The 2015 Gerard W. Ostheimer Lecture: What's New in Labor Analgesia and Cesarean Delivery

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Every year the Board of Directors of the Society for Obstetric Anesthesia and Perinatology selects an individual to review the literature pertinent to obstetric anesthesiology published the previous calendar year. This individual selects the most notable contributions, creates a syllabus of the articles, and then presents his/her overview in an annual lecture named in honor of the late Gerard W. Ostheimer, a pioneering obstetric anesthesiologist from the Brigham and Women's Hospital. This article reviews the literature published in 2014 focusing on the themes of labor analgesia and cesarean delivery. Its contents were presented as the Gerard W. Ostheimer Lecture at the 47th Annual Meeting of the Society for Obstetric Anesthesia and Perinatology, May 16, 2015, in Colorado Springs, Colorado. The syllabus is available as Supplemental Digital Content (http://links.lww.com/AA/B397). (Anesth Analg 2016;122:1524–31)

Obstetric anesthesiology is a dynamic field, the practice of which involves not only knowledge of anesthesiology and obstetrics, but also perinatology, neonatology, cardiology, and hematology among other medical fields. Recent rapid evolution of our practice is evident in a number of areas, such as the prevention and treatment of postpartum hemorrhage and hypotension associated with spinal anesthesia. Annually, the Society for Obstetric Anesthesia and Perinatology (SOAP) selects the Ostheimer Lecturer to help obstetric anesthesiologists review the latest advances across the breadth of the field through a lecture delivered at the annual meeting, the publication of a syllabus of selected articles (Supplemental Digital Content, http://links.lww.com/AA/B397), and the publication of this review.

In this role, the 2015 Ostheimer Lecturer searched >75 journals, websites, and newsletters published from January through December 2014. These journals were chosen based on their scientific and clinical relevance to the field of obstetric anesthesiology. Of the many articles read, 452 were set aside by the author for further study, 194 were included in the syllabus, and 57 were included in the lecture at the 47th Annual Meeting of the SOAP, May 16, 2015, in Colorado Springs, Colorado. Selection was based on the author's assessment of the article's current or eventual potential to influence the practice of obstetric anesthesiology.

This article reviews the literature published in 2014 focusing on the themes of labor analgesia and cesarean delivery. Specifically, the psychology of labor pain and the impact of labor analgesia on pain, fever, mode, and length of delivery will be discussed. Further topics include the impact of emergency cesarean delivery decision-to-delivery interval on obstetric outcomes, the incidence of intraoperative awareness during cesarean delivery, the appropriate role for supplemental oxygen in nonhypoxemic pregnant women, the prevention of spinal anesthesia–associated hypotension, the use of postcesarean oxytocin protocols, and the role of transversus abdominis plane (TAP) blocks in postcesarean analgesia.

LABOR ANALGESIA

Labor Pain and Psychology

An individual woman's labor pain experience is extraordinarily complex. It is influenced not only by obstetric and anesthetic variables, but also by environmental, psychologic, cultural, social, language, economic, preparation, and expectation variables. In 2014, multiple investigators studied the complexity of the psychological aspects of the labor pain experience.[1–4]

Investigators of a prospective observational study administered 4 validated psychologic tests and 3 tests rating anxiety, confidence, and analgesic expectations to 39 women undergoing induction of labor.[1] The authors evaluated the relationship between predictor (psychologic test) and response (analgesic outcomes) variables. A multivariate linear regression analysis identified the tests that contributed to a predictive model. The Anxiety Sensitivity Index was predictive of greater labor pain, as measured by the area under the labor pain × time curve. Pain catastrophizing was associated with greater epidural local anesthetic use, and a greater Fear of Pain Questionnaire-III score was associated with lower maternal satisfaction with labor.

The psychological theory of *attachment* has been shown to relate to labor analgesic outcomes. *Attachment style* is thought to be determined in infancy through one's relationships with primary caregivers and remains unchanged throughout life. Attachment style describes how an individual relates to others, especially under stress, and is measured in 2 dimensions: anxiety (the extent to which one worries about being unloved and abandoned) and avoidance (the extent to which one avoids the closeness of others). A single observational study assessed 81 women during the third trimester with the Adult Attachment Scale-Revised.[2] In labor,

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women with secure attachment styles (low anxiety and low avoidance) reported significantly less labor pain ($P < 0.001$) and consumed significantly lower amounts of analgesics using patient-controlled epidural analgesia ($P < 0.001$) than women with insecure attachment styles (high anxiety and/or high avoidance), even though baseline obstetric and demographic data appeared similar in both groups. The findings that psychologic characteristics predict labor pain and analgesia requirements are interesting and lead one to question whether routinely assessing these characteristics using such tools might eventually inform labor and analgesic planning for women.

