Considerations and Management

Although there has been an increase in observational data regarding placenta accreta spectrum, there are few data from randomized clinical trials to guide management. Most information is derived from cohort studies, retrospective case series, and expert opinion. Nonetheless, there are some generally agreed upon strategies. Relevant considerations in the preoperative planning phase have been proposed and likely have value for coordination and optimization purposes (Box 1).

Timing of delivery decisions need to balance maternal risks and benefits with those of the fetus or neonate. It appears that performing a cesarean delivery followed immediately by cesarean hysterectomy before the onset of labor improves maternal outcomes, yet the optimal timing remains unclear (46). A decision analysis suggests that 34 weeks of gestation is optimal given the ability of most large centers to handle neonatal complications at that gestational age and the increased risk of bleeding after 36 weeks (26, 49–51). Although individual factors are relevant, a window of 34 0/7–35 6/7 weeks of gestation is suggested as the preferred gestational age for scheduled cesarean delivery or hysterectomy absent extenuating circumstances in a stable patient (52). No amniocentesis is necessary at these gestational ages because data regarding pulmonary maturity do not change clinical recommendations for delivery. Earlier delivery may be required in cases of persistent bleeding, preeclampsia, labor, rupture of membranes, or fetal compromise, or developing maternal comorbidities. Waiting beyond 36 0/7 weeks of gestation is not advised because approximately one half of women with placenta accreta spectrum beyond 36 weeks require emergent delivery for hemorrhage. Use of antenatal corticosteroids for lung maturation is appropriate in women with antenatally diagnosed accreta and anticipated delivery before 37 0/7 weeks of gestation and is consistent with current gestational age-based recommendations (53).

As stated previously, planned delivery at a center experienced with this condition is recommended whenever possible. Ideally, preoperative coordination with anesthesiology, maternal–fetal medicine, neonatology, and expert pelvic surgeons (very often gynecologic oncology or female pelvic medicine and reconstructive surgeons) can assist in proper preparations and allow the woman to ask questions, be counseled about the high likelihood and need for cesarean delivery or hysterectomy and potential complications, discuss anesthetic planning, and prepare for delivery. The use of a consistent multidisciplinary team improves maternal outcomes and can drive internal continuous quality improvement as progressive experience is gained by that same group (27, 54).

Notification and collaboration with the blood bank is recommended in concert with delivery and surgical planning given the frequent need for large-volume blood transfusion. This is particularly relevant in cases that are difficult to cross match. Estimates of perioperative blood loss in cases of placenta accreta vary widely (1, 55, 56). Anemia during pregnancy should be evaluated and managed accordingly based on specific diagnosis. Optimizing hemoglobin values during pregnancy makes implicit sense. When iron deficiency is noted, all efforts—including oral replacement, intravenous infusions and, when indicated, use of erythropoietin stimulating agents—can be employed. Autologous advance blood donation and serial hemodilution strategies are infrequently used and not routinely recommended.

Bedrest (or decreased activity) or pelvic rest, or both, is of unproven benefit in all settings, including placenta accreta spectrum, although in the past it was often advised, especially in the setting of bleeding. Without existing evidence to guide practice, clinicians should individualize the decision to modify activity or recommend pelvic rest for women with placenta accreta spectrum. Antenatal bleeding, preterm labor, and preterm prelabor rupture of membranes (also referred to as premature rupture of membranes) are associated with unscheduled delivery as well as maternal and neonatal morbidity (9, 26, 57). Women with these complications are most likely to benefit from hospitalization.

In addition, women with previa and one episode of bleeding may be at increased risk of subsequent bleeding (58, 59). Issues such as distance from a hospital or referral center and other logistic considerations also may influence the decision to hospitalize. Decisions about hospitalization and activity should be based on each patient's individual preference.

