

## Gerard W. Ostheimer "What's New in Obstetric Anesthesia" Lecture

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THE Society for Obstetric Anesthesia and Perinatology was founded in 1968 to provide a forum for the discussion of problems unique to the peripartum period. The "What's New in Obstetric Anesthesia" Lecture was established in 1975 at the annual meeting of the society to update members of the relevant literature published in the previous calendar year. In 1995, this lecture was renamed the "Gerard Ostheimer What's New in Obstetric Anesthesia Lecture" after the death of Gerard W. Ostheimer, M.D., an influential member of the Society for Obstetric Anesthesia and Perinatology and former Professor of Anesthesiology at Brigham and Women's Hospital, Boston, Massachusetts. Each year, the lecturer reviews articles from obstetric anesthesia, obstetrics, and neonatology that may be important to practicing obstetric anesthesiologists. For 2005, 1,159 articles were selected and included in the 38th Annual Meeting syllabus. This review focuses on three areas of interest to obstetric anesthesiologists: preeclampsia, labor analgesia, and spinal anesthesia for cesarean delivery. The individual articles have been selected not only on scientific merit, but also if they have raised important issues or caused controversy.

### Preeclampsia

#### *Predicting Preeclampsia*

Preeclampsia is a syndrome that affects 5% of all pregnancies, producing substantial maternal and neonatal morbidity and mortality (fig. 1). In the first stage of preeclampsia, fetal cytotrophoblast cells fail to invade and remodel the placenta's spiral arteries, important for increasing placental blood flow during pregnancy.<sup>1</sup> This causes placental ischemia, which in turn acts as a trigger for the second stage of preeclampsia leading to the clinical manifestations of the disease. Delivery of the fetus and placenta is then the only definitive cure for preeclampsia. Recent evidence suggests that excess circulating placental soluble fms-like tyrosine kinase 1 (sFlt-1) contributes to the development of preeclampsia.<sup>2</sup>

This is an antiangiogenic protein that binds to proangiogenic proteins, vascular endothelial growth factor (VEGF), and placental growth factor (PlGF), which are thought to be critical for successful human implantation and placentation.<sup>3</sup> The proangiogenic proteins therefore cannot bind to endothelial cell receptors. This causes placental endothelial dysfunction by altering the remodeling of uterine spiral arteries necessary for normal placentation and pregnancy.<sup>4</sup> In the same way, systemic endothelial dysfunction may cause generalized disease including hypertension, proteinuria, eclampsia, and liver abnormalities.<sup>5</sup>

