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The creation of a thousand forests is in one acorn.
—Ralph Waldo Emerson

EVERY year, the Society for Obstetric Anesthesia and Perinatology celebrates the life and legacy of Gerard Ostheimer, M.D., an obstetric anesthesiologist renowned for his wisdom, his passion for life, and his generosity to the society and the specialty. The celebration takes the form of an eponymous lecture given at the Society for Obstetric Anesthesia and Perinatology Annual Meeting with the purpose of evaluating literature contributions from a single year that are pertinent to the clinical care and research of obstetric anesthesia patients. From more than 1,400 contributions in 2003, 841 were abstracted in the Society for Obstetric Anesthesia and Perinatology 36th Annual Meeting program syllabus, with general themes summarized in the lecture. This article focuses on four advances that are of importance to anesthesiologists who practice within an obstetric setting. These include advances in the uniquely human obstetric disease, preeclampsia; a leading cause of maternal death, peripartum hemorrhage; the functional physiology of maternal pain and labor analgesia; and the philosophical issues surrounding delivery of care: ethics and consent.

Preeclampsia

A pregnancy disorder recognized since antiquity that affects 6–8% of all pregnancies,1 preeclampsia is a leading cause of maternal and perinatal morbidity and mortality. Despite the recognition that the disease occurs only within the confines of pregnancy (or in the presence of placental tissue), the etiologic basis of preeclampsia eludes detection.2 The maternal–fetal interface has featured prominently in recent investigations, with the leading mechanistic model postulating that maternal genes dictate disease susceptibility, whereas fetal genes, paternal genes, and environmental factors control the ultimate phenotypic expression.3 The identification of these “preeclampsia” genes, however, has proven difficult because the case–control reports of specific maternal polymorphisms and mutations and the data from the available genome-wide scans have yielded conflicting results.3,4 Molecular variants of the maternal genes responsible for angiotensinogen represent promising etiologic candidates for preeclampsia;5 to great surprise, less convincing data have been observed with a seemingly ideal contender, nitric oxide synthetase.6,7 The chromosome 2p13 locus from the genome-wide scan of Arngrimsson et al.† recently initiated in 10 centers across the United Kingdom offers significant promise; this prospective trial will attempt to identify the genes of 1,000 tightly phenotyped pregnant women with preeclampsia, as well as their parents, children, and partners (or biologic fathers of the children). DNA-marker alleles will be identified in candidate gene regions and ultimately genome-wide; transmitted and nontransmitted marker alleles will then be evaluated to reveal the contribution of maternal, paternal, and fetal genes to the risk of preeclampsia.

Among the difficulties in identifying causes and treatments for preeclampsia has been the absence of animal models that adequately represent the clinical disease.9 This noted, a novel experimental model resembling human preeclampsia, suitable for exploring the pathophysiology of the disease, has been developed. Maynard et al.10 observed the up-regulation of soluble fms-like tyrosine kinase 1 (sFlt1) receptors in the placenta of pregnancies complicated with preeclampsia and a fall within 48 h of delivery; both findings are consistent with the clinical expression of preeclampsia. More importantly, the investigators demonstrated that the exogenous administration of sFlt1 in pregnant rats produced clinical and pathologic findings classically associated with preeclampsia: hypertension, proteinuria, and glomerular endotheliosis.10 Although sFlt1 receptors, a splice variant

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of the vascular endothelial growth factor receptor Flt1 that lack transmembrane and cytoplasmic domains, had previously been observed to be increased in pregnant women with preeclampsia and noted to bind two angiogenic growth factors, vascular endothelial growth factor and placental growth factor. Moreover, the timing and significance of these findings was unknown. The confirmation of sFlt1 receptor’s role in preeclamptic expression by Maynard et al. allows a mechanistic speculation that the relative absence of vascular endothelial growth factor and placental growth factor alters the remodeling of spiral arteries necessary for normal placentation and pregnancy. This paradigm shift in understanding the role of sFlt1 receptors and growth factors in normal and abnormal pregnancies should allow for improvements in the pathogenesis, treatment, and possibly the prevention of preeclampsia.

