The Fetal and Neonatal Effects of Regional Anesthesia in Obstetrics

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Each year millions of parturients throughout the world receive a local anesthetic during labor or delivery. Blockade of pudendal, lumbar epidural, caudal, spinal or paracervical nerves is used to produce freedom from the pain of childbirth. Reasons for the popularity of regional anesthesia in obstetrics include avoidance of narcotic and general anesthetic depression of the fetus and neonate, increased maternal alertness and cooperation during labor and delivery, and decreased risk of aspiration pneumonitis with maintenance of the mother’s laryngeal reflexes. Proponents of regional anesthesia hail its effectiveness, ease of administration and, when properly performed, its safety.

During the past decade, the advent and widespread use of electronic and biochemical fetal monitoring and improved laboratory techniques for measuring uterine and umbilical blood flows have led to a vast amount of new information about the impact of regional anesthesia on the mother, fetus and newborn. Recently, the fetal safety of well-conducted regional anesthesia has been questioned.239,305,301,417,429 Thus, it seemed timely to evaluate the ever-expanding literature on the fetal and neonatal effects of regional anesthesia.

A nerve block administered to a parturient may affect the fetus in one of two ways, either directly through fetal uptake of local anesthetic or indirectly through changes in maternal homeostasis that secondarily alter the fetal environment. Therefore, we review the effects of regional anesthesia under the following headings:

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I. Direct Effects of Local Anesthetics on the Fetus and Neonate

A. PLACENTAL TRANSFER OF LOCAL ANESTHETICS

Previous reviews of placental transfer of drugs have contained little information on local anesthetics.239,305,306,307 Many believed that, barring maternal systemic complications, regional anesthesia provided “optimal conditions for the newborn”239 and that local anesthetics had no direct effect on the fetus or neonate.309 However, other investigators emphasized our ignorance concerning the placental transfer of local anesthetics and their possible fetal and neonatal consequences.306,307 It is now well established that local anes-


<table>
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<tr>
<th>Local Anesthetic</th>
<th>Route of Administration</th>
<th>Number of Parturients</th>
<th>Mean Maternal Dose (mg)</th>
<th>Mean Duration of Anesthesia (h)</th>
<th>Mean Maternal Arterial or Venous Blood Concentration (ug/ml)</th>
<th>Mean Fetal or Neonatal Blood Concentration (ug/ml)</th>
<th>Mean Fetal-to-Maternal Concentration Ratio</th>
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<td>188</td>
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<td>0.58</td>
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<tr>
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<td>275</td>
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<td>2.9</td>
<td>2.3*</td>
<td>0.79</td>
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<td>1.5</td>
<td>1.20</td>
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* Fetal scalp blood samples.

Anesthetics reach the fetus during maternal regional anesthesia (table 1). The possible fetal or neonatal influence of even small quantities of these agents has recently received increased attention. In 1961, Bromage and Robson observed that lidocaine administered to the parturient appeared in measurable quantities in umbilical cord blood. Subsequent studies verified their findings and documented the placental transfer of procaine, lidocaine, prilocaine, and mepivacaine. Furthermore, the effects of pathologic states such as hypoxia, diabetes mellitus, eclampsia, and hypertension on placental permeability to local anesthetics remain unknown.

That local anesthetics traverse the placenta is not surprising. The placenta resembles a lipid membrane barrier. Local anesthetics rapidly cross the placenta by passive diffusion. The quantity of substance transferred per unit time varies directly with the concentration gradient between mother and fetus and the surface area available for diffusion, and indirectly with membrane thickness. In addition, placental transfer depends on several characteristics of the individual drug, such as molecular weight, the fraction of nonionized drug, lipid solubility, spatial configuration and protein binding of the drug. Other factors that may alter placental drug transfer to an unknown extent include the quantity and distribution of maternal and fetal blood flow; drug binding by the placenta itself; active transport of drug molecules from fetus to mother; varying binding affinities of maternal and fetal proteins; and placental or fetal drug metabolism.

Much of the basic pharmacology of local anesthetics is known, including molecular weights, lipid solubilities, pK_a's (the pH at which 50 per cent of drug is ionized and 50 per cent is nonionized), and protein-binding characteristics. On the other hand, there are as yet no data about how changes in placental surface area, permeability, and thickness alter placental transfer of local anesthetics. Furthermore, the effects of pathologic states such as hypoxia, diabetes mellitus, eclampsia, and hypertension on placental permeability to local anesthetics remain unknown.

Local anesthetics all have molecular weights of less than 325, and this factor does not cause differences in placental transfer of individual drugs. Local anesthetics are weak bases, with pK_a's between 7.6 (mepivacaine) and 8.9 (procaine) (table 2). The proportion of local anesthetic drug in the nonionized form (free base) is given by the Henderson-Hasselbalch equation. The pK_a's range from 39 per cent for mepivacaine to 3 per cent for procaine. Thus, for a given maternal arterial concentration level, mepivacaine would cross the placenta more rapidly than procaine.

The maternal arterial concentration of free base available for diffusion at the intervillous space is itself dependent on several factors: 1) the blood concentration is increased with increasing total dose; 2) the peak concentration is higher when injection is into the blood.
itself or into highly perfused tissues; 3) the concomitant administration of epinephrine will reduce peak local anesthetic levels by reducing local blood flow; 4) by removing drug from blood, maternal tissue uptake, metabolism, and excretion will lower the blood levels; 5) local anesthetic binding to maternal blood proteins or lipids may reduce the rate at which local anesthetic molecules cross the placental membrane; finally, 6) uterine blood flow limits the amount of drug available for transfer. Let us examine each of these factors in detail.

1. Total dose of drug

Increasing dosage by epidural, paracervical, pudendal, and, in non-obstetrical cases, axillary, tracheal, or intravenous administration results in a higher peak drug level in the blood.\textsuperscript{20,24,52,239,355,356,367} A single epidural dose of lidocaine (3 mg/kg) produces a peak maternal level of 2–3 μg/ml after 15 to 20 minutes. With a larger single dose or multiple doses during continuous epidural block of labor, maternal levels are higher, although they seldom reach a toxic range (that is, for lidocaine, more than 5 μg/ml\textsuperscript{14,60}). However, Moore \textit{et al.}\textsuperscript{244} demonstrated the potential accumulation of local anesthetic in obstetrical patients during continuous caudal block. Following the single dose of 300–450 mg mepivacaine, 1.5 per cent, maternal venous blood levels were 3–4 μg/ml. Subsequent reinforcing doses of 300 mg given approximately 120 minutes apart resulted in peak blood levels of 6–10 μg/ml after the fourth dose. However, we believe that satisfactory caudal anesthesia can be achieved utilizing lower concentrations of local anesthetic, thus minimizing maternal drug accumulation.

2. Route of administration

Drug absorption occurs more rapidly from areas of greater vascularity.\textsuperscript{258,444} Injection of local anesthetic in the pudendal, paracervical, or lumbar epidural region results in rapid and comparable systemic absorption by the mother.\textsuperscript{350} Caudal epidural administration of lidocaine,\textsuperscript{220} mepivacaine,\textsuperscript{45} prilocaine,\textsuperscript{45} or etidocaine\textsuperscript{208} results in higher peak venous plasma concentrations than occur after lumbar epidural injection, presumably because of the greater vascularity of the caudal canal. Nevertheless, the differences in peak concentrations seen after lumbar versus caudal epidural anesthesia are small and unlikely to be of any clinical significance.

3. Presence of epinephrine in solution

The addition of epinephrine to the injected anesthetic causes local vasoconstriction, reduces regional
blood flow, and thereby lowers anesthetic absorption and, with some local anesthetics, the peak systemic concentration. Blood levels of lidocaine and mepipvacaine are decreased 20 to 50 per cent by the addition of epinephrine, while levels of prilocaine, bupivacaine and etidocaine are not significantly reduced by the inclusion of epinephrine. Covino and Vassalo have suggested that the high lipid solubilities of bupivacaine and etidocaine, which result in marked epidermal adipose tissue uptake, and the greater vasodilating properties of these agents counteract the vasoconstricting effect of epinephrine.

4. Maternal metabolism and excretion

Most local anesthetics can be divided into two groups according to their structures: the amides and the esters. In man, amides are metabolized principally in the liver. The elimination half-life of lidocaine in non-pregnant human subjects is approximately one and a half hours. This relatively long half-life results in part from a large volume of distribution and tissue uptake of lidocaine. For although the liver clears 70 per cent of the lidocaine present in the hepatic blood at any one time, the liver has access to only a small fraction of the lidocaine in the body. Therefore, the rate of plasma decay is slow. Thus, accumulation of amide anesthetics and their metabolites in the blood can occur when large doses are used frequently over a prolonged period. Fetal levels will likewise rise in parallel. The tendency for systemic accumulation can be minimized by the use of the longer-acting amide anesthetics, bupivacaine and etidocaine, which require less frequent injections.