The value of preoperative ureteric stent placement in cases with noted bladder involvement is unclear and is left to a case-by-case evaluation (24). Collaboration with a urologic surgeon or a gynecologic oncologist is advisable in cases with suspected urologic involvement. The role of preoperative placement of catheters or balloons into pelvic arteries for potential interventional radiologic occlusion also is controversial (60–62). Iliac artery occlusion has been reported to decrease blood loss in some (63, 64) but not all case series (60, 65). A small randomized controlled trial also showed no benefit (66). Because serious complications such as arterial damage, occlusion, and infection may occur (67), routine use is not recommended.

Intraoperative Considerations and Management

Preoperative counseling should include review of planned and possible alternate surgical strategies and complications. The most generally accepted approach to placenta accreta spectrum is cesarean hysterectomy with the placenta left in situ after delivery of the fetus (attempts at placental removal are associated with

significant risk of hemorrhage). Many standard routine operative procedures, including use of standard perioperative antibiotic prophylaxis, remain applicable (68). Many clinicians will rapidly close the uterine incision and then proceed with hysterectomy after verification that the placenta will not spontaneously deliver. Attempts at forced placental removal often result in profuse hemorrhage and are strongly discouraged (24, 26). If an antenatal diagnosis of placenta accreta spectrum is uncertain or the preoperative diagnosis is unclear, a period of intraoperative observation for spontaneous uterine placental separation is appropriate as long as preparations for uterine removal are in place. Alternative conservative approaches aimed at fertility preservation have been used and are discussed in subsequent sections.

Patients are frequently best served by being placed in dorsal lithotomy positioning to allow for impromptu access to the vagina and bladder as well as optimal surgical visualization of the pelvis. Because of a lack of comparative data, choice of skin incision is left to operator judgment, although many employ vertical incisions for better access and visualization. Reasonable alternatives are wide transverse incisions such as a Maylard or Cherney incision. Inspection of the uterus after peritoneal entry is obtained is highly recommended to discern the level of placental invasion and specific placental location, which allows for optimizing the approach to the uterine incision for delivery and likely hysterectomy. Whenever possible, the incision in the uterus should avoid the placenta, which sometimes makes a nontraditional incision necessary. Likewise, cystoscopy is sometimes necessary to discern anatomy if bladder involvement is suspected on direct visualization.

In most cases when hysterectomy is necessary, a total hysterectomy is required because lower uterine segment or cervical bleeding frequently precludes a supracervical hysterectomy (55). Regardless, extensive vascular engorgement with challenging anatomy is the rule, and having the most experienced pelvic surgeons involved from the outset is recommended. Careful dissection in the retroperitoneal space with attention to devascularization of the uterine corpus in proximity to the placenta often is required given the overwhelming vascularity and friability of involved tissues. Further technical specifics are beyond the scope of this document. These procedures are preferably performed at a level III or IV center with considerable expertise with placenta accreta spectrum.

Close monitoring of volume status, urine output, ongoing blood loss, and overall hemodynamics is critically important during these cases. Frequent and ongoing dialogue between surgical, anesthesia, and intraoperative nursing staff are recommended to ensure all are continuously apprised of current status, ongoing blood loss, and expectations about future blood loss. Use of hemorrhage checklists also are strongly encouraged given their ability to ensure all options are considered and no details are neglected because of the focus on surgical activities. Ongoing attention to blood loss, hemoglobin, electrolytes, blood gas, and coagulation parameters is key and can inform, in near real time, objective needs for replacement. There have been no controlled studies of the best ratios for blood product replacement in obstetrics. However, data from other surgical disciplines support the use of a 1:1:1 to 1:2:4 strategy of packed red blood cells: fresh frozen plasma: platelets (Table 2) (69, 70). The use of autologous cell-saver technology is an option, particularly now given that theoretical concerns regarding safety and risks from fetal blood and other debris have been reduced with current filtering technologies (71–73).