Researchers investigated why women select epidural labor analgesia even if they are told it may not completely control pain and might, in some cases, prolong labor. Carvalho et al.[3] prospectively surveyed 40 women scheduled for induction of labor both before and after labor (37 women completed both surveys). The surveys asked binary questions such as, "Which scenarios would you prefer? Pain intensity of 2 for 9 hours, or pain intensity of 6 for 3 hours?" The women in the study had a preference for lower pain intensity for a longer duration than higher intensity for a shorter duration rather than the null median (no preference). This was true both before ($P < 0.0001$) and after ($P < 0.0001$) their labor experience.

Whether and how epidural labor analgesia affects postpartum psychiatric outcomes is a fascinating question. Postpartum depression is a leading cause of postpartum maternal morbidity. One prospective, observational cohort study followed 214 women in a Chinese hospital, 107 of whom requested and received epidural analgesia.[4] The women were assessed for postpartum depression at 3 days and at 6 weeks. Women who received epidural analgesia for labor had lower odds of postpartum depression at 6 weeks, as assessed by the Edinburgh Postnatal Depression Scale, than women who did not request analgesia (odds ratio [OR], 0.31; 95% confidence interval [CI], 0.12–0.82). The article was accompanied by an editorial that discussed the possible links between epidural analgesia, diminished intrapartum and postpartum persistent pain, and the risk for depression.[5] A possible explanation of the results is that the baseline psychologic characteristics of the women who were educated and empowered to request epidural analgesia is different from those who were less educated or felt unempowered to request labor analgesia. The editorial acknowledged this possibility and the difficulty in studying this association in a future randomized controlled trial.

Epidural Labor Analgesia and Its Obstetric Effects

Duration of Second-Stage Labor

A controversial investigation evaluated the association of epidural labor analgesia with the duration of second-stage labor.[6] This retrospective cohort study compared the duration of second-stage labor (median and 95th percentile) in women with and without epidural labor analgesia, all of whom had normal neonatal outcomes. The data set involved 42,268 women stratified by parity who experienced vaginal delivery at University of California, San Francisco, between 1976 and 2008. The median duration of second-stage labor in nulliparous women who labored *with* versus *without* epidural labor analgesia was 120 and 47 minutes, respectively—a difference of 73 minutes ($P < 0.001$). The 95th percentile duration of second stage in nulliparous women who labored *with* versus *without* epidural labor analgesia was 197 and 336 minutes, respectively—a difference of >2 hours ($P < 0.001$). Similarly, for parous women, the median duration of second-stage labor *with* versus *without* epidural labor analgesia was 38 and 14 minutes, respectively, a difference of 24 minutes ($P < 0.001$). However, the 95th percentile duration of second-stage labor *with* versus *without* epidural labor analgesia was 81 and 255 minutes, respectively, a difference of approximately 3 hours ($P < 0.001$).

Although some media covered this study thoughtfully,[7] others covered it with titles such as "Epidurals May Make Labor Longer than Originally Thought."[8] Such headlines inappropriately implied that the study demonstrated *causation* between epidural analgesia and prolongation of second-stage labor. Because of its retrospective design, the study contains all the biases of retrospective labor analgesia studies, the most important of which is that women with prolonged and complicated labors are more likely to request, and have time to receive, epidural labor analgesia. Women with short and uncomplicated labors are less likely to request analgesia. Further limitations include that the epidural labor analgesia techniques used at the institution between 1976 and 2008 are not described. The protracted length of time over which data were collected could also confound the study results. For example, because techniques and availability have improved, the prevalence of epidural analgesia has increased since 1976. During this same time, the obstetric practice of instrumented vaginal deliveries has decreased. This obstetric practice change would significantly contribute to longer second-stage labors during the time period when epidural analgesia rates were increasing.

The authors, however, do not claim causation or encourage lesser epidural labor analgesia use, but instead they use the data to question whether obstetricians should redefine prolonged second-stage labor and thereby redefine recommendations for intervention during second-stage labor. Current guidelines by the American College of Obstetricians and Gynecologists define an abnormally long second stage as >3 hours for nulliparous women laboring with epidural analgesia and as >2 hours for those without epidural analgesia. Addressing this topic, the American College of Obstetricians and Gynecologists and the Society of Maternal Fetal Medicine published an Obstetric Care Consensus statement noting that "it may be necessary to revisit the definition of labor dystocia because recent data show that contemporary labor progresses at a rate substantially slower than what was historically thought."[9]

