Anesthesiology 2002; 96:612–6

Increasing Maternal Blood Pressure with Ephedrine Increases Uterine Artery Blood Flow Velocity during Uterine Contraction

Laurent Ducros, M.D., Philippe Bonnin, M.D., Ph.D.,† Bernard P. Cholley, M.D., Ph.D.,* Eric Vicaut, M.D., Ph.D.,‡ Moncef Benayed, M.D.,§ Denis Jacob, M.D.,‖ Didier Payen, M.D., Ph.D.#*

Background: **During labor, ephedrine is widely used to prevent or to treat maternal arterial hypotension and restore uterine perfusion pressure to avoid intrapartum fetal asphyxia. However, the effects of ephedrine on uterine blood flow have not been studied during uterine contractions. The purpose of the study was to assess the effects of ephedrine on uterine artery velocities and resistance index using the Doppler technique during the active phase of labor.**

Methods: **Ten normotensive, healthy parturients with uncomplicated pregnancies at term received intravenous ephedrine during labor to increase mean arterial pressure up to a maximum of 20% above their baseline pressure. Peak systolic and end-diastolic Doppler flow velocities and resistance indices were measured in the uterine artery before and immediately after administration of bolus intravenous ephedrine and after ephedrine washout. Umbilical and fetal middle cerebral arterial resistance indices and fetal heart rate were also calculated.**

Results: **After ephedrine administration, mean arterial pressure increased by 17 ± 4%. End-diastolic flow velocity in the uterine artery at peak amplitude of uterine contraction was restored to 74% of the value observed in the absence of contraction. The systolic velocity was totally restored, and the uterine resistance index was significantly decreased, compared with the values in the absence of contraction. Between uterine contractions, ephedrine induced similar but less marked effects. Fetal hemodynamic parameters were not altered by ephedrine administration.**

Conclusions: **Bolus administration of intravenous ephedrine reversed the dramatic decrease in diastolic uteroplacental blood flow velocity and the increase in resistance index during uterine contraction, without altering fetal hemodynamic parameters. This suggests that the increase in uterine perfusion pressure during labor could in part restore uterine blood flow to the placenta during uterine contraction.**

THE vasopressor ephedrine is administered routinely to parturients during spinal[1] or epidural[2–4] anesthesia for cesarean delivery. The purpose of intravenous ephedrine administration is to correct or prevent the reduction in maternal blood pressure and the resulting decrease in uteroplacental blood flow that could lead to fetal asphyxia. Among all the vasopressors, ephedrine remains a drug of choice because of its mild effect on the uterine artery compared with other α-agonist agents.[5]

During labor, ephedrine is also widely used to preserve maternal blood pressure during regional anesthesia or analgesia.[6,7] It is well-demonstrated that uterine contraction dramatically reduces uterine blood flow with a linear relation to intrauterine pressure.[8–11] However, the effects of ephedrine on uteroplacental circulation have never been studied during the active phase of labor, when the presence of uterine contractions could strongly alter ephedrine effects. The purpose of the current study was to investigate how uterine artery blood flow and resistance indices were affected by ephedrine during uterine contractions in normotensive women during labor.

Materials and Methods

Patients

Ten healthy women with uncomplicated pregnancies, at term, and in the active phase of labor were studied after giving informed consent. Our Institutional Review Board approved the protocol. Subjects with preexisting medical conditions or known fetal antepartum disease, such as cardiac or vascular disorders, maternal gestational or chronic arterial hypertension, preeclampsia, HELLP syndrome (hemolysis, elevated liver enzymes, and low platelet count), abnormal resistance index of uterine or umbilical arteries, body temperature greater than 38.5°C, or suspicion of chorioamnionitis, were excluded from the study. In addition, all women with fetuses suspected to be small for gestational age or with meconium appearance in the amniotic fluid were excluded. Adequate analgesia (epidural analgesia or intravenous meperidine) was provided before the study. At the time of inclusion, all women had a normal heart rate ($<$ 110 beats/min) and stable arterial pressure (90 $<$ systolic pressure $<$ 130 mmHg, and diastolic pressure $<$ 90 mmHg) with less than 10% variation during three consecutive measurements 10 min apart. All fetuses had reactive tracings with baseline heart rate between 120 and 150 beats/min.