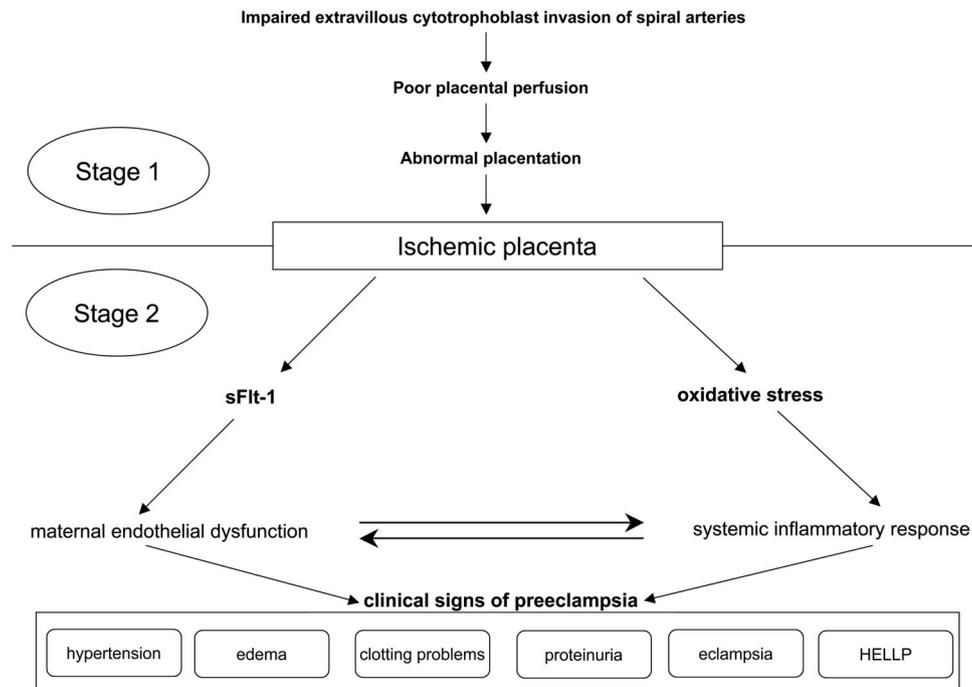
Levine *et al.*<sup>6</sup> demonstrated that high serum levels of sFlt-1 and low levels of PlGF predict subsequent development of preeclampsia. Elevated serum levels of sFlt-1 begin to increase approximately 5 weeks before the clinical onset of preeclampsia. These changes are preceded by low serum concentrations of free PlGF beginning at 13-16 weeks of gestation. The same group of investigators hypothesized that reduced concentrations of urinary PlGF could predict preeclampsia when measured during routine antenatal care. They measured PlGF in urine samples derived from women enrolled in the Calcium for Preeclampsia Prevention trial, which originally evaluated the effect of calcium on the development and severity of preeclampsia.<sup>7</sup> Urinary PlGF, a much smaller protein than sFlt-1, was analyzed because it is readily filtered by the kidney. This study, in which preeclamptic women were matched to normotensive controls (120 matched pairs), showed that the urinary concentration of PlGF was significantly lower beginning at 25-28 weeks of gestation among women who later developed preeclampsia.<sup>8</sup> These differences were more pronounced at 29-36 weeks. After the onset of preeclampsia, urinary PlGF concentrations were even lower. Overall, the adjusted odds ratio for developing preeclampsia before 37 weeks of gestation was 22.5 (95% confidence interval, 7.4-67.8).

In a separate study, Buhimschi *et al.*<sup>9</sup> analyzed the urinary excretion of sFlt-1, VEGF, and PlGF in four groups of women: nonpregnant, healthy pregnant, pregnant hypertensive with proteinuria who did not meet the criteria for severe preeclampsia, and severe preeclampsia. Urinary sFlt-1 concentrations were significantly increased in women with severe preeclampsia relative to all other groups, whereas urinary PlGF levels were significantly increased in pregnant compared with nonpregnant women, but were decreased in all hypertensive women compared with healthy pregnant con-

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**Fig. 1. Pathophysiology of preeclampsia.** HELLP = hemolysis, elevated liver enzymes, low platelets; sFlt-1 = soluble fms-like tyrosine kinase 1.

trols. Urinary VEGF did not vary between groups. Using this data, a sFlt-1/PlGF ratio was found to have 88% sensitivity and 100% specificity in differentiating preeclamptic women at the time of clinical diagnosis from normotensive controls.

Both studies highlight the potential use of noninvasive screening tests to differentiate severe preeclampsia from other proteinuric hypertensive disorders in pregnancy. Further studies are needed to determine whether changes in urinary excretion of angiogenic growth factors reflect overexpression or underexpression of VEGF, sFlt-1, and PlGF or an intrinsic renal glomerular problem causing increased filtration and excretion.

In another study, Parra *et al.*<sup>10</sup> attempted to predict the onset of preeclampsia by using a combination of uteroplacental blood flow assessment and biochemical markers of oxidative stress and endothelial dysfunction to screen for preeclampsia in almost 1,500 asymptomatic pregnant women at 11–14 weeks and 22–25 weeks of gestation. Data from those women who developed preeclampsia were compared with controls. These authors determined that, compared with controls, the mean uterine artery pulsatility index was significantly higher in both the first and second trimesters of women who were eventually diagnosed with preeclampsia.<sup>10</sup> Measurements of biochemical markers did not differ during the first trimester, including increases in sFlt-1, PAI-1/PAI-2 ratio (plasminogen activator inhibitor type-1 and type 2), and F2-isoprostane and reduced PlGF. These data suggest that impaired placentation, antiangiogenic factors, endothelial dysfunction, and oxidative stress predate the development of preeclampsia by several weeks. How-

ever, because these markers were only increased in the second trimester, the authors concluded that uterine artery Doppler measurements during early pregnancy were the best predictors of preeclampsia.