Epidural Labor Analgesia and the Perineum

Two large epidemiologic studies evaluated the association between epidural labor analgesia and the risk of perineal injury during second-stage labor.[10,11] One retrospective cohort study evaluated 61,308 vaginal deliveries that occurred at an Israeli hospital between 2006 and 2011.[10] Within the cohort, 31,631 (51.6%) women received epidural analgesia. Epidural labor analgesia was associated with higher rates of nulliparity, induction and augmentation of

labor, prolonged second stage, instrumented vaginal birth, and episiotomy. Therefore, it is not surprising that univariate analysis showed an association between the use of epidural analgesia and severe perineal tears (OR, 1.78; 95% CI, 1.34–2.36). However, in multivariate analysis, the association disappeared (OR, 0.95; 95% CI, 0.69–1.29). The authors conclude that the "factors that lead to a woman's request for epidural analgesia, such as poor labor and primiparity [sic], may be similar to those that lead to severe perineal tears."

Similarly, a population-based retrospective cohort study using the Danish Medical Birth Registry studied the incidence of obstetric anal sphincter injury among 214,256 nulliparous women undergoing vaginal delivery between 2000 and 2010.[11] Although epidural analgesia was a risk factor in the univariate analysis (OR, 1.12; 95% CI, 1.01–1.17; $P < 0.0001$), after adjusting for birth weight and vacuum extraction, epidural analgesia was protective for sphincter injury (OR, 0.94; 95% CI, 0.90–0.98; $P = 0.0028$). In multivariable analysis that also included multiple fetal and obstetric factors, epidural analgesia became *even more* protective (OR, 0.84; 95% CI, 0.81–0.88; $P = 0.0001$). In this study, as with the previous study,[10] confounding factors masked the potential benefits of epidural analgesia to the perineum. A possible mechanism for benefit is that women with epidural analgesia are able to push with more control, allowing the fetus to slowly stretch the perineum during second-stage labor instead of an uncontrolled delivery as a result of the distress caused by severe second-stage pain.

Epidural Labor Analgesia and Operative Vaginal Delivery

The question of whether epidural labor analgesia contributes to an increased risk of cesarean delivery has been investigated using several types of study designs. Although the results of these trials suggest that epidural labor analgesia does not increase the risk of cesarean delivery, whether it causes increased risk of instrumented vaginal delivery has yet to be determined.

A population-based retrospective cohort study using data from the Perinatal Registry of the Netherlands between 2000 and 2009 contributes to our knowledge in this area.[12] These data showed that among nulliparous women ($n = 616{,}063$), the rate of epidural labor analgesia use tripled over the study period from 7.7% to 21.9%. Although the cesarean delivery rate increased by 2.8% during the study period, the instrumented vaginal delivery rate decreased by 3.3%. In parous women ($n = 762{,}395$), epidural analgesia use increased from 2.4% to 6.8%, whereas absolute rates of cesarean delivery increased by 0.8% and instrumented vaginal delivery decreased by 0.7%. Although the authors conclude that epidural analgesia is not an important causal factor of operative deliveries, further study is needed to determine the role epidural labor analgesia plays on rates of forceps and vacuum deliveries.

Epidural Fever

Women who use epidural labor analgesia have an increased risk for intrapartum fever compared with those who do not use epidural analgesia. This fever has been called "epidural fever." An important new study supports results from the previous studies that suggested that infection is not a likely cause of epidural fever.[13] This double-blinded trial randomly allocated 400 healthy nulliparous women to receive IV cefoxitin 2 g or placebo immediately before initiation of epidural labor analgesia. The primary outcome was the incidence of fever. As hypothesized, antibiotics did not reduce fever rates; 38% (75 of 200) and 40% (79 of 200) of women in the cefoxitin group and placebo group, respectively, developed a fever defined as a tympanic membrane temperature ≥38.0°C ($P = 0.68$). The antibiotics did not reduce neutrophilic inflammation of the placental membranes (cefoxitin group 49% [74 of 150] and placebo group 55% [84 of 152]; $P = 0.30$). However, as prior studies have shown, placental inflammation and fever were linked. Sixty-nine percent (73 of 106) of women who developed fever had placental neutrophilic inflammation compared with 43% (85 of 196) of women who remained afebrile ($P < 0.001$). The reverse relationship was also significant; 46% (73 of 157) of women who had placental inflammation developed fever, whereas only 23% (33 of 144) of those without placental inflammation developed a fever ($P < 0.001$). In summary, prophylactic antibiotic treatment did not alter the incidence of fever, providing strong evidence against an infectious etiology for epidural fever. However, the study supports previous research that has suggested an association between intrapartum fever and noninfectious histologic placental chorioamnionitis. This article is accompanied by an editorial by Goetzl[14] who encouraged future investigators to focus on interventions that block the maternal inflammatory response to epidural analgesia without increasing maternal or fetal risks.