To date, however, the early identification of preeclampsia remains an unsatisfied goal; despite the evaluation of a number of clinical, biophysical, and biochemical tests, no single, reliable, or cost-effective test is available for the diagnosis of preeclampsia. Moreover, methods to reduce the rate or severity of preeclampsia have yet to reveal a consistently effective therapy. Recent therapies have focused on the reduction of the vascular tone through manipulation of the cyclooxygenase and nitric oxide synthetase pathways. Known to preferentially affect thromboxane greater than prostacyclin and thereby reduce vasoconstriction and clotting, low-dose aspirin has historically been advanced as a promising treatment for preeclampsia. A meta-analysis of 14 randomized controlled trials suggested that the use of aspirin during pregnancy was associated with a reduction in the risk of perinatal death and preeclampsia in women with known risk factors. However, the most recent data suggest that low-dose aspirin should not be routinely prescribed for prevention of preeclampsia in nulliparous women. Subtil et al. did not observe a reduction in the incidence of preeclampsia in 3,294 nulliparous women randomly assigned for 14 or 20 weeks to 100 mg aspirin versus placebo per day; of concern, an increase in bleeding complications, mostly minor, was observed in the group taking aspirin. Moreover, in an 1,853-patient subset of the same study population, examination of Doppler flow velocity waveforms of uterine blood flow demonstrated no reduction in flow resistance with aspirin use. Although a framework for individualizing the use of aspirin for the treatment of preeclampsia has been proposed, further work is needed to refine the risks, the benefits, and the patient subset in which the use of aspirin could be beneficial.

The observation that preeclampsia was associated with endothelial cell dysfunction and impaired placental circulation led to the speculation that alterations in nitric oxide were responsible for the pathogenesis of preeclampsia. The demonstration that l-arginine, a precursor of nitric oxide, could reverse the adverse pregnancy changes induced by nitric oxide synthetase inhibition led to a number of studies that noted improvements in uteroplacental and fetal–placental blood flow, reductions in maternal blood pressure, and decreases in platelet activation. Reductions in maternal blood pressure, however, can be of concern in individuals with disturbed cerebral autoregulatory function such as preeclampsia, which has been associated with underperfusion, normal perfusion, and even overperfusion of the brain. A recent advance was the notation that autoregulation, the ability of the brain to maintain a relatively constant level of blood flow over a wide range of mean arterial blood pressures, seems preserved until the very late stages of preeclampsia. This autoregulatory ability is present even with the administration of isosorbide dinitrate, a potent nitric oxide donor, as measured by Doppler velocimetry in the middle cerebral and basilar arteries. This ability represents a therapeutic advantage of isosorbide dinitrate, because other agents may have unpredictable or disadvantageous effects on cerebral perfusion; moreover, because vasospasm is known to occur in eclampsia and severe preeclampsia, nitric oxide donors should prove useful in relieving vasospasm, as similarly demonstrated in the setting of subarachnoid hemorrhage. As an aside, the use of laetabol, which is considered a first-line drug for the control of hypertension in preeclampsia, seems to reduce cerebral perfusion pressure as well as systolic and diastolic systemic pressures without significantly affecting cerebral blood flow. The complex interaction between the maternal vascular endothelial dysfunction of preeclampsia and nitric oxide, reactive oxygen intermediates, and other mediators and medications remains to be elucidated.

Intravenous corticosteroids may offer a promising treatment for severe preeclampsia. Given primarily to women between 24 and 34 weeks of gestation who are at risk of preterm delivery to accelerate the maturation of the fetal lung, corticosteroids have been associated with meaningful improvements in maternal variables. Previously, clinical improvement was observed in a prospective study of women with the syndrome of hemolysis, increased liver enzymes, and low platelet counts who were randomly assigned either to receive or not to receive corticosteroids. Improvements observed included decreases in maternal mean arterial pressure (115 vs. 94 mmHg; P < 0.05) and mean aspartate aminotransferase concentrations; increases in urine output (60 vs. 40 ml/h; P < 0.05) and platelet count (115,000 vs. 70,000; P < 0.05) were also noted. More recently, the use of higher-dose regimens (10-12 mg dexamethasone every 12 h x 24 h or until clinical improvement) during pregnancy has been associated with a reduction in the clinical expression and an improved recovery from the syndrome of hemolysis, increased liver enzymes, and...
low platelet counts. In an additional small prospective trial, dexamethasone seemed to confer a benefit over betamethasone for this syndrome.