Another intriguing fact is that preeclampsia is far more common in women's first pregnancy, but the mechanism is unknown. Wolf *et al.*<sup>11</sup> hypothesized that serum concentrations of sFlt-1 would be higher in nulliparous women compared with multiparous women, suggesting a higher degree of antiangiogenesis in first pregnancies. The authors measured sFlt-1 and PlGF levels in early pregnancy serum samples from the first 2 completed pregnancies of 97 women who participated in the Massachusetts General Hospital Obstetric Maternal Study cohort study. Women who later developed pregnancy hypertension (preeclampsia or gestational hypertension) or who had preexisting chronic hypertension were excluded from the analysis. Levels of sFlt-1 were significantly increased in first compared with second pregnancies. Interestingly, after subgroup analysis, Hispanic women had higher sFlt-1 levels than white women during their first pregnancy, but not during their second pregnancy. There were no differences in PlGF. The authors speculated that other factors may interact in those nulliparous women who go on to develop preeclampsia with further increases in antiangiogenic sFlt-1 levels.

It is important to remember that although sFlt-1 is more likely to be increased in severe preeclampsia, it is not present in all women with severe preeclampsia.<sup>12</sup> In a nested case-control study of 113 normal pregnant women and 55 women with preeclampsia, Powers *et al.*<sup>12</sup> reported similarly increased serum sFlt-1 during

early pregnancy in both groups. Because many studies have shown lower concentrations of maternal free serum PIGF in early pregnancy in women who later develop preeclampsia,<sup>13-15</sup> it is unlikely that levels of sFlt-1, an antiangiogenic protein, can explain these early differences in free circulating PIGF. It is possible that the pathophysiology of preeclampsia is not solely due to raised maternal serum concentrations of sFlt-1, but probably a more complex interaction between angiogenic proteins and other factors that together lead to clinical disease.

#### *Regional Anesthesia for Cesarean Delivery*

Spinal anesthesia is today a well-established technique for severe preeclamptic patients undergoing cesarean delivery. Two studies investigated the hemodynamic effects of regional anesthesia in this group of high-risk women.<sup>16,17</sup> Aya *et al.*<sup>16</sup> hypothesized that such patients were less likely to develop hypotension after spinal anesthesia than controls. The group's previous study showed that compared with women at term undergoing elective cesarean delivery, those with severe preeclampsia were six times less likely to develop hypotension, which was defined as a systolic blood pressure decrease to less than 100 mmHg or a 30% decrease in mean blood pressure.<sup>18</sup> At the time, these findings were criticized on the basis that reduced gestational age resulting in lower fetal weight and less aortocaval compression could have decreased the incidence of hypotension in preeclamptic patients. To answer this criticism, the authors went on to compare preeclamptic women with severe disease with a control group of preterm mothers undergoing cesarean delivery.<sup>16</sup> The control group was chosen so that the fetuses were matched in terms of fetal weight (1,100–1,900 g). This was meant to control for uterine mass between the groups and therefore aortocaval compression. The results showed a significantly reduced frequency of hypotension in the preeclamptic group (24.6% *vs.* 40.8%). However, when hypotension occurred, the magnitude of the decrease in blood pressure was similar between groups, although preeclamptic patients needed less ephedrine to return the blood pressure to baseline values. The authors concluded that preeclampsia-associated factors may account for this reduced incidence of spinal hypotension rather than a smaller uterine mass. These factors, including increased vascular resistance and sensitivity to vasoconstrictors, may limit the decrease in blood pressure resulting from the sympathetic block associated with spinal anesthesia.