When oxytocin was required, the infusion rate was kept constant throughout the protocol. Intrauterine

* Staff Anesthesiologist, # Professor and Chairman, Department of Anesthesiology and Intensive Care, † Staff Physiologist, Department of Physiology, ‡ Professor, Department of Biophysics, ‖ Staff Obstetrician and Gynecologist, Department of Obstetrics and Gynecology, Centre Hospitalier Universitaire Lariboisière. § Staff Anesthesiologist, Department of Anesthesiology and Intensive Care, Centre Hospitalier Universitaire Lariboisière. Current position: Staff Anesthesiologist, Department of Anesthesiology and Intensive Care, University Hospital Mongi Slim, La Marsa, Tunisia.

Received from the Departments of Anesthesiology and Intensive Care, Physiology, Biophysics, and Obstetrics and Gynecology, Centre Hospitalier Universitaire Lariboisière, Paris, France. Submitted for publication June 26, 2001. Accepted for publication November 1, 2001. Supported by Plan Quadriennal (Ministere de l'Education Nationale, de la Recherche, et de la Technologie 1997–2001), Direction de la Recherche Clinique, Assistance Publique-Hôpitaux de Paris, Paris, France.

Address reprint requests to Dr. Ducros: Service d' Anesthésie-Réanimation, Hôpital Lariboisière, 2, rue Ambroise Paré, 75475 Paris cedex 10, France. Address electronic mail to: laurent.ducros@lrb.ap-hop-paris.fr.

pressure measurement using intrauterine catheter was indicated for obstetric management in two subjects.

Parameters

Fetal heart rate and uterine contractions were monitored continuously during labor with an external transducer (Hewlett Packard 8040, Bobligen, Germany). To assess fetal well-being during the protocol, Doppler flow waveforms were acquired in the umbilical and middle cerebral arteries of the fetus to compute resistance indices.[12,13] Maternal heart rate and systolic, diastolic, and mean arterial pressure (MAP) were measured every 5 min using an automated sphygmomanometer (Dinamap®; Critikon Ltd., Tampa, FL). After administration of bolus intravenous ephedrine, these measurements were acquired every 3 min. Blood flow velocity waveforms from the maternal uterine artery were obtained using a 3.75-MHz sector transducer with color flow mapping and pulsed-wave Doppler (Toshiba SSA-340A, Tokyo, Japan) by a trained operator. To ensure accurate and reproducible velocity measurements, the angle between the vessel axis and the ultrasound beam was minimized and kept similar for all recordings. Both peak systolic (V_{sys}) and end-diastolic (V_{dia}) flow velocities were measured. Reproducibility of velocity measurements was assessed in a group of pregnant women at term but in the absence of labor. The mean intraobserver difference for velocity measurement was 3.5% for systole and 8% for diastole.

The resistance index (RI) was calculated according to the formula of Pourcelot[14]:

$$RI = \frac{V_{sys} - V_{dia}}{V_{sys}} \quad (1)$$

Uteroplacental perfusion pressure during diastole (UPP_{dia}) was calculated as:

$$UPP_{dia} = DAP - IUP. \quad (2)$$

where DAP is diastolic arterial pressure, and IUP is intrauterine pressure (intrauterine perfusion pressure is the most accurate way to estimate myometrial activity).[15] However, monitoring of IUP was accepted by our Institutional Review Board only when indicated for an obstetric reason.

Study Protocol

All parameters were acquired successively at (1) baseline, (2) peak effect of ephedrine, and (3) after recovery, when MAP returned to control values. At each time, Doppler parameters were obtained both between uterine contractions and at the peak amplitude of uterine contractions. After baseline measurements, 6-mg boluses of ephedrine (ephedrine chlorohydrate; Aguettant, Lyon, France) were infused every 2 min until MAP increased by 20% above the baseline value, not exceeding a maximum total dose of 30 mg. If MAP did not return to baseline, ultrasound measurements were recorded after a maximum of 100 min, corresponding to a complete washout of ephedrine.[16]

Data Analysis

Data were considered suitable for analysis when the Doppler envelope was well-defined and consistent over several consecutive cardiac cycles. Blood flow velocities were obtained as the averaged value of three consecutive cardiac cycles.