Despite this apparent success with corticosteroids in preeclamptic women in extremis, until specific therapies are conclusively and robustly validated, time-tested clinical responses to the signs and symptoms of preeclampsia will remain the therapy of choice; these include the use of magnesium for prevention of seizures and antihypertensive medications to decrease severe hypertension (systolic pressure greater than 160 mmHg and/or diastolic pressure of at least 110 mmHg). The goal of antihypertensive therapy has been suggested to be a systolic pressure between 140 and 155 mmHg and diastolic pressure between 90 and 105 mmHg. With severe, unremitting preeclampsia that is progressing despite treatment, delivery of the fetus remains the only known solution. Because no randomized trials have compared the optimal mode of delivery in women with preeclampsia, anesthesia providers should be prepared to consider the implications of labor analgesia and operative anesthesia for these patients. Recent discussions on the provision of anesthetic care, coagulation status monitoring, and fluid management in women with preeclampsia are available. A number of these resources focus on the anesthetic management of cesarean delivery, with one prospective cohort study at least partially allaying the concern of severe hypotension after spinal anesthesia in preeclamptic patients. observed that the risk of significant hypotension, defined as a systolic blood pressure decrease to less than 100 mmHg or a 30% decrease in mean blood pressure, occurred approximately six times less often in severely preeclamptic patients (odds ratio, 0.17; \( P = 0.006 \)). Although the preeclamptic patients were at an average gestational age of 32 weeks versus 38 weeks in the control group and the smaller uteri most likely had a reduced effect on aortocaval compression, it is possible that severely preeclamptic women are at no greater risk of severe hypotension after a standard dose spinal technique. The use of smaller doses of spinal medications or sequential combined spinal–epidural analgesia using small-dose spinal and then epidural medications may be other methods for reducing hypotension. The value of a regional approach to the analgesic and anesthetic management of preeclamptic patients, after appropriate attention to possible effects of the disease on the coagulation system, has only grown stronger; the appreciation of the airway narrowing, the concern for the increased systemic and cerebral pressures accompanied with intubation and extubation, and the benefit of assessing an awake, nonsedated patient to evaluate the severity of the disease all serve to augment the benefit of regional techniques in this patient population.

**Obstetric Hemorrhage**

A leading cause of maternal and fetal morbidity and mortality worldwide, obstetric hemorrhage can be masked by early, pregnancy-related physiologic adaptations and complicated by abnormal placentation, amniotic fluid emboli, and infectious etiologies. Because approximately 600–700 ml blood flows through the placental intervillous spaces each minute, obstetric hemorrhage can rapidly result in severe signs of shock. Although ultrasound and magnetic resonance imaging technologies have allowed earlier identification and therapy for women at risk for significant hemorrhage, limitations in diagnostic sensitivity and specificity as well as the underestimation of blood loss and inadequate resuscitation remain common problems. More recently, the involvement of interventional radiology for the placement of prophylactic transcatheter occlusion balloons within the hypogastric or uterine arteries in high-risk parturients has allowed for the timely control of bleeding. Interventional radiologists may also be called on after hemorrhage, although the availability of the equipment and personnel may compromise success. Of interest, a successful term pregnancy has been reported to follow the complete ligation of the uterine arteries.