Types of Labor Analgesia

Combined Spinal-Epidural Analgesia

Combined spinal-epidural analgesia (CSE) is one option to provide neuraxial labor analgesia. In a study using hyperbolic dose-response modeling, investigators demonstrated that intrathecal opioids and local anesthetics work synergistically to provide analgesia.[15] Three hundred nulliparous women in first-stage labor were randomly allocated to receive 1 of 30 different combinations of intrathecal fentanyl and bupivacaine. Hyperbolic dose-response models were calculated using nonlinear regression, and drug interaction was evaluated by comparing observed effects to effects that would be predicted by additivity. Combinations of fentanyl and bupivacaine produced greater effects than that predicted by additivity at 15 minutes ($P < 0.001$) and 30 minutes ($P = 0.015$), indicating a synergistic interaction between the 2 intrathecal drugs administered for labor analgesia.

Studying the incidence of fetal heart rate (FHR) abnormalities associated with the initiation of labor analgesia is difficult because there are many variables as well as outcome measurements that require definition and interpretation. One study showed no difference in FHR abnormalities when labor analgesia was initiated with CSE (intrathecal bupivacaine 2.5 mg and fentanyl 5 μg [$n = 62$]) compared with epidural analgesia (epidural bolus of 20 mL of 0.1% bupivacaine with fentanyl 2 μg/mL [$n = 53$]).[16] The study was criticized in a letter to the editor because the investigators used a low intrathecal fentanyl dose (5 μg). Most published literature supports the use of intrathecal fentanyl ≥15 μg for labor analgesia.[17] Because intrathecal opioids

have previously been shown to be associated with FHR changes, this particularly low dose of intrathecal fentanyl may explain why no difference was observed. Of note, in this study, *both* the CSE and the epidural groups had significant increases in the incidence of abnormal FHR patterns in the 60-minute interval after initiation of analgesia compared with the 30-minute interval before analgesia ($P < 0.0001$).

Intravenous Labor Analgesia

In randomized controlled trials assessing the effects of epidural labor analgesia, the control group is typically randomly assigned to receive systemic opioid analgesia. However, there is a paucity of data on the effects of systemic opioid labor analgesia or on the effects of one opioid compared with another. A prospective randomized controlled trial compared the analgesic efficacy of IM meperidine 150 mg ($n = 240$) to IM diamorphine 7.5 mg (medical heroin) ($n = 244$) for women in labor.[18] This study was conducted in the United Kingdom where medical diamorphine use is legal. There was no difference in the primary neonatal outcome (need for resuscitation) or 1-minute Apgar score of <7 between groups. Diamorphine provided better pain relief at 60 minutes (mean difference in visual analog scale [VAS] score, 1 cm; 95% CI, 0.5–1.5 [0–10-cm scale]). The average duration of labor (interval from first dose of analgesia to delivery) was 82 minutes (95% CI, 39–124 minutes) longer in the diamorphine group than in the meperidine group. Because labor was longer in the diamorphine group, women in the diamorphine group had greater total pain using an area-under-the-curve assessment (VAS × time). The finding of a difference in the duration of labor between the 2 opioid groups leads one to question whether systemic opioids differentially affect labor progress compared with no analgesia, other opioids, or other forms of analgesia. Further research should evaluate various opioids and means of administration with duration of labor as a primary outcome.

IV remifentanil labor analgesia is not as effective as epidural labor analgesia. A systematic review and meta-analysis compared analgesia efficacy among parturients who received IV remifentanil patient-controlled IV analgesia or epidural labor analgesia.[19] Five randomized controlled trials (RCT) ($n = 886$) were included in the analysis. Epidural analgesia provided superior analgesia as assessed by lower VAS pain scores (0–10-cm scale) at both 1 hour (5 RCTs; Mean Difference [MD] = 1.9 cm; 95% CI, 0.5–3.3; $I^2 = 94\%$) and 2 hours (3 RCTs; MD = 3.0 cm; 95% CI, 0.7–5.2; $I^2 = 89\%$) after initiation of analgesia. Of note, the quality of the evidence as assessed with a Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system at 1 hour was relatively low (because of risk for potential bias) and heterogeneity among trials was high. There were no significant differences in secondary outcomes (nausea, pain, pruritus, umbilical artery pH values, or Apgar scores). Because, of the wide CIs in the pooled results for these secondary outcomes, however, the authors note that definite conclusions cannot be drawn.