Ester-linked anesthetics are hydrolyzed by plasma (procaine), and liver (procaine, tetracaine) esterases. There is at present no evidence that placental esterase hydrolyzes ester-linked local anesthetics to any significant extent. Adult plasma cholinesterase rapidly hydrolyzes procaine to para-aminobenzoic acid and diethylamino ethanol. 2-Chloroprocaine (Nesacaine) is hydrolyzed four times faster than procaine, but tetracaine hydrolysis is slower.

Detectable placental transfer of procaine occurs only with large maternal doses. Usubiaga et al. found no placental transmission with a maternal intravenous dose of 4 mg/kg. With larger doses of 7–10 mg/kg, peak umbilical concentrations were 8.5 μg/ml, a level that had an untoward effect on the fetus. As one would expect, para-aminobenzoic acid, the major metabolite of procaine, appeared in both maternal and fetal sera after the administration of only 2 mg/kg procaine. Because ester-linked local anesthetics are rapidly metabolized and cross the placenta in low concentra-

Fig. 1. Plasma binding of four antilice local anesthetics at plasma concentrations of 0.4 to 20 μg/ml. Reproduced from Tucker, G. T., and Mather, L. E.: Pharmacokinetics of local anesthetic agents, Br J Anaesth 47:215, 1975, with permission.

5. Maternal protein binding

Maternal protein binding inhibits the placental transfer of local anesthetics by decreasing the fraction of free base available for diffusion across the intervillous space. Local anesthetics bind to plasma proteins and erythrocytes. The amides are bound more firmly than the esters. Shnider and Way found that the maternal protein binding of lidocaine was concentration dependent. At 12 μg/ml, only 30 per cent was bound, while at 2 μg/ml nearly all the drug was bound. Tucker et al. found 70 per cent of lidocaine bound to plasma proteins over the commonly encountered arterial plasma concentrations of 1–4 μg/ml. Only 60 per cent was protein-bound at 6–10 μg/ml. These findings imply saturation of the protein-binding sites, and also imply that higher doses may cause disproportionately more placental transfer.

Of the local anesthetics studied, bupivacaine and etidocaine are bound to the greatest extent (95 per cent at 1 μg/ml in the plasma), followed in decreasing order by mepipvacaine, lidocaine, and prilocaine.

6. Intervillous blood flow

Though intuitively of obvious importance, the influence of maternal hemodynamic changes on placental transfer of local anesthetics has not been studied. Uterine placental vascular shunts should decrease the quantity of drug delivered to the intervillous space and, therefore, might limit the amount of drug available for fetal absorption. Likewise, a decrease
in utero-placental circulation, from whatever cause, would limit the amount of local anesthetic available for transfer.10,20

7. Fetal-to-maternal concentration ratio

The technique of fetal scalp blood sampling,29 coupled with improved methods of measuring local anesthetics in small volumes of blood7,10,20,39,29 has enabled investigators to determine fetal blood levels during regional anesthesia. However, most human placental transfer studies have relied on single determinations of local anesthetic levels in maternal and cord blood at delivery (table 1). All studies have demonstrated a wide fetal-to-maternal concentration gradient for local anesthetics, with the exception of prilocaine. The mean fetal or neonatal concentration, expressed as a percentage of that in simultaneously drawn maternal blood, for lidocaine is 53 per cent (range 20–100 per cent), for mepivacaine 69 per cent (range 34–89 per cent), for bupivacaine 29 per cent (range 15–86 per cent), and for prilocaine 120 per cent (range 100–180 per cent). This extraordinarily wide variability of the reported gradients for an individual drug may have several explanations. Early studies utilized a variety of noncomparable sampling sources and routes of administration. Maternal arterial blood levels of local anesthetics are usually 20 per cent higher than simultaneously measured venous levels25,12,28; whole-blood lidocaine concentrations are 80–90 per cent of plasma concentrations26; paracervical block may result in higher fetal local anesthetic levels than epidural anesthesia because of possible direct diffusion across the uterine artery into the intervillous space.16,203

Other causes for the fetal-to-maternal concentration gradient include: a) lack of equilibration between maternal and fetal tissues, i.e., an unsteady state; b) maternal and fetal pH differences; c) placental metabolism of local anesthetics; d) vascular shunts at the maternal or fetal placental site; e) differences in maternal and fetal protein or erythrocyte binding of local anesthetics.

a) Lack of equilibration. Goldstein et al.,157 using a computer analog, calculated the maximum rate of equilibration of any drug between fetal and maternal tissue at a constant maternal arterial drug level. The theoretical time was 40 minutes. Equilibrium occurred earlier with a rapidly decreasing maternal level, as would occur in practice. However, Goldstein et al. assumed no impediment to placental transfer, such as protein binding, large molecular size, or a high degree of ionization. Each of these factors might increase the time for equilibration.157 A continuing fetal tissue or amniotic fluid uptake of local anesthetic would decrease fetal arterial blood drug levels. Such fetal tissue redistribution may explain the observed fetal-to-maternal concentration gradient.25 Reverse placental transfer of local anesthetics has been demonstrated to occur when fetal levels exceed maternal.254,255

b) Maternal and fetal pH difference. Differences in maternal and fetal pH's may influence the equilibrium between maternal and fetal blood local anesthetic concentrations.29,34,35,36 A lower fetal pH could theoretically increase the ionized form of local anesthetic in the fetus, thus increasing the fetal blood level and in-

<table>
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<tr>
<th>Patient Number</th>
<th>Interval between I.V. Lidocaine 3mg/kg and Birth</th>
<th>Lidocaine ug/ml</th>
<th>Umbilical Vein Uterine Vein x 100</th>
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<td>3</td>
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<td>1.7</td>
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Mean 2.7 1.2 45%
creasing the fetal-to-maternal concentration gradient. Hydrogen ion concentration likewise affects the relative protein binding of local anesthetics, (acidosis decreases and alkalosis increases protein binding\textsuperscript{205}), and this may alter the fetal-to-maternal concentration differences.

c) Placental metabolism. Although placental metabolism of local anesthetics would contribute to a lower fetal blood level, no evidence of placental metabolism of the amide, \textit{e.g.}, lidocaine\textsuperscript{251} or ester local anesthetics has been found.\textsuperscript{180,181,201,251,405}

d) Vascular shunts. The existence of maternal or fetal vascular shunts past the placental site would cause a local anesthetic concentration gradient (fig. 2). Anatomic shunts have not been demonstrated in the human placenta. However, even in the absence of anatomic shunts, variations in maternal and fetal perfusion in the placenta could result in physiologic shunts, analogous to ventilation-perfusion inequalities in the lung.\textsuperscript{76,237,351} There is considerable experimental evidence for such non-uniform distribution of maternal and fetal flow in the placenta.\textsuperscript{205,237,294,295,296,395}

e) Differences in maternal and fetal protein binding. Recently, differential binding of local anesthetics by maternal and fetal blood has been proposed to explain the fetal-to-maternal concentration gradient of local anesthetics.\textsuperscript{40,63,139,226,251} Maternal plasma protein-binding capacities are much higher than fetal or neonatal capacities,\textsuperscript{19,226,395} resulting in higher maternal total blood concentration of a given drug. A direct relation also exists between the extent of protein binding by maternal serum and the fetal-to-maternal drug ratios for the commonly used local anesthetics. Bupivacaine has the lowest fetal-to-maternal ratio, while prilocaine has the highest (table 1).

Recent evidence comparing lidocaine, bupivacaine and etidocaine in guinea pigs, however, suggests that the lower fetal blood levels may be due solely to higher fetal tissue uptake, rather than a reduced transfer across the placenta\textsuperscript{144,256} from greater maternal protein binding.

B. Uptake and Distribution of Local Anesthetics by the Fetus

The distribution of fetal cardiac output determines the initial distribution of local anesthetics.\textsuperscript{75,321-325,325,326,413} Umbilical venous blood returning from the placenta either perfuses the liver or enters the inferior vena cava through the ductus venosus.\textsuperscript{302} Recent work in previable human fetuses indicates that anywhere from 8 to 92 per cent of umbilical venous blood enters the liver before reaching the systemic circulation.\textsuperscript{224} This hepatic parenchymal perfusion may buffer against attainment of high fetal drug levels. In adults a substantial portion of lidocaine is removed in a single passage through the liver. The capacity of the fetal liver to remove local anesthetics in a single passage is unknown.