Antifibrinolytic therapy is another adjunctive therapy that may be useful in placenta accreta spectrum, especially in the setting of hemorrhage. Tranexamic acid inhibits fibrin degradation and decreases bleeding complications and mortality in nonobstetric patients. A large, recent, multicenter, international randomized clinical trial (74) showed a reduction in maternal death due to hemorrhage in cases of postpartum hemorrhage treated with tranexamic acid (74). These results, as well as a lack of an increase in adverse events related to the use of tranexamic acid in pregnant or postpartum women, led some authorities to advise using tranexamic acid in cases of postpartum hemorrhage (75, 76). The dose should be 1 g intravenously within 3 hours of birth. A second dose may be given 0.5–23.5 hours later if bleeding persists (75).

Prophylactic tranexamic acid given at the time of delivery after cord clamping may reduce the risk of hemorrhage with placenta accreta spectrum. A recent meta-analysis showed decreased bleeding when tranexamic acid is given prophylactically at the time of cesarean delivery (77). However, many of the studies had flawed designs or small numbers of patients, and rare but serious adverse events such as renal cortical necrosis have been reported with postpartum use (78). It is noteworthy that women with this complication received considerably higher doses than are currently recommended (75, 78). Nonetheless, prophylactic use is not currently advised for routine cesarean delivery and large studies are ongoing. Prophylactic use in placenta accreta spectrum is unstudied.

Several other clotting factors may help in cases of refractory bleeding. In the past, the goal of fibrinogen therapy was to achieve levels of 100 mg/dL or greater, but this may be too low in pregnancy. Levels less than 200 mg/dL are associated with severe postpartum hemorrhage (79). Although cryoprecipitate can be used to increase fibrinogen, fibrinogen concentrates may be preferred to reduce the risk of transmitting viral pathogens. Efficacy of fibrinogen transfusion in the setting of obstetric hemorrhage or placenta accreta spectrum is unknown. Recombinant activated factor VIIa has been used in the management of severe and refractory postpartum hemorrhage. Downsides are a risk of thrombosis

and considerable cost. Two large case series that included some placenta accreta spectrum patients noted positive responses in 76–86% of cases. However, there were six thromboses in fewer than 200 patients (33, 80). Thus, use in placenta accreta spectrum should be limited to post-hysterectomy bleeding with failed standard therapy.

Hypofibrinogenemia is the biomarker most predictive of severe postpartum hemorrhage (79). In addition to standard assessment of fibrinogen levels, hypofibrinogenemia can be assessed in functional assays using viscoelastic coagulation testing such as thromboelastography or rotational thromboelastometry. Results of these tests can be obtained quickly, and detection of hypofibrinogenemia by rotational thromboelastometry predicts the severity of postpartum hemorrhage (81). A systematic review also noted that use of these tests reduced bleeding and transfusion, but not morbidity or mortality, in nonobstetric hemorrhage (82). The usefulness of rotational thromboelastometry specifically in placenta accreta spectrum is uncertain but has recently been shown to reduce mortality in trauma surgery and other surgical specialties.

Should uncontrolled pelvic hemorrhage ensue, a few procedural strategies are worthy of consideration. Hypogastric artery ligation may decrease blood loss, but its efficacy has not been proved and it may be ineffective because of collateral circulation. In addition, hypogastric artery ligation can be difficult and time consuming, although it can be easily performed by experienced surgeons. The use of interventional radiology to embolize the hypogastric arteries in cases of persistent or uncontrolled hemorrhage may be useful. Interventional radiology is especially helpful when there is no single source of bleeding that can be identified at surgery. However, it can be difficult to safely perform in unstable patients and the equipment and expertise are not available in all centers. Other methods to address severe and intractable pelvic hemorrhage include pelvic pressure packing and aortic compression or clamping. Pelvic packing, although not standard management, can be highly effective for patient stabilization and product replacement when experiencing acute uncontrolled hemorrhage. Packing may be left in for 24 hours (with an open abdomen and ventilatory support) to allow for optimization of clotting and hemostasis. Aortic clamping is likely best reserved for experienced surgical consultants or heroic measures given the potential risk of vascular-related complications from this approach.