CESAREAN DELIVERY

Decision-to-Delivery Interval for Emergency Cesarean Delivery

Traditionally, the goal has been to perform emergency cesarean delivery within 30 minutes of the decision to operate. However, this goal was not based on outcome data. The interval from decision to delivery was the subject of a systematic review and a study. The systematic review and meta-analysis identified 34 studies (22,936 women) reporting decision-to-delivery (or decision-to-incision) intervals for nonelective deliveries.[20] Differences in neonatal outcomes were compared between procedures in which the decision-to-delivery interval was <30 minutes and those in which the interval was >30 minutes. Only 5 of 34 studies were considered to be of high quality; most studies failed to control for the level of urgency or indication for delivery. Overall, delivery within 30 minutes was not achieved in a substantial proportion of cases; 79% of category I (emergency or crash) deliveries and 36% of category 2 (urgent) deliveries occurred within 30 minutes. When analyses were limited to only high-quality studies, 82% overall and 95% of category 1 deliveries were achieved within 30 minutes. Neonatal outcomes (5-minute Apgar scores and umbilical pH levels) were worse when delivery occurred within 30 minutes compared with >30 minutes; however, the authors stressed the importance of confounding. In these emergency situations, it is more likely that infants will be delivered under nonreversible situations (e.g., umbilical cord prolapse) and therefore, short-term neonatal outcomes are likely to be worse. Upon analyzing only the category 1 deliveries, the neonatal outcomes did not differ by delivery interval. The influence of type of anesthesia on the outcome was not assessed.

A single retrospective observational impact study did show improvements in neonatal outcomes with the implementation of a protocol to shorten the decision-to-delivery interval.[21] The authors examined maternal and neonatal outcomes after implementation of an initiative to shorten the interval from decision to delivery for emergency cesarean delivery performed for nonreassuring FHR. Five hundred ninety-four deliveries were evaluated over 54 months at a single academic center in Israel. As part of the protocol, general anesthesia was preferred in all cases unless a neuraxial catheter was already in place. Results indicated a significant decrease in the mean decision-to-delivery interval (21.7 ± 9.1 minutes before implementation and 12.3 ± 3.8 minutes after implementation). Notably, general anesthesia was used significantly more often after implementation and was found to be an independent predictor (by stepwise analysis) of shorter decision-to-delivery intervals. Composite neonatal outcomes were improved, and there was no change in maternal complications after introduction of this management protocol although the study was not adequately powered to assess for maternal airway complications. Although it will be difficult, future studies should assess decision-to-delivery protocols that do and do *not* encourage general anesthesia. In response to a query,[22] the authors emphasized the importance of monitoring decision-to-delivery intervals in all labor units to identify obstacles leading to delays. They further stated that "increasing the availability of anesthesiologists in labor wards, and improving communication between pediatricians and the surgical team remain essential in improving quality in obstetrical units."

Anesthesia for Cesarean Delivery

Anesthetic requirements are lower in pregnancy. However, *why* this is true has not been fully elucidated. A study by Lee

et al.[23] investigated this topic. Venous blood progesterone levels were assessed in 90 women at >36 weeks of gestation before their scheduled cesarean delivery under general anesthesia. Anesthesia was induced with thiopental and rocuronium and maintained with sevoflurane and nitrous oxide titrated to blood pressure, heart rate, and bispectral index (BIS). Patient-controlled IV analgesia with a solution of morphine, ketorolac, and ondansetron was used for postoperative analgesia. There was a negative correlation between sevoflurane consumption and serum progesterone levels (Pearson correlation $r = -0.26$; 95% CI, −0.44 to −0.05; $P = 0.01$) as well as between postoperative analgesic consumption at 2 ($r = -0.20$; $P = 0.05$), 24 ($r = -0.25$; $P = 0.02$), and 48 ($r = -0.28$; $P = 0.01$) hours and progesterone levels. Furthermore, women with progesterone levels greater than the median value had lower sevoflurane consumption per hour ($P = 0.02$) and lower 48-hour postoperative cumulative analgesic consumption ($P = 0.02$) than women with progesterone levels less than the median value. Therefore, the higher a woman's progesterone levels, the lower were her intraoperative anesthetic and postoperative analgesic requirements. This study not only begins to quantify progesterone's anesthetic and analgesic effects, but also leads one to question the possible therapeutic benefits of progesterone in postsurgical pain control.

Intraoperative Awareness

Intraoperative awareness may be a more significant problem in obstetric anesthesia than previously thought. The 5th National Audit Project (NAP5) of the Royal College of Anaesthetists and the Association of Anaesthetists of Great Britain and Ireland prospectively assessed intraoperative awareness under general anesthesia.[24–26] The study involved 269 coordinators in 329 U.K. hospitals and 41 coordinators in 46 Irish hospitals who provided reports of intraoperative awareness under general anesthesia at their hospitals. The NAP5 panel met monthly, reviewed cases and classified them according to likelihood of true awareness under general anesthesia. The estimated denominator, obtained during the 4th National Audit Project, was 2.8 million general anesthetics. In the NAP5, the incidence of awareness was approximately 1 in 19,000 general anesthetics, with the most pessimistic estimate being 1 in 6000 general anesthetics. The most overrepresented surgical specialty was obstetrics with 12 cases of certain, probable, or possible accidental awareness in 8000 cesarean deliveries under general anesthesia, an incidence of 1:670 (95% CI, 1:380 to 1300).[25] The investigators indicated that the incidence of awareness in obstetrics was associated with the presence of a number of risk factors such as rapid sequence induction of anesthesia, omission of opioids at induction, difficult airway management, obesity, use of neuromuscular-blocking agents, a short time period between anesthetic induction and surgical incision, emergency surgery, and off-hour surgery resulting in higher rates of nonconsultant anaesthetist care.