In a separate study, Visalyaputra *et al.*<sup>17</sup> investigated the hemodynamic effects of spinal *versus* epidural anesthesia for cesarean delivery in women with severe preeclampsia in a large, multicenter, prospective, randomized trial. Spinal anesthesia was associated with a significantly greater incidence of hypotension (51% *vs.* 23%) and a greater use of ephedrine, although the mean

difference in the lowest systolic blood pressure was only 10 mmHg. Furthermore, hypotension was of short duration and easily treated in all patients. Neonatal outcome, measured by Apgar score and blood pH, did not differ between groups. The authors concluded that because the differences in hemodynamic data were of little clinical significance, spinal anesthesia was a safe technique for severe preeclampsia.

#### **Labor Analgesia**

##### *Pharmacology*

Chronobiology is a field of biology that examines time-related phenomena in living organisms. The most important rhythm in chronobiology is circadian rhythm, which refers to the 24-h daily biologic cycle. Examples of such rhythms include variations in heart rate and blood pressure throughout the day. Pan *et al.*<sup>19</sup> investigated whether there was any temporal relation in the analgesic duration of 25  $\mu$ g intrathecal fentanyl used for spinal labor analgesia by assigning 77 nulliparous patients in active labor requesting neuraxial analgesia to one of two groups based on the time of combined spinal-epidural (CSE) initiation. The duration of intrathecal analgesia was 91 min for the day group (12:00 to 18:00 h) compared with 67 min for the night group (20:00 to 02:00 h), a 27% difference in labor analgesia duration ( $P < 0.001$ ). These results could not be explained by parturients reporting higher pain scores at night, because the visual analog pain scale scores both before and after intrathecal fentanyl were similar between groups. Potentially confounding factors, including cervical dilation and frequency of uterine contractions, were also comparable. The results of Pan *et al.* were similar to those of the earlier study of Debon *et al.*<sup>20</sup> using intrathecal sufentanil. The impact of such studies is to emphasize that chronobiology should be considered with other variables such as sex, age, weight, and genetics in pharmacokinetic studies of drugs used in anesthetic practice.

In a randomized study, challenging some of the preconceptions surrounding spinal blockade, Parpaglion *et al.*<sup>21</sup> questioned whether the volume of spinal drug injection was just as important as the actual drug dose/mass of drug when used for spinal labor analgesia. Previous studies evaluating spinal anesthesia for cesarean delivery have not found a difference in final sensory block height with injection volumes ranging from 3 to 18 ml with the same fixed dose of local anesthetic.<sup>22,23</sup> The authors postulated that during intrathecal (labor) analgesia, injection volume may have an important effect, which could result in a reduction of local anesthetic dose required by women in the first stage of labor. In their study, 93 nulliparous women in early labor requesting regional analgesia were randomly assigned to receive different doses of intrathecal levobupivacaine in a spinal injection volume of 2.5, 5, or 10 ml. The dose of

levobupivacaine varied according to an up-down sequential allocation, with the first patient in each group receiving 2 mg. The ED<sub>50</sub> (minimum local anesthetic dose) was reduced as the volume of injection increased, with a unit volume change increasing the odds of an effective response by a factor of 1.8 ( $P < 0.05$ ). Although the ED<sub>95</sub> values, which may be of more clinical relevance, were not estimated, this study implies that satisfactory intrathecal labor analgesia can be achieved by using lower doses of local anesthetic drug within larger injection volumes.