Blood from the lower body and abdominal viscera then mixes with and further dilutes the anesthetic in umbilical venous blood. Inferior vena caval blood returns to the right heart and is largely diverted by the crista dividens to the left heart through the foramen ovale. The fetal heart and brain initially are exposed to a local anesthetic concentration identical to that in the left ventricle, although lower than that in the umbilical vein. From the heart the local anesthetic is distributed to the body in proportion to the flows directed to the various tissues (fig. 3). Consequently, the fetal vessel-rich tissue initially would be exposed to a larger concentration of drug than would less perfused organs. In human fetuses, Rudolph et al.\textsuperscript{324} found an average of 14 per cent of fetal cardiac output delivered to the brain, with a range of 4–26 per cent. Local anesthetic entry across the blood–brain barrier is governed by factors similar to those affecting placental drug transfer.\textsuperscript{205} After epidural administration in the adult, local anesthetic appears in cerebrospinal fluid within minutes,\textsuperscript{208,401,416} reaches a maximal con-
concentration in 20 to 30 minutes, then declines at a rate similar to the plasma decay rate. The blood–brain barrier in the fetus, particularly the low-gestational-age fetus, is poorly developed. The increased permeability of the fetal blood–brain barrier coupled with the greater cerebral blood flow in the human fetus and neonate may enhance local anesthetic uptake by the brain. Although there is no definite proof that the fetus or neonate is more susceptible than the adult to the toxic effects of local anesthetics at equivalent blood levels, there are data that suggest this (see D, 1 below).

The fetal myocardium contains relatively high concentrations of local anesthetics following administration of these drugs to the pregnant guinea pig. Presumably this is due to the large blood flow to the fetal heart. The high myocardial levels of local anesthetic may have significance in the cardiac toxicity seen after paracervical block anesthesia.

Hepatic levels of lidocaine in the fetus and neonate are also high. In two infants who inadvertently received massive injections of mepivacaine during caudal anesthesia, postmortem hepatic tissue levels were 113 and 117 μg/ml (table 4).

Because low pH shifts most local anesthetics to the ionized form, substantial amounts of local anesthetics accumulate in the stomachs of human neonates. In 24 newborn infants whose mothers received 425 mg mepivacaine for epidural anesthesia, the mepivacaine concentration in umbilical artery was 1.50 μg/ml and that in the gastric aspirate, 29.5 μg/ml. The pH of the umbilical artery blood was 7.25 and that of the gastric juice, 6.05. When neonatal gastric fluid pH is higher (7.0–7.8), lidocaine levels from gastric aspirate are predictably lower (gastric fluid lidocaine level 0.2–2.1 μg/ml, umbilical artery blood level 0.4–0.9 μg/ml).

The accumulation of local anesthetic in acidic gastric contents has facilitated drug elimination with gastric lavage in infants who inadvertently received direct local anesthetic injections. Gastric sequestration is unlikely to be a significant factor in protecting the fetus during routine use of local anesthetics, as the drug will be reabsorbed when it reaches the alkaline intestinal contents.

In the adult, lung tissue and pulmonary blood dilute and thereby decrease the arterial concentration of drug delivered to the heart and brain. This buffer is less effective in the fetus, since the fetal pulmonary blood flow is less than 10 per cent of cardiac output.

Fetal asphyxia may alter local anesthetic distribution in several ways. Asphyxia produces fetal catecholamine release, increasing ductus venous blood flow and effectively shunting a larger proportion of umbilical blood flow directly to the heart. The enhancement of fetal Pco₂ seen with asphyxia increases cerebral blood flow. Hypoxia and acidosis increase pulmonary vascular resistance, leading to an increased shunt of superior vena caval blood across the foramen ovale to the left heart. These circulatory adaptations to asphyxia, which attempt to improve oxygen transport to the brain and heart, also increase the delivery of local anesthetic to the same critical organs. In addition, acidosis, per se, may cause accumulation of local anesthetic in fetal blood. Data in the experimental animal indicate that fetal acidemia significantly increases both fetal blood lidocaine levels and the fetal-to-maternal lidocaine ratio (fig. 4). Furthermore, acidosis disrupts local anesthetic protein binding by blood, thereby increasing the proportion of free drug available for entry across the blood–brain barrier. Such an effect of acidosis on bilirubin albumin binding is well documented. Finally, fetal asphyxia increases cerebral vascular permeability, which may enhance local anesthetic delivery to fetal brain tissue.

C. BIOTRANSFORMATION AND EXCRETION OF LOCAL ANESTHETICS BY THE FETUS AND NEONATE

Local anesthetic toxicity is limited by metabolism of the anesthetic. Unfortunately, little is known about metabolism by the human fetus and neonate. Applying data from adult animals or man to the human fetus or neonate may not be justified because of species or developmental differences. Thus, conclusions inferred from these data must be verified by future studies.
For lidocaine the liver is the primary site of inactivation, both in animals and in man. In dogs, partial or complete hepectomy reduces lidocaine metabolism proportionately. In adult man a decrease in hepatic blood flow occurring with a decreased cardiac output is associated with higher blood levels of lidocaine, due to either decreased metabolism or distribution. Mepivacaine, prilocaine, and bupivacaine, like lidocaine, are degraded by oxidative metabolism in the liver.

Fetal hepatic enzymatic activity is generally less than in adults. Oxidative and conjugative detoxification pathways, both of which are involved in the metabolism of amide local anesthetics, are deficient in the fetal or neonatal animal. In man, although fetal metabolism of amide local anesthetics has not been studied, indirect evidence suggests that the fetus can metabolize these drugs. Although hepatic cytochrome P-450 activity is absent in fetuses of several animal species either early or late in gestation, human fetal hepatic microsomes have significant cytochrome P-450 levels as early as the fourteenth week of gestation. The drug-metabolizing cytochrome P-450 levels are quantitatively equal to those in surgical specimens of adult liver. Electron microscopic studies of human fetal liver reveal a smooth endoplasmic reticulum network appearing throughout the cytoplasm at the third month of gestation. This suggests that even the premature human fetus can metabolize numerous drugs, including local anesthetics.

Our knowledge of neonatal metabolism of amide local anesthetics is meager. In the neonatal puppy, lidocaine clearance from the blood is slower than that in the adult (fig. 5). Again, does this mean decreased metabolism, or decreased distribution of blood to the liver? Hypothermia further prolongs the neonatal clearance of lidocaine. Concomitant neonatal acidosis, which often accompanies hypothermia, likewise may impair the clearance of local anesthetics. Smidler and Way found that human maternal and neonatal decay curves with lidocaine were similar. They administered 3 mg/kg lidocaine to the mother before cesarean section and then concomitantly took blood samples at birth from a maternal artery and from the umbilical artery. Maternal and neonatal samples again were obtained 60 to 150 minutes after delivery. Little difference was seen between the slopes of the maternal and neonatal decay curves. The elimination rates of bupivacaine in maternal blood and neonatal blood are also very similar.

Brown et al. measured neonatal plasma levels of lidocaine, mepivacaine, and bupivacaine 2, 4, 8, and 24 hours after delivery with epidural anesthesia. Plasma half-lives were 9 hours for mepivacaine, 3 hours for lidocaine, and less than 2 hours for bupivacaine, a remarkable difference when one considers that in the adult these three local anesthetics have approximately similar half-lives (table 3). Although human neonatal metabolism of mepivacaine appears very limited or nonexistent, the human neonate can eliminate free mepivacaine, more than 90 per cent being excreted in the first 24 hours of life.

Fetal metabolism of the ester type of local anes-

![Graph](https://example.com/graph.png)

**Fig. 5.** Mean concentrations of lidocaine in arterial blood following a single injection (5 mg/kg, intravenously) into 12 newborn puppies at two different environmental temperatures, and into six normothermic adult dogs. Reproduced from Morishima, H. O., and Muller-Heubach, E.: Body temperature and disappearance of lidocaine in newborn puppies, Anesth Analg (Clev) 50:941, 1971, with permission.
1. **Fetal and neonatal central nervous system toxicity**

Central nervous system toxicity is manifested by tremors, twitching, or actual convulsions. Using fetal lambs, Terano et al. recorded EEG evidence of convulsions during infusion of lidocaine into a fetal femoral vein. The fetal arterial blood level at the onset of seizure activity was 6.9–40.0 \( \mu g/mL \). Susceptibility to lidocaine-induced seizures increased with increasing gestational age. Limited evidence suggests that toxicity in the human fetus or neonate, as in the adult, varies with the blood level. Inadvertent fetal injection of massive doses of local anesthetic produces profound central nervous system and cardiovascular depression manifested by convulsions, marked bradycardia, cyanosis, apnea, and unresponsiveness to positive-pressure ventilation with oxygen. Two infants recovered after treatment with gastric lavage; exchange transfusion hastened elimination of the drug. Postmortem meperidine levels in infants who did not survive direct intrafetal meperidine injection are given in Table 4.

Studies in human volunteers and experimental animals suggest that for each drug there is a critical arterial blood concentration above which symptoms appear. Both the peak concentration and the duration of this critical level determine the incidence, severity, and duration of symptoms. Fortunately, regional anesthesia with lumbar epidural, caudal, or pudendal block (paracervical block is discussed below) rarely results in toxic fetal or neonatal blood levels.

