

# Obstetric Anesthesia CME Program

## Module 2

### **Editorial Comment from Patricia Dailey, M.D., Associate Editor:**

Many of us trained when the use of phenylephrine in pregnant patients was verboten and the drug of choice to treat hypotension was ephedrine. This is no longer dogma, as you will see in the following article. Is ephedrine or phenylephrine considered the preferred drug for treating hypotension following spinals and epidurals? The most recent ASA Practice Guidelines for OB Anesthesia<sup>1</sup> say: "Intravenous ephedrine and phenylephrine are both acceptable drugs for treating hypotension during neuraxial anesthesia. In the absence of maternal bradycardia, phenylephrine may be preferable because of improved fetal acid-base status in uncomplicated pregnancies." Based on the opinions of consultants and practitioners surveyed in 2006 by the ASA task force, both drugs were acceptable. However, the consultants preferred phenylephrine, while the practitioners preferred ephedrine.

CSA now is offering its second CME program. This program's topic is obstetric anesthesia and consists of four modules. This second module appears in this issue of the *Bulletin*. The first module was offered in the last issue of the *Bulletin*, and the next two modules will appear in the following two issues.

Mark Rosen, M.D., editor and chair of this program, is professor and vice chair and director of the residency training program at the University of California San Francisco. He also is professor of obstetrics, gynecology and reproductive sciences, and director of obstetric anesthesia at UCSF.

**Registration:** The registration page and test questions for this module are at the end of this article. The 10 questions must be answered and submitted to the CSA in order to receive the CME credit. Your CME certificate will be mailed from the CSA office.

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Alternatively, the full text of each module of this CME program, along with references, will be accessible through the CSA Web Site, [www.csahq.org](http://www.csahq.org), in the Online CME Program section, and as part of the online *CSA Bulletin*. To complete Module 2 online, please read and study the text, complete the self-assessment and the evaluation, and then print your CME certificate. Members will need their usernames and passwords to do the modules online.

**Fees:** This is a free service for CSA members. Nonmembers will be charged \$25 per CME credit hour.

<sup>1</sup>Practice Guidelines for Obstetric Anesthesia: An Updated Report by the American Society of Anesthesiologists Task Force on Obstetric Anesthesia. *Anesthesiology* 106(4): 843-863, April 2007.

## Ephedrine (cont'd)

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**Availability:** This module is available from June 30, 2007, until June 30, 2010.

**Target Audience:** This program is intended for all licensed physicians, including anesthesiologists, residents, and physicians with an interest in obstetric anesthesia.

### Faculty and Disclosures for Module 2:

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All faculty participating in continuing medical education activities sponsored by the California Society of Anesthesiologists are required to disclose any real or apparent conflict(s) of interest related to the content of their presentation(s) or any of the industry sponsors. In addition, speakers must disclose when a product is not labeled for the use under discussion or when a product is still investigational.

Dr. Riley discloses that he has received stock from Indigo Orb, Inc. for his role as the Medical Director of the company and grants from SkyePharma for conducting clinical trials. Neither of these companies has an interest in the topic discussed here. Dr. Macarthur has no conflicts of interest with regard to this topic.

**CME Sponsor/Accreditation:** The California Society of Anesthesiologists is accredited by the Accreditation Council for Continuing Medical Education to sponsor continuing medical education for physicians.

The California Society of Anesthesiologists Educational Programs Division designates this educational activity for a maximum of 1 *AMA PRA Category 1 Credit*<sup>TM</sup>.

**Evaluation:** An evaluation of Module 2 of this series is offered after the test questions. Please fill in your responses and return them to the CSA office. If you choose to do the self-assessment on the CSA Web Site, you may complete the evaluation of Module 2 online also.

**Objectives:** Upon completion of this activity, participants will be able to:

- Describe research that led to ephedrine becoming the preferred vasopressor in obstetric patients

- Comprehend recent clinical research demonstrating the association of ephedrine use with decreases in fetal pH values
- Analyze whether ephedrine should still be used for treatment of hypotension in pregnant women
- Appreciate that aggressive treatment of hypotension is best for the neonate
- Describe methods of phenylephrine use for treatment of hypotension in pregnant women

**Resources:** These materials, including questions, are offered on the CSA Web Site at [www.csaqh.org](http://www.csaqh.org). Instructions for the *Bulletin* version are on the registration page.