Statistical Analysis

Data are presented as mean ± standard error of the mean (hemodynamic, demographic, and labor data) or median and quartiles (25th–75th percentile) (Doppler data). We compared the parameter values during ephedrine administration with baseline values using paired *t* test for hemodynamic, demographic, and labor data, and Wilcoxon test for Doppler data because assumptions of normal distribution or equal variance were generally not fulfilled for this type of measurement. The same procedures were applied when comparing values obtained during the recovery period with baseline values. All tests were two sided. A *P* value of less than 0.05 was considered significant.

Results

Parturients were 30 ± 2 yr old. Five parturients were primiparae, and five were multiparae. The gestational age was 40 ± 1 weeks. Eight parturients underwent epidural analgesia, one received intravenous analgesia with meperidine, and one declined analgesia. Maternal MAP was unaltered by epidural analgesia (−1 ± 6%). The protocol was started at least 1 (3 ± 1.5) h after epidural or intravenous analgesia. Maternal MAP did not vary (+3.6 ± 3.5%) during the 30-min period immediately before data acquisition, confirming hemodynamic stability. No change in analgesic regimen was required during the protocol. The verbal pain scores at the three periods were 0.2 ± 0.2, 0.4 ± 0.2, and 2.2 ± 1.2, respectively (not significant). Cervical dilation increased from 4 ± 1 cm at baseline to 5 ± 1 cm after ephedrine injection ($P = 0.03$) and to 7 ± 1 cm at recovery ($P = 0.01$). The number of uterine contractions per 10 min remained unchanged (4.5 ± 0.4, 4.6 ± 0.4, and 4.7 ± 0.5, respectively). Eight women had vaginal delivery, five required instrumental extraction, and two underwent cesarean delivery because of failure to progress or cephalopelvic disproportion. Data could not be acquired at recovery in two parturients because of lack of time before delivery. No change was noticed on fetal umbilical and mean cerebral artery resistance indices during the protocol (table 1). Fetal heart rate tended to increase after ephedrine and remained increased at re-

Table 1. Fetal Hemodynamic Parameters

	Baseline (n = 10)	Ephedrine (n = 10)	Recovery (n = 8)
UA RI	0.56 [0.53–0.58]	0.51 [0.47–0.57]	0.52 [0.47–0.58]
MCA RI	0.67 [0.59–0.70]	0.67 [0.56–0.71]	0.62 [0.59–0.68]
FHR (beats/min)	139 ± 5	146 ± 6	146 ± 5*

Data are median [quartiles] and mean ± standard error of the mean.

* $P < 0.05$ *versus* baseline.

UA RI = umbilical artery resistance index; MCA RI = middle cerebral artery resistance index; FHR = fetal heart rate.

Table 2. Maternal Hemodynamic Parameters

	Baseline (n = 10)	Ephedrine (n = 10)	Recovery (n = 8)
HR (beats/min)	83 ± 4	96 ± 5*	89 ± 3†
SAP (mmHg)	114 ± 4	131 ± 4*	124 ± 3
DAP (mmHg)	63 ± 3	69 ± 4*	71 ± 4
MAP (mmHg)	81 ± 3	95 ± 5*	89 ± 4

Data are mean ± standard error of the mean.

* $P < 0.05$ *versus* baseline. † $P < 0.05$ *versus* ephedrine.

HR = heart rate; SAP = systolic; DAP = diastolic; MAP = mean arterial pressure.

covery, when compared with baseline (table 1). The 5-min Apgar index at birth was 9.8 ± 0.1, and immediate neonatal outcome was normal.

The dose of intravenous ephedrine required to achieve a 20% increase in MAP was 18 ± 2 mg. Recovery data were acquired 62 ± 7 min after ephedrine injection. Table 2 summarizes maternal hemodynamic data. Maternal heart rate and systolic, mean, and diastolic arterial pressure increased after administration of intravenous ephedrine when compared with baseline values. The mean increase in MAP was 17 ± 4%. Values at recovery were not significantly different from those obtained at baseline. At baseline, V_{sys} and V_{dia} were both reduced during the peak amplitude of uterine contraction, with a major effect on V_{dia} and a marked increase in RI with respect to values obtained between uterine contraction (figs. 1 and 2). After ephedrine administration, V_{sys} and V_{dia} increased and RI decreased, both during and between uterine contractions (figs. 1 and 2). However, the effect of ephedrine on uterine artery flow velocity and RI was more pronounced during uterine contraction. After administration of intravenous ephedrine, V_{dia} during contraction was restored to 74% of the precontraction value. After ephedrine washout, V_{dia} and RI values during uterine contraction returned to baseline values (fig. 1).