The fetus may be more sensitive than the adult to the depressant effect of local anesthetics. Shnider and Way found neonatal depression (reduced Apgar scores) in infants with umbilical venous blood lidocaine levels of more than 2.5 \( \mu g/ml \); a concentration of 5 \( \mu g/ml \) is generally considered necessary to cause toxic signs in normal unanesthetized adults. Similarly, in 56 parturients receiving regional anesthesia with meperidine, Morishima et al. found higher meperidine levels in umbilical blood in five of 12 depressed infants than in the remaining 44 vigorous infants. These values were 50 per cent of the toxic threshold of 5–6 \( \mu g/ml \) reported for meperidine in adults. This difference in toxic levels, however, may be partially explained by differences in adult and fetal protein binding. Since the fetal protein-binding capacity for local anesthetic is only 50–60 per cent that of the adult, the fractions of free drug, the portion responsible for toxicity, may be similar in adult blood and fetal blood.

---

**Table 3. Elimination Rates of Local Anesthetics in the Adult and Neonate**

<table>
<thead>
<tr>
<th>Metabolite</th>
<th>Site of Metabolism</th>
<th>Adult Elimination Half-Life</th>
<th>Neonate Elimination Half-Life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bupivacaine</td>
<td>Liver</td>
<td>3.5 hours*</td>
<td>&lt;2 hours†</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>Liver</td>
<td>2.6 hours*</td>
<td>3 hours†</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>Liver</td>
<td>1.6 hours*</td>
<td>9 hours†</td>
</tr>
<tr>
<td>Methocaine</td>
<td>Liver</td>
<td>1.0 hours*</td>
<td>43 seconds‡</td>
</tr>
<tr>
<td>Chloroprocaine</td>
<td>Plasma</td>
<td>21 seconds‡</td>
<td>43 seconds‡</td>
</tr>
</tbody>
</table>

† Data from reference 46.
‡ References 112 and 114.

**D. Toxicity of Local Anesthetic in Fetus and Neonate**

Toxic reactions to local anesthetics in adults, and presumably in the fetus, typically involve alterations of the central nervous system, peripheral vascular tone, and cardiac function. Toxic reactions to local anesthetics in adults, and presumably in the fetus, typically involve alterations of the central nervous system, peripheral vascular tone, and cardiac function.
In contrast to these reports, other studies suggest no undue sensitivity of the neonate. Moore reported five neonates whose mothers had received 900–1,480 mg mepivacaine during continuous caudal anesthesia. Despite cord blood levels as high as 7.9 μg/ml, all neonates were vigorous (Apgar scores 9 or 10) at 5 minutes of age.

Sinclair et al. described the disappearance of central nervous system toxicity at a mepivacaine level of 8 μg/ml following exchange transfusion treatment after inadvertent fetal injection during caudal anesthesia. Clark et al. reported 11 infants who had umbilical venous blood mepivacaine concentrations greater than 3 μg/ml following epidural anesthesia. In contrast to the infants reported by Morishima, eight of the 11 infants were vigorous. Perhaps the absolute drug level is not the sole determinant of fetal or neonatal toxicity. As already discussed, numerous factors may increase fetal or neonatal susceptibility to the depressant effects of local anesthetics.

Even when neonates are not depressed at birth as ascertained by low Apgar scores, more subtle neurobehavioral changes in the subsequent neonatal period have been reported. Scanlon et al. have developed a neurobehavioral examination that combines standard neurologic testing and evaluation of the newborn’s response to external stimuli. In general, the neonate’s ability to alter his response to repeated application of a stimulus (pin prick, light, noise) is considered a measurement of sophisticated central nervous system functioning. Scanlon et al. found decreased attentiveness, muscular hypotonia, less vigorous Moro and rooting responses, and altered decremental responses to pin prick in neonates 2 to 8 hours old following uncomplicated vaginal delivery with mepivacaine or lidocaine epidural anesthesia. In later studies, Scanlon et al. and Brown were unable to show any neurobehavioral change in neonates after maternal epidural anesthesia with bupivacaine (fig. 6) or 2-chloroprocaine.

Tronick et al. evaluated neonatal neurobehavioral performance for as long as ten days postnatally following maternal regional anesthesia with lidocaine and mepivacaine. Although changes in neonatal muscle tone were demonstrated, these changes were transient. They concluded that the observed changes in neonatal behavior were short-lived and of minimal consequence. At the present time, therefore, although subtle neurobehavioral changes can be demonstrated shortly after birth in neonates following maternal epidural anesthesia with lidocaine or mepivacaine, there is no evidence that these changes are detrimental to the newborn. The long-term clinical significance of these findings, if any, is unknown. Nevertheless, it seems prudent to minimize fetal exposure to local anesthetics that alter neurobehavioral states by using the lowest concentration of drug that will achieve the desired maternal analgesia, and by choosing agents such as bupivacaine or 2-chloroprocaine, which do not alter neonatal neurobehavioral status.

### Table 4. Postmortem Mepivacaine Concentrations in Infants Following Direct Fetal Injection

<table>
<thead>
<tr>
<th>Blood (μg/ml)</th>
<th>Tissue (μg/ml)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>Brain</td>
<td>Kidney</td>
</tr>
<tr>
<td>Infant 1</td>
<td>52</td>
<td>133</td>
</tr>
<tr>
<td>Infant 2</td>
<td>—</td>
<td>117</td>
</tr>
<tr>
<td>Infant 3</td>
<td>9.8</td>
<td>89</td>
</tr>
<tr>
<td>Cortex</td>
<td>81</td>
<td></td>
</tr>
<tr>
<td>Midbrain</td>
<td>77</td>
<td></td>
</tr>
<tr>
<td>Pons</td>
<td>84</td>
<td>59</td>
</tr>
<tr>
<td>Medulla</td>
<td>61</td>
<td></td>
</tr>
<tr>
<td>Cervical cord</td>
<td>78</td>
<td></td>
</tr>
<tr>
<td>Cerebellum</td>
<td>78</td>
<td></td>
</tr>
</tbody>
</table>

2. Fetal cardiovascular toxicity

Fetal circulatory depression not infrequently follows paracervical block and is associated with high fetal levels of local anesthetic. The nature of cardiovascular depression associated with local anesthetics has been studied in the adult, fetus and neonate. In adults, toxic local anesthetic concentrations (5–10 μg/ml or more) are associated with peripheral vasodilatation, decreased myocardial contractility, bradycardia, and arterial hypotension. Nontoxic concentrations of lidocaine (1–5 μg/ml), similar to those needed for anti-arrhythmia therapy, usually do not depress myocardial contractility or cardiac output. Change QRS duration or QT interval or alter cardiac rate.

Various investigators have studied the effects of local anesthetics on the fetal heart. Using mepivacaine, found bradycardia in sheep fetuses only when blood levels were extremely high (40 μg/ml). Morishima and Tachycardia and fetal acidosis ensued, associated with blood levels of 20–30 μg/ml. In an anesthetized fetal lamb preparation, Mann et al. observed fetal bradycardia within 60 seconds after single intravenous injections of massive doses of lidocaine (14–37 mg/kg) into the fetal jugular vein. Fetal heart rate returned...
to normal within 7 to 10 minutes. Teramo et al. found increases in fetal heart rate and blood pressure during constant lidocaine infusion with arterial lidocaine levels of 11.5 ± 3.8 µg/ml. The tachycardia and hypertension, however, were preceded by cortical seizure activity (fig. 7). Bradycardia, of probable reflex origin, then occurred. Only with bolus injection of 30, 40, or 50 mg lidocaine did they observe an initial fetal bradycardia and hypotension. Gestational age also influences the fetal cardiovascular response to local anesthetic-induced seizure activity. Increases in blood pressure and heart rate in response to lidocaine-induced seizures were greater with increasing gestational age. In the young fetus (gestation 120 days or less), blood pressure and heart rate changes were minimal.

In human anencephalic fetuses, massive subcutaneous doses of mepivacaine prolonged the PR interval and widened the QRS complex. Bradycardia did not occur during these ECG changes until shortly before the fetus died. On the other hand, mepivacaine produces significant negative inotropic and chronotropic effects in the denervated hearts of human fetuses obtained after therapeutic abortion at midgestation. In summary, then, the data suggest no change in fetal heart rate at modest local anesthetic levels, with bradycardia appearing at high levels, unless these levels are associated with convulsive activity. Fetal beat-to-beat variability (i.e., the normal fluctuations in baseline fetal heart rate) is diminished following epidural administration of lidocaine. This change is transient, usually lasting 5–20 minutes, and is probably of no clinical significance. Many factors influence fetal heart rate variability, including severe asphyxia, fetal breathing movements, gestational age, sleep states, and time of day. Transient decreases in fetal heart rate variability associated with maternal medication are of no known physiologic consequence.