# Ephedrine Is No Longer the Drug of Choice for Treating Hypotension in the Pregnant Patient

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## Introduction

For many years, ephedrine had been the preferred vasopressor for treatment of regional anesthesia-induced hypotension in obstetric patients, yet more recently it has fallen out of favor. The story behind this transition shows that clinical research is invaluable and indispensable before a treatment option becomes accepted as a practice standard.

## Ephedrine (cont'd)

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In the pregnant ewe model, ephedrine was demonstrated to better preserve uterine blood flow compared with other vasopressors. In addition, laboratory studies of isolated artery segments supported the choice of ephedrine as the recommended vasopressor for use during pregnancy. With strong evidence from the laboratory, ephedrine use was widely adopted and became the favored vasopressor in obstetrical anesthesia practice. However, in the past 10 years, mounting clinical data suggest ephedrine should not be the preferred vasopressor, and, what's more, some data suggest it may be undesirable for the fetus. In this module we will review this history and make recommendations about management of hypotension in the pregnant patient.

### Animal Studies

In the 1970s and 1980s, leading researchers in obstetric anesthesia (Sol Shnider, David Chestnut, Frank James) used the chronically instrumented pregnant ewe model to study the effect of various vasopressors on uterine blood flow and fetal pH for treatment of hypotension induced by spinal anesthesia. Their work had consistent results, finding that ephedrine conserved uterine blood flow, caused little change in uterine vascular resistance, and helped restore fetal pH.<sup>1,2</sup> Other pressors (e.g. metaraminol, phenylephrine) consistently decreased uterine blood flow, increased uterine artery resistance, and tended to decrease fetal pH. In a classic study by Ralston et al, various vasopressors were used to raise blood pressure 60 percent above baseline. Under these conditions, methoxamine lowered uterine blood flow by 70 percent, yet ephedrine maintained normal uterine blood flow.<sup>1</sup>

Later, in the 1990s, mechanistic studies demonstrated why ephedrine raised blood pressure without causing uterine artery vasoconstriction. Tong et al.<sup>3</sup> used arterial vascular rings excised from pregnant and nonpregnant ewes. All pressors caused substantial femoral artery vasoconstriction. However, there was relatively little vasoconstriction of the uterine artery in the pregnant ewe compared with the nonpregnant ewe. This differential effect was particularly pronounced with ephedrine. Li et al.<sup>4</sup> demonstrated that nitric oxide synthase activity was increased in uterine artery endothelium of pregnant ewes compared with nonpregnant ewes. Ephedrine stimulated release of nitric oxide synthase, leading to uterine arterial vasodilation, despite causing systemic arterial vasoconstriction. Release of nitric oxide synthase by ephedrine, more than other pressors, accounts for its beneficial effect of preserving uterine blood flow.

### Human Studies

Based on the overwhelming evidence from animal models, ephedrine was adopted as the preferred vasopressor in obstetric anesthesia. Animal data were so strong that an early clinical study implicating ephedrine was largely ignored. Wright et al.<sup>5</sup> demonstrated that ephedrine administration to laboring women caused dose-related changes in the fetal heart rate pattern (tachycardia, increased variability), possibly indicative of fetal stress or an increase in fetal metabolic activity. However, the authors continued to recommend ephedrine for treatment of hypotension in pregnant women due to the overwhelming animal data supporting its superiority.

In a series of studies of *prophylactic* ephedrine administration to *prevent* hypotension associated with spinal anesthesia for cesarean delivery, investigators concluded that large doses were required. These studies were among the first real blows to the overall acceptance of ephedrine as the drug of choice.<sup>6-8</sup> Large dose administration of ephedrine was associated with umbilical cord blood gas values that were more acidotic compared to fetuses whose mothers were managed with less ephedrine and allowed to have more hypotension. This led to the practice of using ephedrine judiciously for treatment of hypotension, ensuring blood pressure did not elevate above baseline levels.