#### *Maintenance of Labor Analgesia*

Most anesthesiologists will be familiar with maintaining epidural labor analgesia with an intermittent bolus, a continuous infusion, or a patient-controlled epidural analgesia technique. In a modification of the intermittent bolus technique, Lim *et al.*<sup>24</sup> administered epidural analgesia with a specially modified infusion pump, postulating that epidural boluses given at regular intervals would provide superior analgesia to a conventional continuous epidural infusion regimen. Forty nulliparous women requesting CSE labor analgesia were randomly assigned into two groups after receiving 25  $\mu\text{g}$  intrathecal fentanyl to initiate analgesia. Patients received either a continuous epidural infusion of 0.1% levobupivacaine with 2  $\mu\text{g}/\text{ml}$  fentanyl at a rate of 10 ml/h or 5 ml epidural boluses given every 30 min through the automated pump. The bolus group had a significantly lower incidence of breakthrough pain (10% *vs.* 37%) and better satisfaction scores (on a 0–100 scale) compared with the continuous infusion group. The authors suggested that the improvement in analgesia was due to the automated drug delivery system. These results may be explained by higher driving pressures when an intermittent bolus technique is used resulting in more uniform spread in the epidural space.<sup>25,26</sup> Similar improvements in analgesia using a programmed intermittent epidural bolus for labor analgesia have been found recently by other workers.<sup>27</sup>

#### *Labor Outcome*

A study which assessed the risk of cesarean delivery after neuraxial block in early labor generated much publicity in 2005.<sup>28</sup> Because many centers avoid regional analgesia until the parturient reaches a cervical dilatation of greater than 4 cm following a recommendation from the American College of Obstetricians and Gynecologists,<sup>29</sup> Wong *et al.* randomized 750 nulliparous women at term in spontaneous labor at less than 4 cm cervical dilatation to receive CSE labor analgesia (25  $\mu\text{g}$  intrathecal fentanyl) or systemic hydromorphone (1 mg intravenously and 1 mg intramuscularly) at first analgesic request. At second analgesic request, the CSE group received an epidural bolus of low dose bupivacaine with fentanyl if the cervix was less than 4 cm dilated or

bupivacaine alone if the cervical dilatation was 4 cm or greater. In the systemic analgesia group, parturients were given further boluses of hydromorphone if less than 4 cm dilated or epidural analgesia if greater than 4 cm dilated. Epidural analgesia was given at third analgesic request regardless of cervical dilatation. Standard care for patients with epidural analgesia after the bolus injections consisted of patient-controlled epidural analgesia with low-dose bupivacaine and fentanyl. There was no difference in the rate of cesarean delivery between groups (17.8% *vs.* 20.7%; CSE *vs.* systemic groups). However, the CSE group had superior analgesia and a shorter labor duration, a finding similar to that of Tsen *et al.*<sup>30</sup> In addition, patients experienced less nausea and vomiting. Although this is a study of primarily intrathecal analgesia in early labor *versus* epidural analgesia in late labor, the message is clear. Patients should not be denied superior pain relief with neuraxial block based purely on an arbitrary cervical dilatation. The American College of Obstetricians and Gynecologists has recently published a document that supports this.<sup>31</sup>

#### *Breast-feeding*

The American Academy of Pediatrics advises mothers that breast-feeding is the best form of nutrition for infants and should be maintained for 6 months after birth. Several studies have demonstrated a detrimental effect of epidural analgesia on breast-feeding success.<sup>32–34</sup> Most of these studies have yielded conflicting results due to problems with study design; with many being either retrospective or nonrandomized prospective studies. Beilin *et al.*<sup>35</sup> were the first group to conduct a randomized, double-blind trial to determine whether epidural fentanyl had an impact on infant breast-feeding. Based on the results of an initial observational pilot study, the authors randomized 180 women, who had previously breast-fed a child for at least 6 weeks, to one of three groups based on epidural fentanyl use: no fentanyl, intermediate-dose fentanyl (intent to administer 1–150  $\mu\text{g}$  epidural fentanyl), or high-dose fentanyl (intent to administer  $> 150$   $\mu\text{g}$  fentanyl). Results were based on a 24-h assessment by a lactation nurse and the mother followed by a telephone interview with the mother at 6 weeks postpartum. Although there were no significant differences in breast-feeding problems at 24 h ( $P = 0.09$ ), mothers assigned to the high-dose fentanyl group were more likely to have stopped breast-feeding at 6 weeks postpartum. These results were based on an intention-to-treat analysis. However, when the data were reanalyzed by the actual dose of fentanyl administered, patients receiving greater than 150  $\mu\text{g}$  epidural fentanyl were more likely to have difficulty breast-feeding both at 24 h and 6 weeks postpartum. Unfortunately, the results of the study were confounded by several problems, including 11% of patients failing to respond to the 6-week telephone interview and fentanyl levels not be-