Attention has recently been given to the use of erythropoietin-induced erythrocyte production, autologous donation, intraoperative salvage, and acute normovolemic hemodilution in the obstetric population at high risk of maternal hemorrhage. The review article by and evaluates this issue from an anesthesia perspective. Iron supplementation and recombinant human erythropoietin are effective therapies for producing erythrocytes, particularly in patients with preexisting anemia, renal failure, and religious or transfusion-related reasons for using autologous blood predonation. Although there is reason to believe that erythropoietin is a therapy of value in women at high risk of hemorrhage, additional investigation is needed to determine the optimal dosing, hemoglobin goals, and adverse effect profiles. Hypertension, a noted problem in renal patients receiving erythropoietin, is a relevant concern during pregnancy. Although normal pregnancy is associated with a twofold to fourfold increase in maternal erythropoietin concentrations, isolated studies of erythropoietin on placental vessels suggests that dose-dependent vasoconstriction does occur. High erythropoietin concentrations in hypertensive and preeclamptic parturients has fueled speculation that erythropoietin participates in the humoral mechanisms responsible for preeclampsia and intrauterine growth restriction. Should these concerns not be realized, a hyperglycosylated analog of recombinant human erythropoietin (darbepoetin) has been developed with a threefold longer terminal half-life and a more rapid and greater erythropoietic response. This novel protein may be useful in the setting of anticipated or realized obstetric hemorrhage.
Because preoperative autologous donation is limited by the maximum lifespan of stored blood, collection can start only 6 weeks before a planned delivery with an average unit collection interval of between 3 and 7 days. This method is of particular use when maternal antibodies exist to high-frequency antigens, and a number of parturients have been reported to safely undergo this intervention with minimal maternal or fetal hemodynamic effects. When compared with acute normovolemic hemodilution, recent evaluations of preoperative autologous donation for nonobstetric surgeries have suggested comparable efficacy in reducing allogeneic transfusion. Acute normovolemic hemodilution, however, has the advantage of reducing the risk of administrative incompatibility errors and bacterial contamination and allowing the infusion of whole blood replete with functional coagulation factors. Finally, intraoperative blood salvage of shed erythrocytes that are washed and reinfused has been noted to be cost effective with the recovery of 2–3 units. Although intraoperative blood salvage has been used during pregnancy in several clinical series and case reports, the overriding concern has been the efficiency of clearance and the effect of amniotic fluid components. Laboratory investigations suggest effective clearance of solute proteins but incomplete clearance of cellular components, such as fetal squames or erythrocytes, even in the presence of leukodepleting filtration. The relevance of these components is still incompletely understood, given the common demonstration of these elements in maternal circulation after normal and operative deliveries without catastrophic consequences. Currently, intraoperative blood salvage remains the therapy with the most restrictive indications: that of augmenting oxygen carrying capacity to preserving function or life where allogeneic products are not an option. Additional investigations are required to validate the safety and utility of each of these approaches. Future replacement strategies during pregnancy may include synthetic oxyglobin solutions, which have demonstrated favorable characteristics in pregnant sheep.

When uterine bleeding occurs after childbirth, the use of an inflated Sengstaken-Blakemore esophageal balloon catheter has been demonstrated to tamponade and potentially treat intrauterine sources of bleeding and allow time to correct coagulopathies. The Sengstaken-Blakemore esophageal balloon catheter is inserted into the uterus and filled with 70–300 ml warm saline until the distended balloon is palpable per abdomen; if significant bleeding continues into the cervix or the gastric lumen of the catheter, the tamponade test result is considered positive, and a surgical intervention is performed. In a series of 16 cases of intractable postpartum hemorrhage, 14 (87.5%) responded to the tamponade test and did not require surgery. The use of a Foley catheter in a similar manner has been suggested previously, but the amount of fluid is limited to 150 ml, which may not be as effective. A recently introduced tamponade obstetric hemorrhage balloon may offer similar results.

An additional approach for postpartum hemorrhage is the use of human recombinant factor VIIa, a vitamin K–dependent protein recently licensed by the US Food and Drug Administration for the treatment of bleeding episodes in hemophilia A or B patients with inhibitors to factor VIII or factor IX. Off label, recombinant factor VIIa has resulted in an almost complete reversal of severe bleeding refractory to standard hematologic or hemostatic support in a variety of animal and human trials and case reports; a successful treatment of severe postpartum hemorrhage with disseminated intravascular coagulopathy unresponsive to medical or surgical treatments has been reported. The factor works by promoting clotting primarily through the extrinsic (tissue factor) pathway; however, coagulation factors in the intrinsic pathway are also activated. Given as an intravenous bolus dose of 60 μg/kg, recombinant factor VIIa has been reported to have a clinical effect within 10 min in some cases, a half-life of approximately 2 h, and adverse effects consisting primarily of hypertension, hypotension, bradycardia, and renal dysfunction. To date, although observational trials in the setting of traumatic injury are being performed (personal communication), there have been no large randomized studies with recombinant factor VIIa performed in humans. More specific to pregnancy, there are currently no trials being conducted; however, there has been no evidence of teratogenicity in animal studies, and the US Food and Drug Administration has labeled the drug as a Pregnancy Category C therapy.