Several other factors should be considered in the setting of hemorrhage and placenta accreta spectrum. Patients should be kept warm because many clotting factors function poorly if the body temperature is less than 36°C. Acidosis also should be avoided. If blood loss is excessive, often defined as estimated blood loss of 1,500 mL or greater, prophylactic antibiotics should be re-dosed (68). Laboratory testing is critical to the management of obstetric hemorrhage. Baseline assessment at the initiation of bleeding should include platelet count, prothrombin time, partial thromboplastin time, and fibrinogen levels, which are normally elevated in pregnant women. Rapid and accurate results can facilitate transfusion management, although the massive

Table 2. Characteristics of Blood Products, Anticipated Effects, and Complications

Blood Product	Laboratory Values Prompting Transfusion	Volume	Anticipated Effect	Complications
Packed red blood cells	Hct <18	300 mL	Increase Hct 3% per unit	Human error
	Hct <30 in unstable patient or active bleeding			Hemolytic reaction Infection TRALI
Platelets	Platelet count <50,000	50 mL	Increase platelet count 7,500/mm^3/U	Human error
	Microvascular bleeding			Hemolytic reaction
	Massive transfusion: 1:1 with RBC			Infection TRALI
Fresh frozen plasma	INR >2 X normal	250 mL	Increase fibrinogen 10–15 mg/dL/U	Human error
	aPTT >1.5 X normal			Hemolytic reaction
	Massive transfusion: 1:1 with RBC			Infection TRALI
Cryoprecipitate	Fibrinogen <100 mg/dL	40 mL	Increase fibrinogen 10–15 mg/dL/U	Human error Hemolytic reaction Infection TRALI

Abbreviations: aPTT, activated partial thromboplastin time; Hct, hematocrit; INR, international normalized ratio; RBC, red blood cells; TRALI, transfusion related acute lung injury; U, units.

transfusion protocol is not based on laboratory studies. Thus, developing a protocol that allows for rapid results from a centralized laboratory or having point of care testing on the labor and delivery unit or in the general operating room is desired.

As with any case of uncontrolled hemorrhage, the following are key concepts to remember: treat the patient based on clinical presentation initially and do not wait for laboratory results, keep the patient warm, rapidly transfuse, and when transfusing in the setting of acute hemorrhage, be sure to transfuse packed red blood cells, fresh frozen plasma, and platelets in a fixed ratio.

Postoperative Considerations and Management

Given the extensive surgery, placenta accreta spectrum patients require intensive hemodynamic monitoring in the early postoperative period. This often is best provided in an intensive care unit setting to ensure hemodynamic and hemorrhagic stabilization. Close and frequent communication between the operative team and the immediate postoperative team is strongly encouraged. Postoperative placenta accreta spectrum patients are at particular risk of ongoing abdominopelvic bleeding, fluid overload from resuscitation, and other postoperative complications given the nature of the surgery, degree of blood loss, potential for multiorgan damage, and the need for supportive efforts.

Continued vigilance for ongoing bleeding is particularly important. Obstetricians and other health care providers should have a low threshold for reoperation in cases of suspected ongoing bleeding. Pelvic vessel interventional radiologic strategies may be useful, but not all cases are amenable to these less invasive approaches and their use should be considered on a case-by-case basis. Clinical vigilance for complications such as renal failure; liver failure; infection; unrecognized ureteral, bladder, or bowel injury; pulmonary edema; and diverse intravascular coagulation is warranted. Lastly, attention to the small but real possibility of Sheehan syndrome (also known as postpartum pituitary necrosis) is warranted given the clinical scenario and the potential for hypoperfusion.

Despite antenatal diagnosis of placenta accreta spectrum and extensive delivery planning, it is possible that a patient may develop unexpected complications that may or may not be related to placenta accreta spectrum and that require an unscheduled delivery.