ing measured in breast milk. Furthermore, based on previous studies of maternal/placental fentanyl pharmacokinetics, it is unlikely that fentanyl would be present in either the newborn circulation or maternal breast milk at 24 h, let alone 6 weeks postpartum.<sup>36,37</sup> Despite the negative study findings of breast-feeding after epidural fentanyl administration, the authors continue to support epidural fentanyl administration. Removing fentanyl from epidural infusions would increase local anesthetic concentrations and the risk of instrumental delivery.<sup>38</sup> Instead, they suggest the need for a greater awareness of potential problems between epidural fentanyl and breast-feeding.

## Spinal Anesthesia for Elective Cesarean Delivery

### *Reducing Hypotension*

An effective method for preventing hypotension during spinal anesthesia has been referred to as the "Holy Grail" of obstetric anesthesia.<sup>39</sup> Although ephedrine is usually recommended as a first-line vasopressor to treat hypotension in obstetrics, its superiority over other vasopressors has not been proven in humans and has been associated with fetal acidosis.<sup>40,41</sup> The infusion of the  $\alpha$ -adrenergic agonist phenylephrine to maintain baseline systolic blood pressure during elective cesarean delivery has also been associated with further improvements in umbilical cord gases.<sup>42</sup> To further reduce the incidence of hypotension during cesarean delivery, fluid preloading has been used, but with limited effect.<sup>43,44</sup> However, fluid coload or cohydration, rapid fluid administration at the time of spinal injection, is now known to reduce the incidence of hypotension.<sup>45</sup> Ongoing studies by Ngan Kee's group in Hong Kong culminated in a randomized study comparing a rapid 2-l fluid cohydration technique with crystalloid to a standard method without cohydration.<sup>46</sup> Both groups were given a phenylephrine infusion to maintain baseline systolic blood pressure. Only 1 of 53 patients in the cohydration group (1.9%) became hypotensive compared with 15 of 53 patients (28.3%) in the control group ( $P = 0.0001$ ). Phenylephrine requirements were also significantly reduced in the cohydration group. Cohydration combined with strict control of systolic blood pressure to baseline values with an  $\alpha$ -agonist infusion may potentially be the optimum method of eliminating hypotension after spinal anesthesia for cesarean delivery.

### *Predicting Hypotension*

Of course, if we could predict and treat only those patients who may become hypotensive after spinal anesthesia, so much the better. Hanss *et al.*<sup>47</sup> tried to do just that by measuring autonomic system activity in pregnant women before their spinal anesthetic for cesarean

delivery using fast Fourier transformation of heart rate variability. Because hypotension during neuraxial block primarily results from decreased systemic vascular resistance after blockade of preganglionic sympathetic fibers and an increase in sympathetic regulation during pregnancy,<sup>48</sup> the authors predicted that patients with a higher sympathetic drive were more likely to develop hypotension. An initial retrospective study showed that parturients who had a higher sympathetic (and a lower parasympathetic) drive pre-spinal had a greater degree of moderate to severe hypotension. Using this information, the authors devised a prospective study to test this model. Prospectively, the model ( $n = 19$ ) accurately predicted that those with a higher sympathetic drive immediately before spinal injection (*i.e.*, before fluid hydration) were more likely to develop severe hypotension. Contrary to what one might expect, the incidence of hypotension did not correlate with heart rate variability at other measurement time points, including the baseline measurements on the day before surgery and the day of surgery. A follow-up study by the same group found that prophylactic treatment with vasopressor or colloids successfully reduced the incidence of hypotension in those patients who, on the basis of heart rate variability measurements, had been predicted to become hypotensive during spinal anesthesia for cesarean delivery.<sup>49</sup>