Obstetric Labor Analgesia Mechanisms

Despite the successful provision for almost a half-century of central neuraxial techniques for labor and delivery and numerous investigations into neuraxially mediated pain, limited work has been performed on the neurophysiologic mechanisms specifically responsible for parturitional pain. Although peripheral nociception during childbirth is known to be shared by visceral and somatic sensory fibers from the pelvic, uterine, cervical, and perineal structures via the low thoracic, lumbar, and sacral nerve roots, clarity in the location and relative contributions of each of each type of fiber and their spinal cord location has not been achieved. The pathways involved in lower uterine and cervical nociception, believed to be supplied by the neri erigentes to the sacral segments, was advanced previously by Bonica, who demonstrated conclusively through a series of experiments over two decades that the upper part of the lower uterine segment and cervix were supplied by the same low thoracic and lumbar afferents to the body of the uterus. The contributions of visceral versus somatic pathways to maternal nociception, however, remain in-
completely understood because of the predominance of work focusing on somatic pain. This investigational imbalance was provoked by the belief that viscera were not capable of encoding pain, because clinical observations demonstrated that cutting or burning visceral tissue often did not induce a painful response.\textsuperscript{58} Subsequently, it was observed that mechanical, electrical, chemical, and ischemic stimuli could induce visceral pain in humans and animals, leading to more extensive research. To date, however, investigations into the visceral contributions to parturitional pain have been abbreviated because of a lack of suitable experimental models and noninvasive neurophysiologic techniques to assess visceral afferent pathways.\textsuperscript{58} A classic study by Berkley \textit{et al.},\textsuperscript{59} using a rat model consisting of balloon distention to the uterine horn, observed that a response to uterine distension occurred only at or above inflation volumes causing ischemia; by contrast, vaginal distention resulted in responses at lower, nonischemic volumes. These results suggest significant differences in uterine and vaginal sensitivity and contribution to labor pain; the conduit between the two structures, the uterine cervix, remained of unknown significance until the recent development of a rat uterine cervical dilation model by Sandner-Kiesling \textit{et al.}\textsuperscript{65}

Using this model, Tong \textit{et al.}\textsuperscript{61} evaluated the spinal distribution of neurons activated through cervical dilation by harvesting the T12-L2 levels of spinal cord and performing an immunohistochemical analysis for cFos, an immediate-early gene involved in transcribing the nociceptive transmission protein Fos. Significant differences in cFos expression in the deep dorsal horn and supraspinal regions were observed; this location contrasts from cFos expression in the deep dorsal horn and noninvasive neurophysiologic techniques to assess visceral afferent pathways.\textsuperscript{58} A classic study by Berkley \textit{et al.},\textsuperscript{59} using a rat model consisting of balloon distention to the uterine horn, observed that a response to uterine distension occurred only at or above inflation volumes causing ischemia; by contrast, vaginal distention resulted in responses at lower, nonischemic volumes. These results suggest significant differences in uterine and vaginal sensitivity and contribution to labor pain; the conduit between the two structures, the uterine cervix, remained of unknown significance until the recent development of a rat uterine cervical dilation model by Sandner-Kiesling \textit{et al.}\textsuperscript{65}

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ritual pain and the stimuli and mediators involved in their initiation and control.