3. Paracervical block bradycardia: direct or indirect fetal toxicity?

The fetal and neonatal consequences of paracervical block have received much study. The fetal bradycardia remains
the most frequent complication, occurring in 20 to 30 per cent of patients.\textsuperscript{116,292,371,377} Bradycardia usually develops within 2 to 10 minutes and lasts 3 to 30 minutes. Recent evidence suggests that post-paracervical-block bradycardia is directly related to high fetal levels of local anesthetics.\textsuperscript{16,139,141,342,343,371,375,377,379,408} Increasing the dose of mepivacaine for paracervical block increases the incidence and severity of fetal bradycardia.\textsuperscript{277} Supporting the thesis that bradycardia is produced by the local anesthetic is the finding that maternal intravenous administration of mepivacaine, in the absence of maternal hypotension, produces fetal bradycardia.\textsuperscript{277} Fetal drug levels in infants with bradycardia are occasionally higher than levels in simultaneously drawn maternal blood,\textsuperscript{116} suggesting that local anesthetics may reach the fetus by a more direct route than maternal systemic absorption. Transarterial diffusion of mepivacaine has been demonstrated,\textsuperscript{283} leading some investigators to postulate that high concentrations of local anesthetics reach the fetus by diffusion across the uterine arteries (fig. 8).

Yet, it is still unclear whether the fetal blood levels that result after paracervical block are high enough to depress the fetal heart directly. Fetal electrocardiographic changes during paracervical block-induced bradycardia have been examined by Freeman \textit{et al.}\textsuperscript{128} and Paul \textit{et al.}\textsuperscript{282} They described development of a shortened PR interval and a slow nodal rhythm, a pattern more typical of fetal hypoxia. Only when massive doses of mepivacaine were injected directly into anecphaletic fetuses did the characteristic lengthening of the PR interval and widening of the QRS complex appear.\textsuperscript{128,282} They suggested, therefore, that a decrease in uterine blood flow, possibly induced by uterine hyperactivity,\textsuperscript{85} was the primary event leading to fetal asphyxia and subsequent hypoxia-induced bradycardia.

Alternative suggested causes of post-paracervical-block fetal bradycardia include decreased uterine blood flow from direct mechanical compression of the uterine arteries, and uterine vasoconstriction either from the local anesthetic itself applied in close proximity to the artery (fig. 8) or from concomitantly administered epinephrine or maternal hypotension. The constrictive effects of local anesthetics on the uterine vessels are described below.

As we believe that the fetal distress that sometimes

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{fig8.png}
\end{figure}
accompanies paracervical block is probably the result of a combination of fetal asphyxia secondary to uterine vasoconstriction and high fetal uptake of local anesthetic. Regardless of the etiology, because the bradycardia is associated with fetal acidosis and an increased likelihood of neonatal depression, we recommend that paracervical block be avoided in cases of utero-placental insufficiency, prematurity, or pre-existing fetal distress.

II. Indirect Effects of Local Anesthetics on the Fetus and Neonate

Fetal survival requires the delivery of adequately oxygenated maternal blood to the intervillous space. Maternal oxygen transport decreases with a reduction in uterine blood flow or oxygen content. Conduction anesthesia may adversely affect uterine blood flow by causing hypotension, adrenergic stimulation, or uterine hyperactivity. Complications of conduction anesthesia also may cause maternal hypoxia.

A. Changes in Uterine Blood Flow

Uterine blood flow varies directly with perfusion pressure across the uterine vascular bed (i.e., mean uterine arterial pressure minus mean uterine venous pressure) and inversely with uterine vascular resistance. A decrease in mean arterial blood pressure during conduction anesthesia will reduce uterine blood flow proportionately. On the other hand, epidural anesthesia uncomplicated by arterial hypotension is associated with no alteration in uterine blood flow. Uterine vascular resistance, in turn, is determined by the intrinsic vasomotor state of the uterine vessels and the influence of external mechanical compression during and between uterine contractions. In the unanesthetized parturient, the uterine arteries at term are almost maximally dilated but will constrict in response to a variety of stimuli. There is recent experimental evidence that local anesthetics, at blood levels in the toxic range, constrict uterine vessels directly. Endogenous or exogenous catecholamines with alpha-adrenergic stimulating activity increase uterine vascular resistance and reduce uterine blood flow. Although maternal hormonal factors as well as the fetus itself may play a role in the regulation of uterine blood flow, acute changes in flow depend primarily on the balance between uterine perfusion pressure and vascular resistance.

1. Hypotension

Maternal hypotension remains a common complication of conduction anesthesia and may have profound effects on uterine blood flow and fetal well-being. The reported incidences of hypotension in the parturient after conduction anesthesia vary, depending on the authors’ definitions of hypotension, adequacy of monitoring, height of the block, and use of prophylactic measures to maintain maternal blood pressure. For example, we have found in groups of parturients undergoing elective cesarean sections with epidural anesthesia that the incidence of hypotension is decreased from 82 to 14 per cent by prophylactic administration of ephedrine, lactated Ringer’s solution, and left uterine displacement. The inclusion of epinephrine in the local anesthetic solution may contribute to transient maternal hypotension. Der Yuen et al. and Akamatsu...
found decreases in mean arterial blood pressure, stroke volume, and total peripheral resistance in parturients undergoing epidural anesthesia for cesarean section. The decrease in blood pressure was greater when epinephrine was added to the local anesthetic. In contrast, Levinson et al. found no difference in the incidence of hypotension during epidural anesthesia whether epinephrine was included in the local anesthetic or not. Different methods of hypotension prophylaxis may account for these conflicting results.

The parturient at term is particularly susceptible to hypotension during major conduction anesthesia. Nearly a sixth of her blood volume is contained in the uterus, enhancing the effect of additional peripheral venous pooling occurring with sympathetic block. Partial or complete inferior vena caval and lower aortic occlusion from compression by the gravid uterus is present in the majority of supine parturients. This obstruction impedes venous return to the heart and may cause hypotension. In most parturients, an increase in resting sympathetic tone compensates for the effects of vena caval compression and blood pressure is maintained. However, when sympathetic tone is abolished, as with spinal or epidural anesthesia, marked reductions in blood pressure may result. Finally, a diminished extracellular fluid volume, either from blood loss or from dehydration during labor and delivery, may further promote maternal hypotension.

2. Local anesthetic-induced uterine vasoconstriction

Gibbs and Noel, using an in vitro preparation, observed development of uterine artery contraction after exposure to high concentrations of lidocaine. The concentrations used were generally well above systemic lidocaine levels achieved during clinical use. Greiss et al. recently studied the uterine effects of intra-arterial injections of procaine, lidocaine, mepivacaine, and bupivacaine in nonpregnant ewes and demonstrated a dose-related decrease in uterine blood flow (fig. 9). Subsequent unpublished studies in the pregnant ewe by Fishburne et al. and Pue et al. produced similar findings. Uterine vasoconstriction occurred only at very high blood levels which might be found in the uterine vasculature during routine paracervical blocks (close proximity of the injected drug to the uterine arteries) or during systemic toxic reactions. The lack of uterine vasoconstriction with low blood levels of lidocaine was recently confirmed by Biehl et al. These investigators infused the local anesthetic intravenously to produce blood levels (2–4 μg/ml) in the pregnant ewe comparable to those usually found in the human parturient undergoing epidural anesthesia during the first and second stages of labor. They found that a two-hour exposure to these low concentrations of lidocaine did not significantly decrease uterine blood flow.

3. Adrenergic stimulation

Adrenergic stimulation can constrict uterine vessels and reduce uterine blood flow. High blood epinephrine levels achieved by inadvertent intravascular injection produce alpha effects with consequent uterine vasoconstriction, increase in uterine activity, and decrease in uterine blood flow. In ewes given 0.10–1.00 μg/kg/min epinephrine, maternal blood pressure rose to 50 to 65 per cent above control values, and uterine blood flow was reduced 55 to 75 per cent. Vasopressors with strong alpha-adrenergic activity similarly diminish uterine blood flow and may adversely affect the fetus. Methoxamine, phenylephrine, angiotensin, or norepinephrine treatment of spinal hypotension in animals diminishes uterine blood flow and leads to fetal asphyxia. Metaraminol, with mixed alpha- and beta-adrenergic activity, restores uterine blood flow, but does not prevent progressive fetal acidosis. Mephenadrine and ephedrine restore uterine blood flow toward normal and improve the fetal acid–base status. Prophylactic vasopressor administration also may be deleterious. Eng et al. reported that methoxamine infusion in pregnant primates decreased uterine blood flow and produced fetal asphyxia. Infusion of ephedrine, a predominantly beta-adrenergic stimulating drug, had no discernible effect on uterine blood flow or fetal acid–base status during the infusion (fig. 10). In normotensive pregnant ewes, we found that methoxamine and metaraminol decreased uterine blood flow at all dose levels. On the other hand, ephedrine doses that increased blood pressure by 50 per cent had no detrimental effect on uterine blood flow or fetal acid-base status (fig. 11). It thus appears that drugs such as ephedrine or mephenadrine, which support maternal blood pressure primarily by central adrenergic stimulation (positive inotropic and chronotropic activity) have minimal effects on uterine blood flow in the normotensive mother and restore uterine blood flow with treatment of spinal hypotension.