While some investigators looked at *prophylactic* ephedrine administration, others conducted clinical studies comparing ephedrine to phenylephrine for *treatment* of hypotension from spinal anesthesia for cesarean delivery. The results of these studies were puzzling in light of the animal studies, showing lower pH values in the umbilical cord blood from the groups treated with ephedrine (well summarized by Lee et al. in a meta-analysis<sup>9</sup>). Although the differences were small (0.02 to 0.06 pH units), outcomes always favored the phenylephrine treatment groups.

Some would argue that a small respiratory acidosis is not sufficient to cause fetal harm. However, Lee et al. showed that ephedrine not only caused decreases in umbilical artery blood pH; it also caused an increase in base deficit.<sup>10</sup> This led to the conclusion that, although ephedrine may be safe most of the time, it had a potentially adverse effect on the fetus.

Co-administration of phenylephrine was another approach to decrease ephedrine dose, yet maintain the theoretical advantage of less uterine artery vasoconstriction. Using this strategy, outcomes (as measured by umbilical artery blood gas values) were more favorable compared to use of ephedrine alone,<sup>11,12</sup> yet no different than use of phenylephrine alone.<sup>12</sup> Since co-administration was more complicated than single-agent administration, this practice was never widely adopted.

### Mechanism of Ephedrine Causing Acidosis

Why would ephedrine cause more fetal acidosis than other pressors if it were indeed doing a better job of preserving uterine blood flow? The answer may be that ephedrine causes a metabolic acidosis in the human fetus. Is this possible? Cooper and colleagues compared ephedrine and phenylephrine for treatment of maternal hypotension,<sup>12,13</sup> and, consistent with other recent studies, they found ephedrine caused more fetal acidosis. A unique aspect of this study was quantitative evaluation of umbilical vessel blood acidosis. They calculated the difference between  $p\text{CO}_2$  in the umbilical artery and umbilical vein ( $p\text{CO}_2$  (art–vein)). Small values for  $p\text{CO}_2$  (art–vein) indicate poor placental perfusion or gas exchange. For example, conditions such as placental abruption have a small  $p\text{CO}_2$  (art–vein). Large values for  $p\text{CO}_2$  (art–vein) suggest acidosis secondary to a process in the fetus. Cooper and colleagues found a strong correlation between ephedrine use and increased  $p\text{CO}_2$  (art–vein). From these data they concluded that ephedrine stressed the fetus and contributed to fetal acidosis.

Besides changes in fetal pH, is there other evidence that ephedrine can cause metabolic derangement in humans? Actually, the subject is not well studied. We know that maternal administration of terbutaline can cause a hypermetabolic state in the fetus.<sup>13</sup> Also, we have indirect evidence that ephedrine can cause hypermetabolic states. In the four most recent cases of athletes dying from heat stroke, all had evidence of ephedrine use.<sup>14</sup> In addition, ephedra or *Ma Huang*, a common herbal medication containing ephedrine, accounted for 64 percent of emergency room visits related to herbal medicines in 2001.<sup>15</sup> Most of the untoward side effects were related to indices of a hypermetabolic state (e.g., tachycardia, hyperthermia, etc.).

### Clinical Significance

Are these small changes in arterial blood gas values of any clinical significance? No study reveals detrimental long-term outcomes associated with fetal exposure to maternal ephedrine administration and the associated lower umbilical artery pH. So, what are deleterious umbilical artery pH values, and more importantly, umbilical artery base deficits? When should we be concerned that acidotic intrapartum conditions are responsible for long-term, deleterious neonatal outcomes? In 1999, a consensus paper of the American, Canadian, and Australian obstetric societies defined the evidence required to associate a significant intrapartum asphyxial event as severe enough to cause neonatal neurological injury.<sup>16</sup> The committee concluded that such associations were unlikely without umbilical artery pH values less than 7.0 and base deficit values more than 12 mmol/L. In studies to date, conducted on healthy women

## Ephedrine (cont'd)

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and fetuses undergoing uncomplicated elective cesarean delivery, ephedrine use is seldom associated with umbilical artery pH and base deficit values in these ranges.