"Unexpected" and Unplanned Intraoperative Recognition of Placenta Accreta Spectrum

Sometimes placenta accreta spectrum is unexpectedly recognized at the time of cesarean delivery, either before the uterine incision (optimal) or after the uterus is opened, the fetus is delivered, and attempts to remove the placenta have failed. It is also possible to make the diagnosis of placenta accreta spectrum after vaginal delivery. The level and capabilities of the response will vary depending on local resources, timing, and other factors. It is important, however, that all facilities performing deliveries have considered the possibility of a case of placenta accreta spectrum and have plans in place to manage or rapidly stabilize patients in anticipation of transfer to a higher level facility (per established institutional agreements) (3). With these caveats, a few general principles apply.

If placenta accreta spectrum is suspected based on uterine appearance and there are no extenuating circumstances mandating immediate delivery, the case should be temporarily paused until optimal surgical expertise arrives. In addition, the anesthesia team should be alerted and consideration given to general anesthesia, additional intravenous access should be obtained, blood products should be ordered, and critical care personnel should be alerted. If available, cell salvage technologies should be brought into the operative suite. Patience on the part of the primary operative team is key, and they should not proceed until circumstances are optimized. If mobilization of such a team is not possible, consideration of stabilization and transfer is appropriate, assuming maternal and fetal stability.

Many of the same principles apply when placenta accreta spectrum is inadvertently discovered with the uterus already open immediately after delivery. Once the diagnosis of placenta accreta spectrum is established and it is clear that placental removal will not occur with usual maneuvers, then rapid uterine closure and proceeding to hysterectomy as judiciously as possible should be considered. Mobilization of appropriate resources should occur concurrently with ongoing hysterectomy in conjunction with the operating room nursing staff and anesthetic team. If the patient is stable after delivery of the fetus and the center is unable to perform the hysterectomy under optimal conditions, transfer should be considered. Temporizing maneuvers, packing the abdomen, tranexamic acid infusion, and transfusion with locally available products should be considered.

Uterine Preservation and Expectant Management

Uterine preservation, referred to here as conservative management, is usually defined as removal of placenta or uteroplacental tissue without removal of the uterus. *Expectant management* is defined as leaving the placenta either partially or totally in situ. Because placenta accreta spectrum is potentially life threatening, hysterectomy is the typical treatment. Consideration of conservative or expectant approaches should be rare and considered individually. Major complications of treatment of placenta accreta spectrum are loss of future fertility, hemorrhage, and injury to other pelvic organs. To reduce these complications, some have advocated conservative or expectant management in patients with placenta accreta spectrum (83, 84).

As defined previously, conservative management is removal of the placenta or uteroplacental tissue without

removing the uterus. For patients with focal placental adherence, removal of the placenta by either manual extraction or surgical excision followed by repair of the resulting defect has been associated with uterine preservation in some cases (83). Although randomized trials that compared hysterectomy to this approach are not available, it is apparent that blood loss is significantly less in a patient with a small defect using this approach. In patients with too large a defect to subsequently repair, there are data that suggest that en bloc removal of the entire uteroplacental defect followed by uterine closure results in reduced blood loss and maintains potential fertility (85). Alternatively, in a recent report, placental removal alone followed by insertion of a Bakri balloon was successful in preventing hysterectomy in 84% (16/19) of patients with placenta accreta spectrum (86). It is noteworthy that these conservative approaches have been reported only in small numbers of cases and it is unclear that all the patients included actually had placenta accreta spectrum. Accordingly, efficacy remains uncertain.