4. Uterine hypertonus

Uterine hypertonus increases uterine vascular resistance and may result in fetal distress by de-
creasing uterine blood flow. Both local anesthetics and the vasoactive drugs given during the course of conduction anesthesia may cause uterine hyperactivity and tetanic contractions.\textsuperscript{24-106} Uterine muscle possesses both alpha- and beta-adrenergic receptors. Strong alpha-adrenergic agents, such as methoxamine, may cause uterine hypercontraction and abrupt decreases in uterine blood flow.\textsuperscript{358} Following administration of methoxamine (10–20 mg, im, or 3–5 mg, iv) to prevent or treat hypotension during conduction anesthesia, Vasicka et al.\textsuperscript{406} observed intense uterine contractions with severe fetal bradycardia. Kendall\textsuperscript{107} reported a similar response. Epinephrine, which is commonly administered with local anesthetics to decrease absorption, has both alpha and beta activity. Alpha effects from high blood levels cause generalized vasoconstriction and uterine hypotonus and may occur during inadvertent direct vascular injection of epinephrine-containing local anesthetics. Beta effects, on the other hand, produce generalized vascular smooth muscle relaxation, and uterine hypotonus. Beta activity predominates with the low blood levels that follow absorption from the epidural space.\textsuperscript{190,358} Local anesthetics may directly cause uterine hypotonus. When Greiss et al.\textsuperscript{148} injected local anesthetics directly into the uterine artery of the pregnant ewe a dose-related increase in uterine tone occurred. In vitro studies of uterine muscle strips demonstrate that local anesthetics increase tone but decrease the rate and strength of contractions.\textsuperscript{231} This effect is antagonized by calcium.\textsuperscript{181}

Although direct intrauterine injection of local anesthetics may cause uterine hyperactivity and fetal bradycardia,\textsuperscript{24,105} the commonly encountered clinical blood levels of local anesthetics have little, if any, direct uterine stimulating activity.

5. Fetal and neonatal consequences of decreased uterine blood flow

The fetal hazard of maternal hypotension depends on the severity and duration of hypotension, its etiology, and the concurrent fetal status. The risk to the fetus appears directly related to the consequent reduction in uterine blood flow. When uterine blood flow is further reduced by uterine arterial vasoconstriction or concomitant uteroplacental insufficiency, the risk to the fetus is increased. When uterine blood flow is reduced sufficiently, fetal asphyxia results.\textsuperscript{12,97,207,264,270,380}

The greatest hazards of fetal asphyxia are to the central nervous system, the heart, and the lungs. Perhaps the most devastating result of maternal hypotension in the fetus and neonate is central nervous system damage.\textsuperscript{30,40,270} In monkeys (anesthetized with halothane) the fetus tolerates a reduction in mean maternal pressure to 50 torr for as long as one to two hours, but pressures of 40 torr or lower regularly

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{figure10.png}
\caption{Percentage changes in maternal and fetal hemodynamics (mean ± SE). MABP = mean maternal arterial blood pressure (9M, 7E). HR = heart rate (9M, 7E). CO = cardiac output (6M, 7E). SV = Stroke volume (9M, 7E). TPR = total peripheral resistance (9M, 7E). FHR = fetal heart rate (9M, 6E). FBP = fetal arterial blood pressure (8M, 6E). UBF = uterine blood flow (6M, 6E). Number in parentheses indicates the number of animals included in a methoxamine (M) or ephedrine (E) treatment. Reproduced from Eng, M., Berges, P. U., Ueland, K., et al.: The effects of methoxamine and ephedrine in normocaricotic pregnant primates, Anesthesiology 35: 356, 1971, with permission.}
\end{figure}
produce fetal asphyxia. Fetal P<sub>N</sub> is reduced from a normal control value of 29–34 torr to 13–16 torr. Fetal pH ranges from 7.10 to 7.15, and concomitant fetal heart rate deceleration characteristic of fetal hypoxia occurs. Fetal brain damage is related to the severity and duration of acidosis. With mild asphyxia (pH 7.10) no damage occurs. With severe asphyxia (pH 7.00) lasting several hours, fetal death from myocardial failure results. With intermediate severity or duration of fetal asphyxia, permanent brain injury occurs, with lesions similar to those of human cerebral palsy.

Intrauterine asphyxia may contribute to neonatal idiopathic respiratory distress syndrome (IRDS). Fetal hypoxia and acidosis cause pulmonary hypopfusion with depletion of surfactant and consequent instability of the neonatal lung. Maternal hypotension resulting in fetal asphyxia may, therefore, predispose to IRDS in the neonate. Numerous additional studies in man and experimental animals have examined fetal well-being during maternal hypotension. Application of animal data to the human fetus is difficult because of species differences, inherent differences in fetal reserve, and variable experimental conditions. Human studies suffer from our limited ability to monitor the fetus and measure maternal uterine blood flow. Studies of the fetal effects of maternal hypotension in man usually are limited to measurement of changes in fetal heart rate and acid–base status during labor. Neonatal effects have been evaluated by Apgar scores, umbilical cord blood gases, and, tragically, in some cases, by postmortem examination.

Human fetal distress from hypotension during regional anesthesia is well-documented. During epidural anesthesia, pathologic or late deceleration fetal heart rate changes can develop when maternal systolic blood pressure is less than 100 torr for 5–7 minutes. The fetal heart rate reverts to normal with administration of oxygen and attainment of normotension. Fetal bradycardia consistently occurs with spinal anesthesia when maternal systolic blood pressure is less than 70 torr. Bradycardia develops in some fetuses when maternal systolic pressure is less than 80 torr for 4 minutes or longer. Transient decreases to 70 to 100 torr, systolic, apparently do not cause bradycardia. Heart rate abnormalities generally develop in healthy fetuses after 5–9 minutes of maternal systolic blood pressure of less than 80 torr. When hypotension and decreased uterine blood flow are transient there usually is no fetal complication.

Stenger et al. observed a decrease in systolic blood pressure of 58 per cent after spinal anesthesia...
and a decrease of 13 to 59 per cent after caudal or epidural block in parturients undergoing cesarean section. Bradycardia was not seen; all infants were delivered with good Apgar scores, and cord blood gases showed no abnormality. The hypotension was brief; and treatment, consisting of leg elevation and/or ephedrine administration, was instituted promptly. During elective cesarean section, Moya and Moya and Smith demonstrated an increased incidence of fetal depression as measured by low Apgar scores when maternal systolic blood pressure fell to between 90 and 100 torr and was allowed to remain there for longer than 15 minutes. Parturients who had blood pressure depressions to less than 90 torr, but were promptly treated, had infants who were vigorous at birth. Bonica likewise reported late deceleration fetal heart rate patterns when maternal systolic pressure was less than 100 torr for longer than 4 minutes. Schiffrin reported that in a series of 200 patients receiving epidural anesthesia alone or in combination with oxytocin, hypotension (defined as a reduction in maternal systolic pressure of 20 torr or more) developed in 25 (12.5 per cent). Latc decelerations developed in 18 of the fetuses (72 per cent). These decelerations usually disappeared when the patient was turned on her side and given an infusion of Ringer's lactate solution. Ziliandi reported his experience with 39 patients receiving epidural anesthesia. Fetal heart rate abnormalities were observed in 30 of these patients, 27 of whom had associated hypotension (systolic pressure less than 100 torr). Fetal bradycardia disappeared after the correction of hypotension with ephedrine. Ziliandi concluded that a systolic pressure of less than 100 torr for 10–15 minutes led to fetal acidosis and bradycardia. In summary, data acquired in human studies, although indirect, suggest that a maternal systolic pressure of less than 100 torr in a previously normotensive parturient, when left untreated, can lead to fetal asphyxia.

Moment-to-moment changes in maternal and fetal homeostasis during spinal hypotension have been extensively studied in experimental animals. Lucas and others found that spinal hypotension in pregnant ewes decreased maternal mean arterial pressure and uterine blood flow by 50 and 65 per cent, respectively. Despite this reduction for a 20-minute period, there was no significant change in fetal arterial or venous pressure, umbilical blood flow, or fetal arterial blood pH. Metaraminol administration corrected maternal blood pressure and uterine blood flow while producing no effect on the fetus. Greiss and others confirmed the decrease in uterine blood flow that occurred with spinal hypotension in sheep. Norepinephrine, angiotensin, and phenylephrine restored maternal blood pressure, but uterine blood flow remained depressed. Maternal infusion of dextran of 5 per cent dextrose in water restored both blood pressure and uterine blood flow. Fetal effects, however, were not studied. Using a similar model, Shnider and others found considerable variability in the fetal responses to maternal hypotension. A 40 per cent reduction in mean maternal arterial pressure led to fetal asphyxia in as little as 9 minutes or required as long as 160 minutes. Ephenedrine corrected both maternal blood pressure and fetal acid-base values.