Intrauterine pressure was measured in two parturients who underwent intrauterine catheter placement for obstetric management. Doppler parameters were acquired at a matched level of intrauterine pressure during uterine contraction (40 mmHg), before and after administration of bolus intravenous ephedrine. Diastolic arterial pressure increased from 68 to 94 mmHg and from 50 to 67 mmHg in each patient, respectively, after ephedrine administration. Concomitantly, uterine perfusion pressure in diastole during contractions increased from 28 to 54 mmHg and from 10 to 27 mmHg, respectively. Simultaneously, V_{dia} increased from 0.12 to 0.40 m/s and from 0.25 to 0.41 m/s, while resistance indices decreased from 0.75 to 0.72 and from 0.83 to 0.71, respectively.

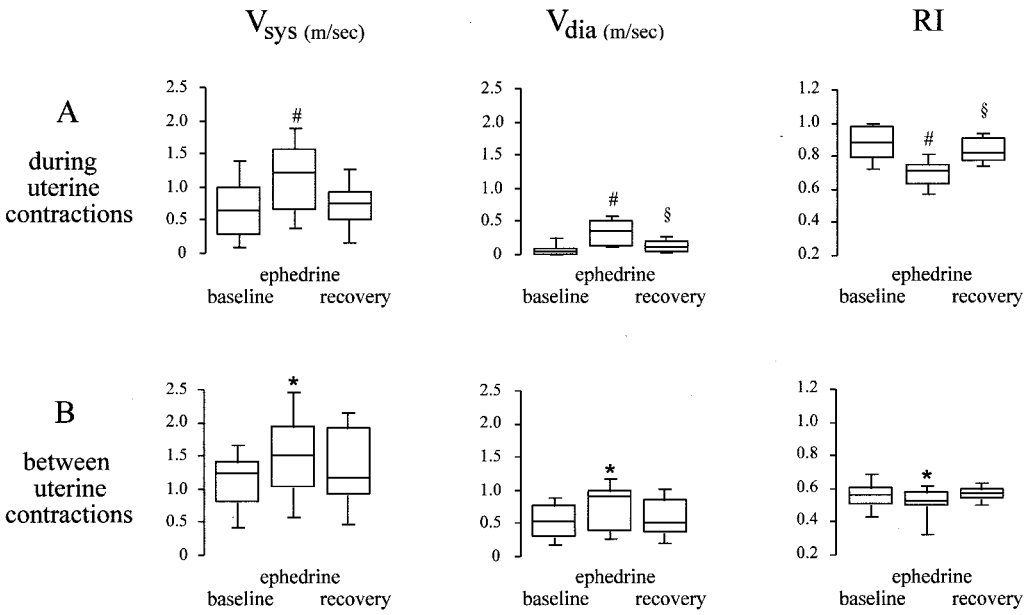

Fig. 1. Box plots (median, 10th, 25th, 75th, and 90th percentiles) of peak systolic (V_{sys}) and end-diastolic (V_{dia}) flow velocities and resistance indices (RI) in the uterine artery at the peak amplitude of uterine contraction (*A*) and between uterine contractions (*B*). Values were obtained at baseline, immediately after administration of bolus intravenous ephedrine, and during recovery. **P* < 0.05 *versus* baseline; #*P* < 0.01 *versus* baseline; §*P* < 0.05 *versus* ephedrine.

Discussion

In the current study, we observed that intravenous ephedrine almost completely reversed the reduction in uterine blood flow velocities and the increase in resistance indices due to uterine contraction. Fetal hemodynamic parameters and progression of labor were not affected after ephedrine administration.

During normal pregnancy, trophoblast invasion converts the spiral arteries into wide flaccid low resistance vessels, resulting in high-flow uteroplacental circulation.[17,18] End-diastolic flow velocity measured in the uterine artery outside the myometrium is commonly used as an index of uteroplacental blood flow.[9,18] During pregnancy, uteroplacental flow velocity waveform changes progressively toward a pattern of high end-diastolic velocity, reflecting the increasing blood flow associated with a low resistance index. During labor, the placenta is mainly perfused between uterine contractions. During contractions, blood flow decreases and the resistance index increases dramatically because surrounding myometrial pressure compresses vessels.[8–10,17]