### *Fetal Outcome*

Fetal outcome is generally accepted to be better after regional anesthesia for cesarean delivery than general anesthesia, with spinal anesthesia being more widely used because it is considered safer than other techniques.<sup>50</sup> This was disputed by a meta-analysis of 27 studies using different forms of anesthesia for cesarean delivery which found that umbilical cord gas pH/base excess was significantly better with epidural or general anesthesia compared with spinal, although the absolute differences were small.<sup>51</sup> Because ephedrine is known to increase metabolic acidosis in the fetus,<sup>41</sup> these differences could be explained by an increased use of ephedrine to treat the hypotension associated with spinal anesthesia. An alternative explanation could be the inadequate treatment of hypotension. It would be interesting to repeat this study in the future with the increasing trend of using a phenylephrine infusion in conjunction with a more aggressive approach to maintaining baseline systolic blood pressure.

### *Drugs and Techniques*

Posture and baricity during induction of spinal anesthesia are thought to be important in determining spread of local anesthetic within the cerebral spinal fluid.<sup>52</sup> Both the sitting and the lateral position are used during induction with commercially available hyperbaric bupivacaine being more commonly used for intrathecal injection.

tion because of a high incidence of unpredictable blocks and hypotension with plain (hypobaric) bupivacaine.<sup>53</sup> Although plain and hyperbaric bupivacaine have been evaluated in clinical studies,<sup>54,55</sup> there may be a theoretical advantage to a true isobaric preparation with regard to its spread and cardiovascular stability. In a study analyzing the interaction of both posture and baricity, Hallworth *et al.*<sup>56</sup> in a randomized controlled study used hyperbaric, hypobaric, or isobaric bupivacaine, 10 mg, injected in either the sitting or right lateral position using a CSE technique. Isobaric bupivacaine was prepared according to a previously published protocol.<sup>57</sup> The lateral position had no effect on the sensory level of spread, whereas when hypobaric bupivacaine was injected in the sitting position, there were higher sensory levels (often cervical) with more hypotension. The isobaric solution had the smallest incidence of both cervical analgesia and block failure, although it was still associated with a moderate degree of hypotension.

Many anesthesiologists believe that much smaller doses of spinal local anesthetic than commonly administered can be used for cesarean delivery by using an epidural volume extension (EVE) technique. This involves injecting normal saline into the epidural space after an intrathecal injection, usually as part of CSE, and has been shown to increase the cephalad spread of the block.<sup>58,59</sup> MRI work has demonstrated that this is probably due to dural sac compression by the saline injection enabling the local anesthetic to spread further within the dural sac, with any reduction in cerebrospinal fluid volume being injection-volume dependent and lasting for at least 30 min.<sup>60</sup> It is unclear whether EVE, used for cesarean delivery, causes a dose sparing effect that allows smaller doses of injected intrathecal local anesthetic to achieve a similar effect. Beale *et al.*<sup>61</sup> attempted to answer this question in a randomized controlled trial comparing EVE with no EVE during CSE anesthesia for cesarean delivery. Using a double-blind up-down sequential allocation technique, varying doses of intrathecal bupivacaine with 25  $\mu$ g fentanyl were administered to estimate the ED<sub>50</sub> of bupivacaine. The authors found that there was no significant difference in the ED<sub>50</sub> of bupivacaine (6.1 *vs.* 5.1 mg) between the groups, confirming that EVE was ineffective in reducing dosing requirements of intrathecal bupivacaine.

## Conclusion

The legacy of Gerard Ostheimer is for an obstetric anesthesiologist each year to evaluate the relevant literature in the specialty. To review studies that can potentially change clinical practice as well as those that raise controversy and debate and to disseminate this information to ones peers is an important facet of the lecture-ship. It reminds obstetric anesthesiologists to look be-

yond their subspecialty and focus on the wider arena of caring for the mother and the neonate and ways of improving clinical outcomes.

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