Based on studies to date, we can conclude that use of ephedrine is unlikely to adversely impact long-term outcome for the normal mother, placenta and fetus. However, the effect of either ephedrine or phenylephrine on the compromised fetus remains unknown. Datta and Brown<sup>17</sup> showed that umbilical artery pH was only slightly decreased after cesarean delivery among healthy mothers who experienced transient hypotension secondary to their spinal anesthetic. However, among infants of diabetic mothers who developed similar degrees of hypotension, umbilical artery pH decreased to clinically significant levels. It is possible that situations in which the healthy fetus would be fine, the compromised fetus would benefit by avoiding an agent that decreases pH values. Given the current knowledge, we *believe* it's best to avoid use of ephedrine in the pregnant patient.

### Blood Pressure Management

Given the above data, how should we manage blood pressure for women undergoing spinal anesthesia for cesarean delivery? In an important study, Kee et al. concluded that maintaining homeostasis led to the best outcome.<sup>18</sup> In this study, maternal arterial pressure was maintained at 80 percent, 90 percent or 100 percent of baseline. Maintaining arterial pressure at 100 percent of baseline was associated with the best outcome for the baby (highest umbilical artery pH values) and the mother (less nausea). To maintain blood pressure at baseline values, Kee et al. used large doses of phenylephrine (up to 2000 mcg before delivery of the fetus). These large doses were associated with better fetal outcomes and without significant maternal reflex bradycardias.

### Pharmacology of Ephedrine and Phenylephrine

Ephedrine has both indirect and direct actions on the sympathetic nervous system. Its indirect effects are due to the stimulation of postganglionic sympathetic nerve endings, which cause norepinephrine release. Release of norepinephrine primarily stimulates beta-1 and alpha-1 receptors. Ephedrine has a weak direct effect on receptors. This direct effect provides ephedrine with some beta-2 receptor activity.

Phenylephrine has a direct effect on the alpha-1 receptor with no beta effect at all. Its effect on the venous circulation is somewhat greater than the arterial circulation. Blood pressure is increased by both an increase in pre-load as well as an increase in after-load. Compensatory reflex bradycardia can result when blood pressure is elevated above baseline.

## Ephedrine (cont'd)

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Elimination of phenylephrine is by the same mechanism as other catecholamines (catchol-O-methyltranserease and monamine oxidase). Phenylephrine is rapidly metabolized, and best administered as an infusion or by repeated boluses of 25 to 100 mcg every one to five minutes. On the other hand, ephedrine is excreted unchanged in the urine and eliminated from the site of effect by reuptake into nerve terminals. In obstetric anesthesia, ephedrine is typically administered intravenously, and more rarely by intramuscular injection.

### Clinical Use in Obstetric Anesthesia

The easiest way to use phenylephrine is by small frequent boluses of 25 to 50 mcg administered in response to any blood pressure decrease after spinal anesthesia is initiated. At Stanford, for cesarean section, we set the automatic blood pressure cuff to cycle every minute immediately after spinal drug administration. We then give a bolus of phenylephrine any time there is a 10 percent decrease in blood pressure relative to the preoperative baseline blood pressure. An alternative is use of an infusion. Kee et al. reported considerable success in avoiding hypotension by use of a phenylephrine infusion of 100 mcg/min titrated to changes in blood pressure.

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## Ephedrine (cont'd)

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### Obstetric Anesthesia CME Program

In this issue of the *Bulletin*, Module 2 of the new Obstetric Anesthesia CME Program is available. Modules 1 through 4 will be available on the CSA Web Site [www.csaHQ.org](http://www.csaHQ.org). The online module is a self-assessment where you can complete the test and evaluation, and then print your CME certificate right then. You also may contact the CSA office at 800-345-3691, and we will send you the materials by fax or mail.