**Ethics**

Clinical dilemmas forced by increasing complex technology, changing practitioner-patient relationships, and an emerging concept of the fetus as a possessor of independent moral status have promoted ethics as the final theme of growing significance. Defined as the disciplined study of morality in medicine, medical ethics serves to define physicians through their possession of virtues and their behaviors toward patients.72,73 Within the setting of obstetric anesthesia, Chervenak et al.74 discuss four virtues of a physician, i.e., self-effacement, self-sacrifice, compassion, and a practice consistent with standards of intellectual and moral excellence, and acknowledge that tension exists between the applications and limitations of these virtues. Within the obstetric anesthesia setting, patient conflicts with the beneficence-based clinical judgments of the physician can be observed with the decision to consume solid foods during labor or a demand for a general anesthetic for cesarean delivery. Fetal issues, including decisions regarding an independent moral status (and thus rights at least equal to that of the mother) and which factors determine viability are also harnessed with theological, philosophical, physical, and technical arguments. Although consensus on many of these issues is a dynamic process governed by the scenario, the individuals involved, and the hospital and regulatory practice environment, awareness by anesthesiologists to the content and direction of these issues is becoming increasingly relevant to care.

Ethical considerations are also central to relationships that govern the consent by an individual to allow another individual to perform an act. In law, this consent process ideally respects the moral foundations of autonomy, in that individuals competent to decide should be given information on which to base decisions and be allowed to make decisions voluntarily.72 Ultimately, this consent allows an individual to define and protect his or her interests as well as provide control over body privacy. Although recognized by the courts as early as the 18th century, the concept of “informed” medical consent was defined in 1957 as requiring the physician to explain to the patient the “risks, benefits, and alternatives” of a procedure. The landmark ruling, from the case of Salgo vs. Trustees of Leland Stanford Hospital, contained an informed consent paragraph which was adopted verbatim from the amicus curiae brief submitted by the American College of Surgeons.75 The discussion of the risks, benefits, and alternatives of anesthesia has historically been subsumed within the consent for surgery; of interest, in the United Kingdom, as well as many states within the United States, a separate consent for anesthesia is not required and is only now being discussed.72,73

The concern that the pain and stress of labor invalidates the process of informed consent seems unfounded, with demonstrations in prospective studies and legal reviews that the process of labor does not interfere with the ability to hear and comprehend information within the consent process.73 Some physicians have even suggested that the consent for pain-relieving procedures is only valid when the person knows what the pain is like74; this suggestion may be relevant to the ethical and philosophical decisions regarding compliance with birth plans forbidding the use of labor analgesia, which often rely on the Ulysses directive (desire to be bound by original directives).75

In part, the difficulty with informed consent lies in determining what risks are significant enough for disclosure; as White and Baldwin72 articulate:

Anesthesia is by nature a practical specialty, every procedure performed carrying a range of risks, which may be minor or major in consequence, common or rare in incidence, causal or incidental to the harm sustained (if any), convenient or inconvenient in timing, expected or unexpected, relative or absolute, operator-dependent or any combination of the above. In addition, there are significant difficulties in communicating risk, caused by patient perceptions, anesthetists perceptions and the doctor-patient interaction, and complicated by the range of communication methods (numerical, verbal, or descriptive).

In an effort to provide an available resource of common anesthetic complications for the purposes of patient education during the consent process, Jenkins and Baker76 surveyed the literature for published incidences of morbidity and mortality associated with anesthesia as well as comparable risks associated with acts of daily living. They conclude that the perception by surgeons, anesthesiologists, and the public of anesthesia being generally safe is somewhat optimistic and that conversations about risk are in need of a more educated and realistic disclosure. As such, anesthesiologists are encouraged to engage rather than withhold a discussion of anesthetic risks, to recognize their own biases that may influence the presentation of risks, to understand how the perception of risks are modified by the situation, and to present relative everyday risks to help place potential complications in perspective. When recognized as an opportunity to foster a closer patient-physician relationship and greater involvement of the patient in their care rather than a tool to avoid litigation, informed consent can help to guide the medical, philosophical, ethical, and legal issues associated with anesthetic care.

**Conclusion**

Significant changes have been witnessed in the obstetric and anesthetic care of pregnant patients, fetuses, and newborns, particularly in the realms of preeclampsia,
peripartum hemorrhage, the functional anatomy and pharmacology of maternal pain and analgesia, and the philosophical issues of ethics and informed consent. Through reflection, integration, and participation in these advances, as well as the numerous unmentioned and ongoing contributions, the opportunity to echo the words of Emerson and the practice of Ostheimer has been offered. The ability to nourish ideas, patients, colleagues, and family members is truly a gift that can affect thousands.

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