In patients with more extensive placenta accreta spectrum, expectant management is considered an investigational approach. With expectant management, the cord is ligated near the placenta and the entire placenta is left in situ, or only the placenta that spontaneously separates is removed before uterine closure. Data are limited to case series when evaluating expectant management. In the largest series, 22% (36/167) of patients required hysterectomy after an attempt at expectant management, whereas 78% (131/167) did not require hysterectomy (87). These data are consistent with other smaller case series where hysterectomy was required in 42% (14/33) and 94% (17/18) of patients (88, 89). In the larger series, those with successful expectant management had a median time to placental involution of 13.5 weeks. Of the 36 patients who required hysterectomy, 18 were primary failures, occurring within 24 hours of primary cesarean, and 18 were delayed failures, occurring more than 24 hours after delivery (87). All early failures and the majority of secondary failures were secondary to increased bleeding. In addition to bleeding, infection or febrile morbidity was common and occurred in 28% (47/167) of patients but was an indication for hysterectomy in only 14% (5/36) of patients that failed expectant management. *Severe morbidity*, defined as sepsis, septic shock, peritonitis, uterine necrosis, fistula, injury to adjacent organs, acute pulmonary edema, acute renal failure, deep vein thrombophlebitis or pulmonary embolism, or death occurred in 6% (10/167) of patients, with 70% (7/10) of these severe outcomes occurring in the delayed hysterectomy group. Maternal sepsis occurred in 70% (7/10) of patients with severe morbidity (87).

The degree of success with *expectant management*, defined as leaving the placenta in situ, of placenta accreta spectrum appears to correlate with the degree of placental attachment abnormality. In the case series previously described, the failure rate of expectant management was 44% (8/18) in patients with a percreta compared with 7% (10/149) in those with other less extensive defects (87). In addition, the severe adverse complication rate was also increased to 17% (3/18) in the group with placenta percreta compared with 5% (7/149) in those without a percreta. This finding is consistent with a small case series and systematic review that reported that 44% (25/57) of patients with a percreta ultimately required hysterectomy, although major morbidity was higher and occurred in 42% (24/47) (90). Although these outcomes with expectant management are promising, it is unclear that these women truly had placenta accreta spectrum because successful cases had no histologic confirmation; in general, case series of expectant management included far fewer women with traditional risk factors such as previa and prior cesarean deliveries than cases reported using planned cesarean hysterectomy (90). Thus, the chance of favorable outcomes may be overestimated.

Taking these limited published data together, and the accepted approach of hysterectomy to treat placenta accreta spectrum, conservative management or expectant management should be considered only for carefully selected cases of placenta accreta spectrum after detailed counseling about the risks, uncertain benefits, and efficacy and should be considered investigational.

Adjuncts to Conservative and Expectant Management

In addition to leaving the placenta in situ, investigators have used adjunctive measures to diminish blood loss, hasten placental reabsorption, or both. Techniques have included uterine devascularization with uterine artery balloon placement, embolization or ligation, and postdelivery methotrexate administration (87–89).

Methotrexate use in expectant management of placenta accreta spectrum is advocated by some authors who contend that it will hasten placental involution and resorption (91). The biologic plausibility of this premise may be questioned because methotrexate targets rapidly dividing cells and division of third trimester placental cells is limited. Further, methotrexate has the potential for maternal hematologic and nephrologic toxicities and is contraindicated in breastfeeding because of neonatal morbidity (83, 87). In a large case series of expectant management of placenta accreta spectrum, there was one maternal death, which was ascribed to severe methotrexate toxicity and subsequent septic shock (87). Given the unproven benefit and possible harm, methotrexate to hasten placental resorption is not recommended (83).