**Registration**

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Available June 30, 2007, to June 30, 2010

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## Questions

1. Ephedrine is eliminated from site of effect by:
  - a. Hepatic elimination
  - b. Renal clearance
  - c. Monamine oxidase metabolism
  - d. Nerve terminal reuptake
  - e. Pseudocholinesterase metabolism
  
2. Phenylephrine is a:
  - a. Weak alpha-2 agonist
  - b. Strong alpha-1 agonist
  - c. Weak vasoconstrictor
  - d. Strong beta-1 agonist
  - e. Weak beta-1 antagonist
  
3. In the pregnant ewe model:
  - a. Ephedrine decreases umbilical blood flow
  - b. Phenylephrine decreases uterine artery resistance
  - c. Ephedrine maintains uterine blood flow
  - d. Phenylephrine increases pH
  - e. Ephedrine lowers fetal pH
  
4. In humans, use of intravenous ephedrine in small doses after spinal anesthesia:
  - a. Prevents hypotension
  - b. Avoids fetal acidosis
  - c. Causes reflex bradycardia
  - d. Decreases fetal pCO<sub>2</sub>
  - e. Causes tachyphylaxis
  
5. Deleterious neonatal effects of ephedrine are probably due to:
  - a. Vasoconstriction of umbilical vessels
  - b. Decreased maternal cardiac output
  - c. Increased maternal metabolism
  - d. Ineffective vasoconstriction
  - e. Increased fetal metabolism
  
6. Goal-directed use of vasopressor therapy for prevention or treatment of spinal induced hypotension should be to:
  - a. Treat only when maternal systolic pressure is <20% of baseline
  - b. Prevent changes in maternal systolic blood pressure with intramuscular vasopressor therapy
  - c. Maintain maternal systolic pressure within 100% of baseline
  - d. Maintain mean arterial blood pressure within 80% of baseline
  - e. Prevent fetal tachycardia

## Ephedrine (cont'd)

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7. True statements regarding intrapartum asphyxial events severe enough to be associated with harmful neonatal neurologic outcome include:
  - a. Umbilical artery pH < 7.00 and base deficit > 12 mmol/L are expected
  - b. Umbilical artery pH is not predictive of outcome
  - c. Umbilical artery base deficit is less important than umbilical artery pH
  - d. Umbilical artery pCO<sub>2</sub> > 50 are predictive of outcome
  - e. Umbilical vein pH is more predictive than umbilical artery pH
  
8. Studies show ephedrine affects the human fetus/neonate in all the following ways, EXCEPT:
  - a. Increases heart rate
  - b. Increases base deficit
  - c. Increases heart rate variability
  - d. Improves Apgar scores
  - e. Decreases fetal pH
  
9. For treatment of hypotension associated with spinal anesthesia, *compared to phenylephrine*:
  - a. Ephedrine is more effective if used prophylactically
  - b. Ephedrine only causes fetal acidosis with large prophylactic doses
  - c. Reflex bradycardia makes ephedrine a superior choice
  - d. Combination treatment with ephedrine and phenylephrine is associated with similar levels of acidosis
  - e. Large doses of intramuscular ephedrine are not associated with umbilical artery acidosis
  
10. When using phenylephrine clinically, it is best to:
  - a. Use large boluses immediately after spinal anesthesia (500 to 1000 mcg)
  - b. Use infusions without boluses
  - c. Avoid cumulative doses over 1000 mcg
  - d. Co-administer ephedrine
  - e. Use unlimited cumulative doses administered in small boluses

**Evaluation of Module 2**

As part of the CSA Educational Programs Division's ongoing efforts to offer continuing medical education, the following evaluation of this program is requested. This is a useful tool for the EPD in preparing future CME programs.

- 1. How well were the learning objectives of this program met?

Very Well	5	Above Average	4
Average	3	Below Average	2
Not Well at All	1		
  
- 2. How relevant was the information in this program to your clinical practice?

Very Relevant	5	Above Average	4
Average	3	Below Average	2
Not Relevant	1		
  
- 3. How would you rate this program overall?

Excellent	5	Above Average	4
Average	3	Below Average	2
Poor	1		
  
- 4. Did you detect any commercial bias in this module?

Yes		No	
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