In the current study, we observed an 85% reduction in uterine end-diastolic velocity during uterine contraction *versus* precontraction values, associated with a 58% increase in the resistance index. Ephedrine increased blood pressure and restored end-diastolic velocity to 74% of the precontraction value. Whether the increase in uterine artery flow velocity corresponds to an in increase in uteroplacental blood flow is open to debate. Indeed, if vessel diameter is reduced, an increased velocity can coexist with similar or reduced flow. In the current study, the resistance index was reduced, and this does not support the hypothesis of a reduction in uterine artery diameter. In addition, during pregnancy, the main uterine artery, where Doppler measurements were obtained, has been shown to be poorly constricted by ephedrine[5] and is not squeezed during uterine contractions because of its extramyometrial location. Therefore, variations in flow velocity are likely to reflect true variations in blood flow. This restoration of flow could be secondary to the increase in pressure during diastole (uteroplacental driving pressure). This is supported by the data obtained in the two patients in whom intrauterine pressure was measured. The increase in uterine perfusion pressure was accompanied by an increase in end-diastolic flow velocity in the uterine artery. The effect of

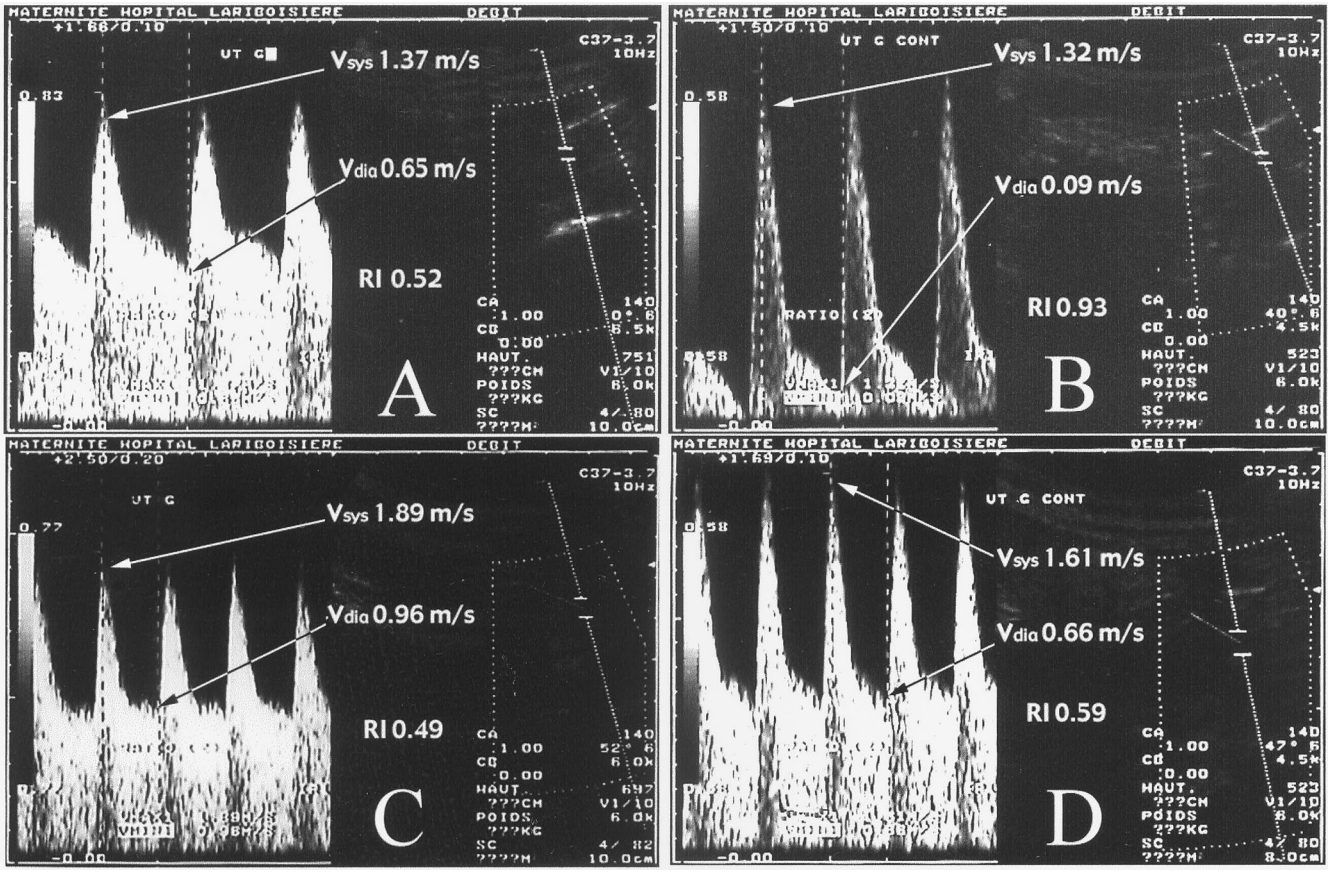

Fig. 2. Representative example of uterine artery velocity waveform in a single parturient at baseline (*A* and *B*) and after 18 mg ephedrine (*C* and *D*) in the absence of uterine contraction (*A* and *C*) and at the peak amplitude of uterine contraction (*B* and *D*). Arrows indicate peak systolic (V_{sys}) and end-diastolic (V_{dia}) flow velocities in the uterine artery. (*B*) Dramatic reduction in V_{dia} during contraction. (*D*) Complete restoration after administration of intravenous ephedrine. Note that scaling is different among panels. RI = resistance index.

intravenous ephedrine on diastolic velocity and resistance index during uterine contractions may reflect the reopening of uteroplacental vessels compressed by the myometrium. Conversely, when the myometrium is relaxed, the effect of intravenous ephedrine is minor because uterine vessels are already patent.