6. Treatment of hypotension

Thus, both human and animal data show that during spinal or epidural anesthesia maternal hypotension reduces uterine blood flow. The fetal effects of reduced uterine blood flow are variable, and depend on the magnitude and duration of the impairment in uterine blood flow, fetal oxygen consumption, and the presence of concomitant maternal or fetal complications. It is prudent, however, to institute prompt therapy when, in a previously normotensive parturient, arterial systolic pressure falls below 100 torr or below 70 per cent of normal. Maintenance of adequate maternal blood pressure is particularly important when placental function is already impaired, as in pre-eclampsia or diabetes. In such cases, it seems advisable to institute therapy when maternal pressure falls below 75 per cent of preanesthetic values. Therapy of maternal hypotension includes left uterine displacement, of positioning the parturient on her left side to relieve aorto–vena caval obstruction; volume expansion with intravenous fluids; and oxygen administration. In the few parturients in whom these measures are ineffective, a vasopressor with predominantly beta-adrenergic properties (ephedrine, 5–10 mg, iv) is necessary.

B. Maternal Hypoxia

Complications of regional anesthesia that may seriously impair both maternal and fetal oxygen content include convulsions from toxic blood levels of local anesthetics or an excessively high dermatome level and paralysis after subarachnoid or epidural anesthesia, the so-called "total spinal." Fortunately, maternal hypoxia is rare with properly conducted regional anesthesia. Even with high subarachnoid block or epidural block (T2), arterial blood gases

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Anesthesiology
V 48, No 1, Jun 1978

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### Table 5. Regional Anesthesia for Obstetrics: Incidence of Serious Complications

<table>
<thead>
<tr>
<th>Regional Technique</th>
<th>Number of Patients</th>
<th>Toxic Reaction (Convulsions)</th>
<th>Resultant Mortality</th>
<th>Dural Penetration</th>
<th>Total Spinal</th>
<th>Paralysis (Permanent)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epidural</td>
<td>9,000</td>
<td>0.03</td>
<td>0</td>
<td>—</td>
<td>0.03</td>
<td>0</td>
<td>276</td>
</tr>
<tr>
<td></td>
<td>300</td>
<td>—†</td>
<td>N/S</td>
<td>0.8</td>
<td>—</td>
<td>?</td>
<td>293</td>
</tr>
<tr>
<td></td>
<td>1,035</td>
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<td>704</td>
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<td>2</td>
</tr>
<tr>
<td></td>
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* One case of foot drop in each series (possibly related to spinal, lumbosacral trunk injury or peroneal nerve injury)—one had progressive return of function to 95 percent of normal by seven months, while the other had significant but not disabling symptoms four and a half years later.

† Not specified.

In fact, Moya and Smith found that although parturients anesthetized to a dermatome level of C5 complained of dyspnea, they usually hyperventilated. Convulsions during obstetric conduction anesthesia are rare, occurring in as many as 0.7 per cent of patients (table 5). Maintenance of adequate maternal ventilation and oxygenation is the principal treatment. Small doses of a short-acting barbiturate or diazepam may be necessary to control seizures.

"Total spinal" after caudal or lumbar epidural anesthesia occurs in 0.05 to 0.06 per cent of patients. Improperly treated "total spinal" anesthesia may lead rapidly to profound hypotension, unconsciousness, aspiration, and cardiac arrest. Assuring maternal ventilation and oxygenation is of prime importance to treatment. Simultaneous support of maternal circulation with vasopressors and or intravenous fluids may be necessary.

Among local anesthetics, prilocaine is unique in its ability to lower blood oxygen-carrying capacity by the conversion of hemoglobin to methemoglobin. Probably the conversion is caused by a metabolite of prilocaine (O-toluidine), rather than prilocaine itself. The amount of methemoglobin formed is directly related to the total dose of anesthetic. Conversion occurs in both mother and fetus, with the highest measured amounts of fetal conversion reported to be less than 30 per cent of total hemoglobin. Twenty to fifty per cent conversion usually is necessary to produce symptoms in adults. Probably the fetus does not produce appreciable amounts of O-toluidine from prilocaine, since fetal hepatic amidase activity is low. However, sufficient metabolite comes from the mother to produce cord blood methemoglobin levels higher than those in maternal samples. The higher fetal or neonatal methemoglobin may be caused by a transient deficiency of methemoglobin reductase activity in erythrocytes and, therefore, an impaired conversion of methemoglobin to hemoglobin. The methemoglobinemia that is present following large or repeated doses of prilocaine usually will subside in a few hours. When necessary, methylene blue, 5 mg/kg, iv, is an immediate and effective antidote in mother and infant.
C. Changes in Duration of Labor and Rate of Forceps Delivery

Epidural, spinal, paracervical, or pudendal anesthesia may alter the forces of parturition through changes in uterine contractility or maternal expulsive efforts. In non-anesthetized patients, factors that lengthen either the first or the second stage of labor are associated with a higher incidence of neonatal morbidity and mortality. In contrast, although major regional anesthesia may prolong labor, there is no evidence that this harms the fetus. In fact, less fetal acidosis develops during a prolonged first or second stage of labor in parturients during epidural anesthesia than in non-anesthetized mothers.

Nearly all methods of analgesia can slow or stop labor in the latent phase of the first stage. This applies to narcotics, sedatives, paracervical block, or major conduction anesthesia. In well-established labor, i.e., during the latter part of the first stage or during the second stage, analgesia usually has little effect on the progress of labor. A T10 sensory analgesia level produced by spinal or lumbar epidural block has no significant effect on uterine contractility or cervical dilation in the absence of hypotension or fetal malposition or malpresentation. Some investigators report a small, transient (10–20 minutes) decrease in uterine contractility after spinal or epidural block administered during the active phase of the first stage of labor. On the other hand, others report enhanced and more effective uterine contractility after epidural or caudal anesthesia. In fact, these techniques have been used effectively to manage parturients with multiparity, breech presentation, or incoordinate uterine activity during labor. In a large prospective series of parturients with dysfunctional labor, Studd et al. observed shorter labors, decreased need for instrumental delivery, and higher neonatal Apgar scores when oxytocin was used to augment labor than when the dysfunctional labor was left unstimulated. Epidural anesthesia was utilized in more than 30 per cent of these labors. The judicious use of oxytocin rather than the presence or absence of epidural anesthesia appeared to be the crucial factor in determining the overall duration and outcome of labor.

No completely satisfactory explanation for inhibition of uterine contractility by regional anesthesia exists. Local anesthetic concentrations attained in vivo are not high enough to inhibit uterine contractility directly, although some evidence suggests that local anesthetics may antagonize the membrane effects of oxytocin and, thus, inhibit uterine contractility indirectly. Epinephrine inhibits uterine contractility, but the epinephrine concentration commonly used with local anesthetics has generally been considered insufficient to affect the course or duration of labor. However, Gunther et al. showed that the first stage of labor was prolonged in parturients receiving lidocaine or mepivacaine with epinephrine, compared with those receiving lidocaine or mepivacaine without epinephrine, during continuous caudal anesthesia. In addition, almost twice as many parturients needed oxytocin augmentation when solutions containing epinephrine were used. The doses of epinephrine ranged from 100 to 125 µg. Sensory analgesia, causing interruption of Ferguson’s reflex (oxytocin release in response to cervical dilatation) may cause uterine inhibition. However, this reflex has not been demonstrated in man.

Regional anesthesia may modify the second stage of labor by removing the parturient’s reflex urge to bear down or by interfering with motor function. Johnson et al. compared the effects of pudendal, spinal, and epidural anesthesia on uterine contractility and maternal expulsive efforts during the second stage of labor. Subarachnoid block with an upper dermatone level of T3 to T12 as associated with a prolonged second stage and decreased voluntary effort when compared with the pudendal group. No change in intensity of uterine contractions was seen. Epidural anesthesia with a T10 to S5 block reduced the intensity of uterine contraction and voluntary effort, but no overall prolongation of the second stage occurred. The parturients were able to deliver spontaneously.

Of greater concern from the standpoint of neonatal risk, however, is the greater reported incidence of mid-forceps deliveries occurring in parturients with conduction anesthesia. Relaxation of the pelvic musculature interferes with flexion and internal rotation of the fetus. Withholding the perineal dose of anesthetic until descent and rotation of the infant has occurred, or utilizing a lower concentration of anesthetic to preserve skeletal muscle tone, should obviate this problem. Furthermore, parturients who are properly instructed can deliver spontaneously during epidural anesthesia.