For expectantly managed patients with persistent placental tissue with or without substantial bleeding, hysteroscopic resection of the placental remnants has been proposed as an adjunctive treatment. In the largest series in which specific outcomes were delineated, 12 women with persistent placental tissue underwent hysteroscopic resection with only one requiring a subsequent hysterectomy (92). One half of the women required more

than one procedure and one third required more than two procedures. Of the 11 successful cases, nine women resumed normal menstruation. High-intensity focused ultrasonography has also been used in conjunction with hysteroscopic resection. The procedure was deemed a success in all 25 patients, but 9 required more than one hysteroscopic resection (93). Two patients had uterine perforations at the time of resection, which was attributed to the thinning of the uterine wall by the high-intensity focused ultrasonography; one had hemorrhagic shock and required emergent uterine repair. Given these limited data, the frequency of adverse events, and the proportion of patients who needed a repeat procedure, routine hysteroscopic resection with or without antecedent high-intensity focused ultrasonography is not recommended.

Delayed Interval Hysterectomy

Delayed interval hysterectomy is a derivative of an expectant approach to placenta accreta spectrum, except that future fertility is not a consideration, and minimizing blood loss and tissue damage are the primary goals. Patients with placenta percreta are optimal candidates for this procedure because they have an increased risk of blood loss and tissue damage if hysterectomy is performed at the time of cesarean delivery (94). In the largest series to date, 13 women with suspected placenta percreta underwent delayed hysterectomy at a median of 41 days after elective cesarean delivery (95). Total blood loss for the primary cesarean delivery was 900 mL and 700 mL for the delayed hysterectomy, which is lower than the median 3,500 mL blood loss reported for primary removal in the largest review (94). Additionally, transfusion was required in 46% (6/13) of patients, but none of the patients required large volume transfusion of greater than 4 units. This compares very favorably to the universally 100% (96, 97) transfusion rate and 42% massive volume transfusion rate of more than 10 units reported (96) when the percreta is removed at the time of primary surgery. With regard to organ damage, incidental cystotomy was reported in two patients and ureteral injury in one. No patient required bladder resection. Additionally, 23% (3/13) of patients were able to have a robotic hysterectomy and avoid a repeat laparotomy. Although these preliminary data are encouraging, use of this method warrants caution. The reported cases are small in number and were performed at one academic medical center. Accordingly, counseling should acknowledge significant uncertainty regarding efficacy and significant potential risks, and this approach should be considered investigational without additional data.

Future Fertility

Expectant management of placenta accreta spectrum appears to have minimal effect on subsequent fertility but does carry a high recurrence risk of placenta accreta spectrum. In a large series of women monitored after expectant management, 30% (27/91) desired subsequent pregnancy (98). Three women had been attempting pregnancy for approximately 1 year, and 24 women had 34 pregnancies. Of the 32 continuing pregnancies, 10 were miscarriages, 1 was an ectopic pregnancy, and 21 gave birth after 34 weeks of gestation. Of the third trimester deliveries, 6 out of 21 women (28.6%) had recurrent placenta accreta spectrum. Other series reported similar rates of pregnancy success and also described increased placenta accreta spectrum recurrence rates ranging from 13.3% to 22.8% (8, 99).

Summary

Placenta accreta spectrum is becoming increasingly common and is associated with significant morbidity and mortality. Knowledge of risk factors and antenatal imaging expertise can help guide the diagnosis. Preparation for delivery and postpartum care should involve a multidisciplinary team and early antepartum consultations guided by the levels of maternal care (3). Cesarean hysterectomy can be challenging and should be performed by the most experienced surgeons. Because of intrapartum and postpartum bleeding risk for women with placenta accreta spectrum, centers caring for these patients should have the ability to rapidly mobilize blood products for transfusion. When placenta accreta spectrum is encountered at the time of delivery without a prior suspicion or diagnosis and there are no extenuating circumstances mandating immediate delivery, anesthesia staff should be alerted, and the case should be temporarily paused until optimal surgical expertise can be garnered. If the delivering center lacks the expertise to perform a hysterectomy and the patient is stable after delivery of the fetus, the patient should be transferred to a facility that can perform the necessary level of care. Taking these limited published data together, and the accepted approach of hysterectomy to treat placenta accreta spectrum, conservative management or expectant management should be considered only for carefully selected cases of placenta accreta spectrum after detailed counseling about the risks, uncertain benefits, and efficacy and should be considered investigational.