A prospective study evaluated depth of anesthesia in cesarean delivery by studying the relationship between BIS values and patient responses to the isolated forearm technique.[27] This technique involves inflating a forearm blood pressure cuff to 200 mm Hg during and after induction of anesthesia to isolate the forearm muscles from the effects of neuromuscular-blocking agents. Earphones are placed in the patient's ears and the patient is told to "open and close your right hand" every 30 seconds for 20 minutes during and after induction. Hand movement is recorded. After an induction using thiopental 4 to 5 mg/kg and succinylcholine 1 to 2 mg/kg, followed by inhaled 50% nitrous and 1.8% to 2.2% end-tidal sevoflurane, 41%, 46%, and 23% of parturients had positive isolated forearm test results at laryngoscopy, intubation, and skin incision, respectively. BIS could not reliably differentiate the forearm test responders and nonresponders during these times. However, no patients had evidence of recall during a structured interview performed 12 to 24 hours postoperatively. Both this study and the NAP5 work expose the current lack of knowledge regarding anesthetic requirements in pregnant women. Further studies are necessary to prevent future cases of intraoperative awareness during cesarean delivery under general anesthesia.

Supplemental Oxygen Administration

Prior work has shown that maternal oxygen administration for women undergoing elective cesarean delivery with neuraxial anesthesia increases oxygen free radical activity in both the mother and in the fetus.[28] Some obstetric anesthesiologists, therefore, have questioned whether maternal supplemental oxygen administration by nasal cannula or face mask should be routinely administered during cesarean delivery under neuraxial anesthesia. The results of one study suggested that there is little fetal/neonatal benefit of oxygen administration to nonhypoxemic mothers.[29] The effects of maternal oxygen administration on fetal oxygenation were evaluated by magnetic resonance imaging (MRI) in 9 healthy volunteer pregnant women at 21 to 33 weeks of gestation. Five nonpregnant adults were also enrolled in the study. During MRI, the gas administered via face mask to subjects was changed from medical air (21% oxygen) to medical oxygen (100% oxygen). Tissue oxygenation alters the magnetic longitudinal relaxation time, T1, in the brain and in other tissue, and this was monitored over time in the placenta, the fetal brain, and the adult brain using a periodically repeated MRI sequence. The nonpregnant and pregnant adults had MRI changes in their brain with oxygen administration. Although significant placental changes were seen with the maternal oxygen administration, the authors found no significant changes in the fetal brains. The authors conclude that short-term maternal oxygen administration does not improve fetal brain oxygenation in utero. This implies little fetal benefit of oxygen administration to a nonhypoxemic mother.

A review article questioned whether supplemental oxygen should be used as an adjuvant to intrauterine fetal resuscitation in nonhypoxemic laboring women.[30] The review found that only 2 randomized trials have investigated the use of maternal oxygen supplementation in laboring women, and neither study found benefit to the fetus. The authors propose that maternal oxygen supplementation in labor should be reserved for maternal hypoxemia. Maternal supplemental oxygen administration as a therapy for nonreassuring fetal status in labor is deeply entrenched in obstetric practice, and more research will be needed in this area before practice change will occur.

Spinal Anesthesia Hypotension: Fluid Bolus

A fluid bolus administered before (preload) or at the time of initiation of (co-load) spinal anesthesia is a routine part of spinal anesthesia for cesarean delivery. A multicenter double-blind study found that 6% hydroxyethyl starch preload is more effective than saline in preventing hypotension.[31] Women undergoing elective cesarean delivery were randomly allocated to receive a preload of either 500 mL of 6% hydroxyethyl starch (n = 82) or 1000 mL lactated Ringer's solution (n = 85). All women received phenylephrine bolus doses between 50 and 150 μg, depending on the percent decrease in systolic blood pressure from baseline. The primary outcome was the incidence of systolic arterial pressure <80% of baseline. Although there was no significant difference in total phenylephrine requirements, the incidence of hypotension was significantly lower in the hydroxyethyl starch group (36.6% vs 55.3%; P = 0.025), as was the incidence of symptomatic hypotension (3.7% vs 14.1%). The use of various starches has been criticized because of coagulation and renal impairment in a number of patient populations. However, in this healthy obstetric population, there were no differences between study groups from baseline to postoperative day 1 in plasma hemoglobin, activated partial thromboplastin time (aPTT), prothrombin time (PT), platelet count, or plasma creatinine. Six umbilical cord blood samples did not detect any hydroxyethyl starch in the neonatal blood, and neonatal outcomes were comparable.

