EFFECTS OF PREGNANCY ON LOCAL ANESTHETIC ACTION AND TOXICITY

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It has been known since the early 1960s that the dose requirement for lumbar epidural or spinal anesthesia is reduced during pregnancy and parturition (1-3). This altered response to local anesthetics persists into the early puerperium (4,5). Engorgement of epidural veins resulting in decreased capacity of the spinal and epidural spaces was the commonly accepted explanation for this phenomenon until 1979, when it was noted that a facilitated spread of epidural analgesia occurs even during the first trimester of pregnancy, at a time when mechanical factors are unlikely to play a significant role (6). The authors proposed that hormonal changes of pregnancy, particularly the increase in progesterone levels, may alter the susceptibility of nerve membrane to local anesthetics. Datta et al found that indeed there was a significant correlation between lidocaine dose requirement for spinal anesthesia and CSF progesterone concentration (5). Less lidocaine was required in parturients and postpartum patients than in nonpregnant patients.

Increased susceptibility to local anesthetics during pregnancy was also noted in peripheral nerves. Lidocaine inhibited impulse conduction in median nerve fibers to a greater extent in pregnant than nonpregnant women (7). Similarly, conduction blockade, induced by exposure to bupivacaine, was greater and occurred more rapidly in A and C fibers of isolated vagus nerves obtained from pregnant rabbits than in nerves from nonpregnant animals (8,9). Administration of progesterone to rabbits, over a 4-day period, increased the susceptibility of excised vagus nerve to bupivacaine (10), but an acute nerve exposure to progesterone had no effect (11).

In an editorial published in 1979, Albright suggested that bupivacaine and etidocaine may be more cardiotoxic than the less potent agents such as lidocaine and mepivacaine (12). This idea was based on six cases of sudden cardiovascular collapse which happened shortly after intravascular injection of large doses of bupivacaine (and etidocaine in one instance).
intended for epidural anesthesia. Over 50 such cases have become known to date; in approximately 30 of them, resuscitation was unsuccessful.

Since cardiac arrests occurred predominantly in parturients, the question arose as to whether the pregnant patient is more sensitive to the cardiotoxic effects of local anesthetics or, more simply, whether the widespread use of bupivacaine for obstetric anesthesia was responsible for the number of cases reported in pregnant women. In our study, the CNS and cardiovascular toxicity of bupivacaine was compared in pregnant and nonpregnant ewes during continuous intravenous infusion of the drug (13). The mean dose of the drug resulting in cardiovascular collapse was significantly lower in pregnant ewes than in nonpregnant animals. Similarly, bupivacaine blood concentrations at circulatory collapse were lower in the pregnant group. In order to ascertain whether pregnancy enhances the toxicity of other local anesthetics as well, similar studies were conducted using mepivacaine, lidocaine, or ropivacaine (14-16). None of these drugs appeared to be more toxic to pregnant than nonpregnant sheep.

The reasons for the altered toxicity of bupivacaine during pregnancy have not been fully elucidated. A recent study has shown that pretreating rabbits with progesterone increases the in vitro effects of bupivacaine, but not of lidocaine or ropivacaine, on transmembrane action potential parameters in Purkinje fibers and ventricular muscle cells (17,18). Data from our laboratory suggest that the gestational decrease in the protein binding of bupivacaine may be the cause of increased cardiotoxicity of the drug (14). Protein binding of bupivacaine was also lower in parturients than in nonpregnant volunteers (19).

In summary, pregnancy is associated with altered sensitivity of biological membranes to some local anesthetics, resulting in enhanced neural blockade and cardiotoxicity.

REFERENCES

2. Hehre FW, Moyes AZ, Senfield RM et al: Continuous lumbar peridural anesthesia in obstetrics. II. Use of minimal amounts of local anesthetics during labor. Anesth Analg 44:89-93, 1965