For More Information

The American College of Obstetricians and Gynecologists has identified additional resources on topics related to this document that may be helpful for ob-gyns, other health care providers, and patients. You may view these resources at www.acog.org/More-Info/PlacentaAccreta.

These resources are for information only and are not meant to be comprehensive. Referral to these resources does not imply the American College of Obstetricians and Gynecologists' endorsement of the organization, the organization's website, or the content of the resource. The resources may change without notice.

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Society for Maternal–Fetal Medicine Grading System: Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Recommendations

Obstetric Care Consensus documents will use Society for Maternal-Fetal Medicine's grading approach: http://www.ajog.org/article/S0002-9378%2813%2900744-8/fulltext. Recommendations are classified as either strong (Grade 1) or weak (Grade 2), and quality of evidence is classified as high (Grade A), moderate (Grade B), and low (Grade C)*. Thus, the recommendations can be 1 of the following 6 possibilities: 1A, 1B, 1C, 2A, 2B, 2C.

Grade of Recommendation	Clarity of Risk and Benefit	Quality of Supporting Evidence	Implications
1A. Strong recommendation, high-quality evidence	Benefits clearly outweigh risk and burdens, or vice versa.	Consistent evidence from well-performed randomized controlled trials or overwhelming evidence of some other form. Further research is unlikely to change confidence in the estimate of benefit and risk.	Strong recommendations, can apply to most patients in most circumstances without reservation. Clinicians should follow a strong recommendation unless a clear and compelling rationale for an alternative approach is present.
1B. Strong recommendation, moderate-quality evidence	Benefits clearly outweigh risk and burdens, or vice versa.	Evidence from randomized controlled trials with important limitations (inconsistent results, methodologic flaws, indirect or imprecise), or very strong evidence of some other research design. Further research (if performed) is likely to have an impact on confidence in the estimate of benefit and risk and may change the estimate.	Strong recommendation, and applies to most patients. Clinicians should follow a strong recommendation unless a clear and compelling rationale for an alternative approach is present.
1C. Strong recommendation, low-quality evidence	Benefits appear to outweigh risk and burdens, or vice versa.	Evidence from observational studies, unsystematic clinical experience, or from randomized controlled trials with serious flaws. Any estimate of effect is uncertain.	Strong recommendation, and applies to most patients. Some of the evidence base supporting the recommendation is, however, of low quality.
2A. Weak recommendation, high-quality evidence	Benefits closely balanced with risks and burdens.	Consistent evidence from well-performed randomized controlled trials or overwhelming evidence of some other form. Further research is unlikely to change confidence in the estimate of benefit and risk.	Weak recommendation, best action may differ depending on circumstances or patients or societal values.
2B. Weak recommendation, moderate-quality evidence	Benefits closely balanced with risks and burdens; some uncertainty in the estimates of benefits, risks, and burdens.	Evidence from randomized controlled trials with important limitations (inconsistent results, methodologic flaws, indirect or imprecise), or very strong evidence of some other research design. Further research (if performed) is likely to have an effect on confidence in the estimate of benefit and risk and may change the estimate.	Weak recommendation, alternative approaches likely to be better for some patients under some circumstances.
2C. Weak recommendation, low-quality evidence	Uncertainty in the estimates of benefits, risks, and burdens; benefits may be closely balanced with risks and burdens.	Evidence from observational studies, unsystematic clinical experience, or from randomized controlled trials with serious flaws. Any estimate of effect is uncertain.	Very weak recommendation, other alternatives may be equally reasonable.
Best practice	Recommendation in which either (i) there is enormous amount of indirect evidence that clearly justifies strong recommendation (direct evidence would be challenging, and inefficient use of time and resources, to bring together and carefully summarize), or (ii) recommendation to contrary would be unethical.		

*Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. GRADE Working Group. BMJ 2008;336:924–6.

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