A group of investigators performed an intriguing study assessing the effects of crystalloid preload bolus on the endothelial glycocalyx in patients preparing for a cesarean delivery.[32] The glycocalyx is a network of negatively charged proteoglycans and glycoproteins that is bound to the luminal membrane of endothelial cells. In the past decade, scientists have discovered that the glycocalyx acts as a vascular permeability barrier. It also inhibits coagulation within the blood vessels, prevents leukocyte adherence to the blood vessel wall, and mediates shear stress-induced nitric oxide release from the endothelium. If these proteins get disrupted from the endothelial cells, the function of the glycocalyx and also the endothelium diminishes, and the biomarkers can be detected in plasma.

In this study, investigators assessed baseline endothelial glycocalyx biomarkers in venous blood and then administered 750 mL warm lactated Ringer's solution to healthy parturients in the preoperative holding area. This was followed by postinfusion reassessment of the biomarkers as well as cardiac parameters via thoracic impedance cardiography. There was a significant increase in the endothelial glycocalyx biomarkers heparan sulfate (P = 0.0098) and syndecan-1 (P = 0.045) between the baseline and postinfusion assessments, indicating that a prophylactic fluid bolus disrupts the endothelial glycocalyx. Of note, atrial natriuretic peptide remained unchanged (P = 0.29) and cardiac parameters changed only slightly; cardiac index increased over time by 2.2×10^{-3} L minutes/m^2 (95% CI, 0.1×10^{-3} to 3.5×10^{-3}; P = 0.0005), and systemic vascular resistance decreased over time by −0.5 dyn.s/cm^5 per 15-second interval (95% CI, −0.8 to −0.2; P = 0.0025). The authors conclude that "because of the endothelial glycocalyx's importance in modulating transvascular fluid exchange, the potential disruption of (it)… may be counterproductive with respect to maintaining intravascular volume in normovolemic parturients." Further research is necessary to determine whether the disruption of the glycocalyx demonstrated in this study has any adverse clinical implications. Designing studies that show meaningful outcome differences with various fluid administration protocols will be the challenge to pursuing this line of research.

Spinal Anesthesia Hypotension: Prophylactic Phenylephrine

In the past decade, phenylephrine has become the drug of choice for preventing and treating spinal anesthesia-associated hypotension in women undergoing cesarean delivery. A systematic review emphasized that prophylactic phenylephrine is remarkably effective in preventing spinal hypotension.[33] The review included 21 randomized controlled trials (n = 1504) that compared (1) a prophylactic phenylephrine infusion to a placebo infusion, (2) a prophylactic phenylephrine infusion to an ephedrine infusion, or (3) a prophylactic phenylephrine infusion to a phenylephrine *plus* ephedrine infusion. The primary outcome was the incidence of maternal hypotension (defined as a systolic blood pressure [SBP] <80% baseline in all but 5 studies). The authors found that a prophylactic phenylephrine infusion reduced the risk of hypotension compared with all 3 comparator groups: placebo infusion (relative risk, 0.36; 95% CI, 0.18–0.73; P = 0.004), ephedrine infusion (relative risk, 0.58; 95% CI, 0.39–0.88; P = 0.009), and a combined phenylephrine *plus* ephedrine infusion (relative risk, 0.73; 95% CI, 0.55–0.96; P = 0.02). Prophylactic phenylephrine infusions also reduced the risk for nausea and vomiting. The remarkable efficacy of a prophylactic phenylephrine infusion in preventing spinal hypotension is likely why many obstetric anesthesia practices have embraced the practice.

Given the efficacy of phenylephrine in preventing and treating hypotension, the optimal method of administration has been examined. Proposed methods include prophylactic infusion, prophylactic bolus, or rescue bolus. A group of investigators studied this question by randomizing 80 patients to receive (1) a variable-rate phenylephrine infusion (titrated to arterial blood pressure and heart rate) with rescue phenylephrine boluses or (2) no phenylephrine infusion and just rescue phenylephrine boluses.[34] The primary outcome, the number of rescue phenylephrine boluses, was less in the phenylephrine infusion group. The secondary outcomes showed that the phenylephrine infusion group had a far lower incidence of hypotension (8 of 40 [20%] vs 35 of 39 [90%]; P < 0.001), a lower incidence of nausea and vomiting (4 of 40 [10%] vs 17 of 39 [44%]; P = 0.001), but a greater incidence of hypertension (6 of 40 [15%] vs 0 of 30 [0%]; P = 0.026).