Intravenous ephedrine improves systemic perfusion because it increases both mean arterial pressure (increased systemic arterial resistance) and cardiac output (increased heart rate and better venous return due to a decrease in venous capacitance). Interestingly, ephedrine has minor direct effects on the uterine artery during pregnancy compared with other α-agonist agents[5] and does not constrict smaller uteroplacental spiral arteries because they are devoid of a muscular layer.[19] Angiotensin II has also been shown to restore maternal blood pressure with limited increase in maternal heart rate and limited effects on uteroplacental circulation when administered before spinal anesthesia for cesarean delivery.[20] Angiotensin II might yield similar increases in uterine blood flow velocities to ephedrine during uterine contractions, but this agent has not yet gained wide acceptance for the care of women in labor.

Similar findings might be obtained in patients with increased uteroplacental resistances (*i.e.*, preeclampsia, diabetes), although the increase in uterine blood flow would probably be less marked. However, during preeclampsia, trophoblastic invasion is not associated with the normal loss of the uterine arteriolar muscular layer,[21] and potent vasoconstriction could occur with the use of high doses of ephedrine.

During normal pregnancy, provided that less than 30 mg ephedrine is administered, placental transfer of ephedrine is minimal and does not affect fetal hemodynamic parameters and neonatal outcome, as confirmed by the current findings.[4,22] This is not true with atropine, which has been shown to diminish fetal oxygenation when used to correct fetal bradycardia.[23]

Study Limitations

This was not a blinded study; however, each parturient was used as her own control, and the return to baseline values after ephedrine was assessed to rule out a time factor. Almost every woman underwent epidural analgesia, which may alter uteroplacental circulation for at least two reasons: (1) pain may affect uterine vascular resistance, and (2) the presence of sympathectomy may also alter uteroplacental hemodynamics. Therefore, the relevance of these findings cannot be generalized to women without epidural analgesia. This study was performed in women with a normal obstetric course and without any sign of fetal asphyxia. Further studies are required to assess whether ephedrine administration is therapeutically valuable in normotensive women in labor presenting with signs of fetal asphyxia.

In conclusion, intravenous bolus ephedrine increased baseline uteroplacental blood flow velocity and, most importantly, prevented its dramatic reduction during uterine contraction while resistance index decreased. These results suggest that the increase in uterine perfusion pressure during labor could in part restore uterine blood flow to the placenta during uterine contraction.

The authors thank Alexandre Mebazaa, M.D., Ph.D., Department of Anesthesiology and Intensive Care, Centre Hospitalier Universitaire Lariboisière, Paris, France, for his helpful comments.