III. Safety and Benefits of Regional Anesthesia in Obstetrics

A. Safety

The reported incidences of serious complications such as convulsions, cardiovascular collapse, or
permanent neurologic sequelae in most large series are extremely low (table 5). In approximately 32,459 reported cases in which lumbar epidural or caudal anesthesia was used, there were 30 cases of maternal convulsions, and four “total spinals.” In none of these series was there any maternal death attributable to the regional anesthesia. Similarly, permanent neurologic injury is extremely rare. There was no case in the patients receiving epidural or caudal anesthesia, and only two cases occurred in the approximately 29,000 patients receiving spinal anesthesia. Both these patients sustained foot drop, which may have been related to obstetric injury to either the lumbosacral trunk or the peroneal nerve. This low incidence of serious complications is comparable to that found in surgical patients.7,278,409,163 Although maternal toxic reactions, dural puncture and “total spinal” occur, with appropriate management by experienced anesthesiologists resultant maternal morbidity is minimal.

Despite potential and often only theoretical neonatal hazards, regional anesthesia for obstetrics also has an impressive record of safety for the newborn. Apgar et al.14 were among the first to report the very low incidence of neonatal depression associated with maternal conduction anesthesia. Numerous subsequent reports have confirmed the relative lack of neonatal depression after spinal,50,117,256,258,260,460,466,468 locus epidural anesthesia,50,117,256,258,260,460,466,468 and lumbar epidural anesthesia.104,123 Marx et al.122 found less acidosis in infants born after subarachnoid anesthesia than after general anesthesia. Similar results were found by Fox et al.122 after maternal epidural anesthesia. Shnider147 recently reported the impacts of various types of regional anesthesia on the neonate following complicated and uncomplicated vaginal delivery. No significant differences in the percentages of vigorous babies (Apgar scores 7–10 at 1 and 5 minutes) were found among those parturients receiving spinal, lumbar epidural, or local–pudendal anesthesia when compared with a group of mothers receiving no anesthesia. The incidences of fetal depression were minimal and similar in all groups.

Numerous reports thus attest to the fetal and neonatal safety of maternal regional anesthesia. Nevertheless, recent several investigators250,325,417,428 have suggested an adverse fetal effect from epidural anesthesia despite the avoidance of maternal hypotension and excessive local anesthetic administration. Schiffrin,305 McDonald et al.300 and Wingate417 reported increased incidences of late deceleration of the fetal heart rate during epidural anesthesia even when maternal hypotension was absent and minimal doses of local anesthetics were employed. In the study by McDonald, however, no control group was included. Furthermore, fetal pH and base excess were not adversely affected by epidural anesthesia, reflecting the transient nature of the fetal heart rate decelerations. All neonates were vigorous at birth, including a group of 13 neonates born to mothers with pre-eclampsia.197 In the cases reported by Schiffrin,303 the fetal heart rate returned to normal after positioning the parturient on her side and increasing the intravenous infusion rate. Oxytocin was used to augment labor in these studies250,325; its role in aggravating fetal heart rate abnormalities is unclear.

In contrast, several well-controlled studies have confirmed the fetal safety of epidural anesthesia when maternal hypotension and large doses of local anesthetics are avoided.23,380,384,424,426 Belfrage et al.21 reported that during epidural anesthesia fetal scalp blood pH was within normal limits and no pathologic fetal heart rate tracings were elicited by the blockade. Thalme et al.380,381 found less maternal and fetal metabolic acidosis during lumbar epidural analgesia with bupivacaine than in a non-epidural-anesthesia group of parturients. Zador et al.424,426 confirmed that less fetal and neonatal acidosis occurred during either low-dose intermittent or continuous lumbar epidural anesthesia compared with a non-anesthetized control group. Ominous fetal heart rate patterns indicating hypoxia were rare, and occurred almost exclusively in association with transient maternal hypotension.

B. Benefits

The most obvious maternal benefit of well-conducted major regional anesthesia is complete alleviation of pain in the fully awake cooperative parturient. In addition, less maternal metabolic acidosis23,170,263,380,424,425 and less hyperventilation occur.298,336 The obstetrician may perform a well-controlled, unhurried delivery and a thorough postpartum pelvic examination and repair when indicated.

The fetus and neonate benefit from well-conducted regional anesthesia. Neonatal central nervous system depression from placental transfer of narcotics or sedative–hypnotics is avoided. Forcible delivery, when indicated, should result in less trauma to the neonate in a cooperative mother with a relaxed perineum.

In a Canadian study of ten university teaching hospitals,298 the perinatal death rate in babies delivered without anesthesia was 8.2 per 1,000, compared with 4.9 per 1,000 when conduction anesthesia was given. In premature babies the difference was even more striking. The perinatal mortality rate
was 440 per 1,000 when no anesthesia was administered, compared with 140 per 1,000 when conduction anesthesia was administered. These differences probably reflect a large number of precipitous or poorly controlled deliveries with subsequent fetal head injury.

Recent evidence suggests that relief of maternal pain and apprehension may in itself benefit the fetus.220,268,353 Myers268 reported fetal bradycardia and asphyxia in the pregnant rhesus monkey in association with maternal stress and anxiety, probably due to increased maternal catecholamine release causing uterine vasoconstriction. Shnider et al.353 have found that in pregnant sheep, stress sufficient to produce maternal hypertension and tachycardia resulted in a precipitous reduction in uterine blood flow. Similarly, Martin et al.226 found a marked reduction in uterine blood flow in response to severe stress in the pregnant rhesus monkey.

Presumably, relief of maternal pain and anxiety with regional anesthesia will reduce endogenous catecholamines and thus improve uterine blood flow. The relationship of anesthesia to maternal plasma catecholamines and fetal well-being deserves investigation.

Conclusion

Properly conducted, regional anesthesia for obstetrics provides effective pain relief for the parturient while avoiding the maternal central nervous system depression associated with general anesthesia or systemic narcotic analgesics. Thus, the mother can participate in and enjoy the birth of her baby with minimal risk of maternal respiratory depression, airway obstruction, or vomiting and aspiration. Although local anesthetics rapidly cross the placenta, the concentrations of drug seen in the fetus and neonate generally are low and do not cause significant clinical depression. There are two potential exceptions to the general safety of regional anesthesia in obstetrics. One results from paracervical blocks and the other results from administration of large doses of local anesthetics. Both may produce excessive fetal and neonatal blood levels, leading to cardiovascular and central nervous system toxicity. This risk may be minimized by using the smallest amount of local anesthetic necessary for analgesia. The use of local anesthetics that are rapidly metabolized (such as procaine or 2-chloroprocaine) and highly protein-bound (such as bupivacaine and etidocaine) may offer further protection. Hypotension from any cause, including caudal, lumbar epidural, or spinal anesthesia, remains a significant risk to the fetus. Careful monitoring of maternal blood pressure is essential when these techniques are employed. Rapid diagnosis of hypotension, immediately followed by treatment with left uterine displacement, fluids, and/or ephedrine, can abolish or minimize fetal morbidity.

Labor may be prolonged by epidural or caudal anesthesia, but such prolongation of itself has not been shown to be detrimental to the fetus.

There is no ideal anesthetic or anesthetic method for childbirth. Nevertheless, the advantages of properly conducted regional anesthesia for both mother and infant justify its increasing popularity.

The authors are deeply appreciative of the advice and efforts of Doctors Gershon Levinson, Richard Wright, and Edmond I. Eger, II, in helping to edit this manuscript.

References

reference to transmission of cyclopropane across the placenta. JAMA 165:2155–2161, 1957


48. Brown WU Jr: Personal communication


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D. H. RALSTON AND S. M. SHNIDER
Anesthesiology
V 48, No 1, Jan 1978

pulmonary hypoperfusion syndrome. Pediatrics 35:733–742, 1965


75. Dawes GS: Fetal and Neonatal Physiology. Chicago, Year Book Medical Publishers, 1968, p 120


102. Epstein BS, Banerjee SG, Coakley CS: Blood concentration of prilocaine and lidocaine with epinephrine during


152. Gunther RE, Bellville JW: Obstetrical caudal anesthesia: II. A randomized study comparing 1 per cent meperidine with 1 per cent meperidine plus epinephrine. Anesthesiology 37:288–298, 1972


213. Lund PC, Cwik JC: Propitocaine (Citanest™) and methemoglobinemia. Anesthesiology 25:569–571, 1965


217. Malpas P: The pattern of the contractions of the pregnant uterus under spinal anaesthesia, the attendant changes in the reactivity of the myometrium. J Obstet Gynecol Br Emp 51:112–120, 1944


280. Ontario Perinatal Mortality Study Committee: Second Report
REGIONAL ANESTHESIA AND THE FETUS


352. Shinder SM: Personal communication, 1977
353. Shinder SM, Wallis LK, Lewiston G: Personal communication
REGIONAL ANESTHESIA AND THE FETUS

63


411. Wagner IH, de Jong RH, Prince DA: Effects of lidocaine