This article was accompanied by an editorial by Ngan Kee,[35] one of the pioneers of phenylephrine infusions for cesarean delivery. The editorial pointed out that the debate has shifted from *whether* we should use phenylephrine to *how* we should use it. Ngan Kee suggested that practices, patients, clinical scenarios, and providers are different and, that in normal clinical practice, the strict protocols that are performed in studies are not necessary. Instead, he recommended an initial phenylephrine infusion rate at the time

of intrathecal injection of 50 μg/min or 0.75 μg/kg/min, followed by titration of the infusion based on blood pressure and heart rate. He went on to state that anesthesia providers should develop a phenylephrine regimen based on their local experience that provides an acceptable balance between the elimination of maternal symptoms and the risks of hypertension and bradycardia.

Postcesarean Oxytocin Protocols

Oxytocin is routinely administered for third-stage labor as prophylaxis for uterine atony. Some experts have called for protocol-driven administration of postcesarean delivery oxytocin because of oxytocin's therapeutic ceiling as well as its side effects, specifically, a profound decrease in systemic vascular resistance as well as ST-segment depression and chest pain. Such protocols place a limit on maximal oxytocin dose and control the timing and rate of infusion of oxytocin after delivery. An impact study compared the estimated blood loss, vasopressor administration, and supplemental uterotonic use before and after the implementation of a postcesarean oxytocin infusion protocol.[36] Data from 901 cesarean deliveries revealed that total intraoperative oxytocin preprotocol was 20 U (interquartile range, 20–30 U) and postimplementation was 12.5 U (interquartile range, 9–18 U) (difference in medians, 8.4 U; 95% CI, 7.4–9.4 U; $P < 0.001$). There were no differences in vasopressor administration, estimated blood loss, or supplemental uterotonic use. The authors concluded that an oxytocin management protocol reduced the amount of intraoperative oxytocin without increasing the rate of postpartum hemorrhage or the need for additional uterotonic agents. The next step in studying the usefulness of postcesarean oxytocin protocols is to determine whether this reduction of overall oxytocin administration provides meaningful outcome benefits to the mother.

Cesarean Delivery Postoperative Pain: TAP Blocks

TAP blocks were introduced into obstetric anesthesia practice with great enthusiasm; however, they may not benefit all patients. In agreement with previous work, another study showed that ultrasound-guided TAP blocks do not provide postpartum benefit to women undergoing cesarean delivery who receive multimodal analgesia that includes intrathecal morphine.[37] Furthermore, 2 additional cases of generalized tonic-clonic seizures attributed to local anesthetic systemic toxicity in obstetric patients who received ultrasound-guided TAP blocks for postcesarean analgesia were reported.[38] One patient weighed 56 kg; 20 mL of plain 0.375% levobupivacaine was injected on each side (total 150 mg or 2.68 mg/kg). The patient experienced a seizure 10 minutes after injection. The second patient weighed 61 kg; 20 mL of plain 0.75% ropivacaine was injected on each side (total 300 mg or 4.9 mg/kg). This patient experienced a seizure 25 minutes after injection. Both cases were treated successfully with lipid emulsion, and both cases were thought secondary to systemic absorption, the first as a result of IM injection and the second from overdose. Similarly, a randomized trial of TAP block compared with continuous wound infusion for postcesarean analgesia was terminated early after a study subject in the TAP block group experienced a generalized tonic-clonic seizure "a few minutes" after ultrasound-guided TAP block.[39] Women in the TAP block group received bilateral ultrasound-guided injections with 20 mL of 0.375% levobupivacaine (total 150 mg). A 2013 study found that TAP blocks for postcesarean analgesia using 2.5 mg/kg ropivacaine resulted in plasma ropivacaine concentrations, which exceeded the potentially toxic threshold of 2.2 μg/mL in 12 of 30 patients.[40] Toxic levels of local anesthetic have also been identified in nonobstetric patients who receive TAP blocks.[41] Further study is required to determine the optimal concentration/dose of local anesthetic for TAP blocks that maximizes analgesia and minimizes the risk of local anesthetic systemic toxicity.

CONCLUSIONS

Providing analgesia for labor and anesthesia for cesarean delivery is common practice for most anesthesiologists. Every year, the field of obstetric anesthesiology discovers ways for anesthesiologists to perform this work more safely and effectively with improved patient satisfaction. Staying abreast of progress in the field allows us to better care for mothers and their babies. Each year, the Ostheimer Lecture at the annual SOAP meeting provides a means for anesthesiologists to efficiently do so.

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