References

1. Shnider SM, de Lorimier AA, Holl JW, Chapler FK, Morishima HO: Vasopressors in obstetrics: I. Correction of fetal acidosis with ephedrine during spinal hypotension. Am J Obstet Gynecol 1968; 102:911–9
2. Hollmen AI, Jouppila R, Albright GA, Jouppila P, Vierola H, Koivula A: Intervillous blood flow during caesarean section with prophylactic ephedrine and epidural anaesthesia. Acta Anaesthesiol Scand 1984; 28:396–400
3. Ramanathan S, Grant GJ: Vasopressor therapy for hypotension due to epidural anesthesia for cesarean section. Acta Anaesthesiol Scand 1988; 32: 559–65
4. Wright RG, Shnider SM, Levinson G, Rolbin SH, Parer JT: The effect of maternal administration of ephedrine on fetal heart rate and variability. Obstet Gynecol 1981; 57:734–8
5. Tong C, Eisenach JC: The vascular mechanism of ephedrine's beneficial effect on uterine perfusion during pregnancy. ANESTHESIOLOGY 1992; 76:792–8
6. Parer J: Diagnosis and management of fetal asphyxia, Anesthesia for Obstetrics. Edited by Shnider SM, Levinson G. Baltimore, Williams & Wilkins, 1993, pp 657–70
7. Norris MC: Intrathecal opioids and fetal bradycardia: Is there a link? Int J Obstet Anesth 2000; 9:264–9
8. Brar HS, Platt LD, DeVore GR, Horenstein J, Medearis AL: Qualitative assessment of maternal uterine and fetal umbilical artery blood flow and resistance in laboring patients by Doppler velocimetry. Am J Obstet Gynecol 1988; 158:952–6
9. Janbu T, Nesheim BI: Uterine artery blood velocities during contractions in pregnancy and labour related to intrauterine pressure. Br J Obstet Gynaecol 1987; 94:1150–5
10. Borell U, Fernström I, Ohlson L, Wiqvist N: Influence of uterine contractions on the uteroplacental blood flow at term. Am J Obstet Gynecol 1965; 93:44–57
11. Fleischer A, Anyaegbunam AA, Schulman H, Farmakides G, Randolph G: Uterine and umbilical artery velocimetry during normal labor. Am J Obstet Gynecol 1987; 157:40–3
12. Bonnin P, Guyot B, Bailliard O, Blot P, Martineaud JP: Relationship between umbilical and cerebral blood flow velocity waveforms and umbilical venous blood gases. Ultrasound Obstet Gynecol 1982; 2:18–22
13. Sonesson SE, Fouron JC, Teyssier G, Bonnin P: Effects of increased resistance to umbilical blood flow on fetal hemodynamic changes induced by maternal oxygen administration: A Doppler velocimetric study on the sheep. Pediatr Res 1993; 34:796–800
14. Pourcelot L: Applications cliniques de l'examen Doppler transcutané, Vélocimétrie ultrasonore Doppler 34. Edited by Perroneau P. Paris, INSERM, 1974, pp 213
15. Harbert GM Jr: Assessment of uterine contractility and activity. Clin Obstet Gynecol 1992; 35:546–58
16. Sympathomimetic agents, Drug Information. Edited by ASHP. Bethesda, 2000, pp 1176
17. Greiss FC Jr: A clinical concept of uterine blood flow during pregnancy. Obstet Gynecol 1967; 30:595–604
18. Fairlie FM: Doppler flow velocimetry in hypertension in pregnancy. Clin Perinatol 1991; 18:749–78
19. Brosens I, Robertson WB, Dixon HG: The physiological response of the vessels of the placental bed to normal pregnancy. J Pathol Bacteriol 1967; 93:569–79
20. Vincent RD Jr, Werhan CF, Norman PF, Shih GH, Chestnut DH, Ray T, Ross EL, Bofill JA, Shaw DB: Prophylactic angiotensin II infusion during spinal anesthesia for elective cesarean delivery. ANESTHESIOLOGY 1998; 88:1475–9
21. Khong TY, De Wolf F, Robertson WB, Brosens I: Inadequate maternal vascular response to placentation in pregnancies complicated by pre-eclampsia and by small-for-gestational age infants. Br J Obstet Gynaecol 1986; 93:1049–59
22. Hughes SC, Ward MG, Levinson G, Shnider SM, Wright RG, Gruenke LD, Craig JC: Placental transfer of ephedrine does not affect neonatal outcome. ANESTHESIOLOGY 1985; 63:217–9
23. Parer JT: The effect of atropine on heart rate and oxygen consumption of the hypoxic fetus. Am J Obstet Gynecol 1984; 148:1118–22