Why Question Established Practice?

Francis M. James III, M.D.*


Abstract: During hypotension resulting from conduction anesthesia in gravid ewes, uterine blood flow (UBF) decreased roughly in proportion to the decrease in maternal blood pressure. Ephedrine or mephentermine significantly increased UBF over that accomplished by metaraminol. Presumably, the preferential effects of these agents were the result of increased cardiac output owing to inotropic and chronotropic actions. However, UBF never exceeded 90% of prespinal levels with any vasoactive agent, and, for a given maternal system, the UBF response was variable, generally increasing but frequently remaining constant or decreasing. For these reasons, all other methods of combating hypotension should be used initially. If vasopressors are still required, agents of choice are those whose principal mode of action lies in cardiac stimulation rather than peripheral vasoconstriction.

Hypotension presents significant problems during spinal anesthesia for cesarean section. Mothers experience associated nausea and vomiting, and legitimate concern arises regarding presumed decreases in uterine blood flow (UBF) and potential fetal compromise. In addressing this issue, Frank C. Greiss, Jr. M.D., Richard A. Kemp, M.D., and I explored the efficacy of several vasopressors and found those with significant β-agonist properties more effectively improved UBF. How did I become involved in this influential study, and what lessons does it offer today?

A month-long rotation on the obstetric service as an intern at Philadelphia General Hospital and 2 yr spent delivering babies as a general medical officer in the United States Air Force ignited my initial interest in obstetric anesthesia. That interest grew during a residency and 1 yr on the faculty
of the Department of Anesthesia at the Hospital of the University of Pennsylvania. Knowing that Frank Greiss, an obstetrician, was on the faculty at the Bowman Gray School of Medicine (BGSM) influenced my decision to accept the 1968 invitation from Thomas H. Irving, M.D., to join him in the Section of Anesthesia in Winston-Salem. At the 78th Annual Meeting of the American Gynecological Society in May 1955, Frank R. Lock, Sr., M.D., chair of Obstetrics and Gynecology at BGSM, presented a lecture on maternal deaths related to anesthesia (personal communication, Frank C. Greiss, M.D., February 2012). Lock and Greiss published the lecture in the American Journal of Obstetrics and Gynecology and noted that spinal shock caused 25.4% of maternal deaths because of anesthesia, whereas the aspiration of gastric contents produced 24.5%. Stimulated by Lock’s work, Greiss became interested in the problems associated with anesthesia, and began to investigate uterine blood flow during spinal anesthesia. He employed a pregnant sheep model in his studies. In 1965, Greiss and D. LeRoy Crandell, M.D., head of the Section of Anesthesia, reported that spinal anesthesia decreased UBF and rapidly infusing intravenous fluid improved UBF more effectively than vasopressor therapy with norepinephrine, phenylephrine, or angiotensin amide. Upon my arrival at BGSM, now the Wake Forest School of Medicine, Tom Irving granted me 1 day a week to work in Greiss’s laboratory. The first study on which Greiss and I collaborated helped to cement ephedrine as the vasopressor of choice to restore maternal blood pressure and UBF when hypotension occurred during spinal anesthesia.

The square wave electromagnetic flowmeter (EMF) manufactured by the Carolina Medical Electronic Company in Winston-Salem enabled UBF to be monitored. This device evolved from the interest of Merrill Spencer, M.D., a member of the Department of Physiology at BGSM, in renal blood flow in humans and in how the giraffe maintained cerebral blood flow upon rapidly raising its head to an erect position after drinking, a distance of 10 m. Spencer and John Kiger, a technician at the Western Electric Company in Winston-Salem, both sang in the choir of their church and the idea of the EMF evolved from their choir loft conversations. They enlisted the help of Adam B. Denison, M.D., in the research laboratory. These activities fostered a positive relationship. Both departments benefited from our positive relationship.

Until the last few decades of the 20th century, general anesthesia was often the method of choice for cesarean section. In the 1960s, approximately 2,500 women in the United States were dying of causes related to childbirth, with 10% of these women dying from obstetrical anesthesia. Anesthesia ranked as the sixth leading cause in a series of 2,065 maternal deaths reviewed by Kaunitz in 1985. Failed tracheal intubation, the aspiration of gastric contents, maternal awareness, and respiratory depression of the newborn during surgery all represented problems associated with general anesthesia. Maternal hypotension frequently accompanied spinal and epidural anesthesia. Intravenous fluid administration, left uterine displacement, and vasopressor therapy all served to prevent and treat hypotension during regional anesthesia. The question was which type of vasopressor most effectively combated maternal hypotension and the accompanying decrease in UBF. Both maternal and fetal outcome had to be considered. Our animal study of ephedrine, mephentermine, and metaraminol indicated that ephedrine and mephentermine provided better restoration of UBF (fig. 1); whereas Shnider et al. reported that ephedrine decreased acidosis and corrected fetal bradycardia after restoration of blood pressure in gravid ewes. Additional laboratory studies supported the efficacy of ephedrine with its mixed α and β effects over pure α-acting agents such as phenylephrine. For decades ephedrine remained the vasopressor of choice to counter maternal hypotension during spinal and epidural anesthesia. Ephedrine proved successful in combating maternal hypotension, and newborn outcome was favorable. However, debate and research continued to
develop regional anesthesia for cesarean section. α and β agonists were investigated using a variety of dose ranges and bolus versus continuous infusion methods to prevent and to treat maternal hypotension.

During the last 15 yr, multiple studies in humans have demonstrated that both ephedrine and phenylephrine are effective, but the latter seems to more reliably prevent maternal nausea and vomiting while producing measurably better newborn status. In 2009, Ngan Kee et al. studied 102 women and found that ephedrine crossed the placenta more readily than phenylephrine and was associated with both lower fetal pH and base excess values. Ephedrine resulted in higher uterine artery and uterine vein lactate levels and greater uterine artery and uterine vein lactate levels. Ephedrine resulted in higher fetal pH and base excess values. Ephedrine resulted in higher uterine artery and uterine vein lactate levels and greater uterine artery and uterine vein lactate levels. Ephedrine resulted in higher fetal pH and base excess values.

Fig. 1. Comparison of variations of uterine blood flow (UBF) responses. Light lines describe curves of two standard deviations around the mean response, or heavy lines. With ephedrine and mephentermine, UBF rarely decreased below spinal hypotensive levels. With metaraminol, UBF frequently decreased further during therapy. Reprinted with permission from James FM III, Griess FC, Kemp RA: An evaluation of vasopressor therapy for maternal hypotension during spinal anesthesia. Anesthesiology 1970; 33:25–34.

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References