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Surgery and Pregnancy

Vol 7#5, February 2000

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Up to two percent of all pregnant women undergo surgery during pregnancy. Each year, thousands more women of reproductive age chronically inhale trace amounts of anesthetic gas while working in operating rooms and dental offices. The risks and benefits of possible surgery or occupational exposure must be carefully considered in any pregnancy. This RISK//NEWSLETTER will review the potential reproductive risks in women acutely exposed to anesthesia during surgery or chronically exposed to anesthetic gases in their occupation.

Surgery and anesthesia in pregnancy

Knowledge regarding the safety of surgery and anesthesia during pregnancy is based primarily on animal studies and retrospective human surveys conducted mostly in the 1970's and early 1980's. These studies have a number of confounding variables. Women are generally given multiple anesthetic agents and other agents (including analgesics, antiemetics and sedatives), making it difficult to discern the effects of individual agents. When surgery is combined with anesthesia, it is not possible to determine whether adverse outcomes are due to the operative procedure, the underlying maternal condition, maternal stress, fever or the anesthetic agent. While animal studies make it possible to separate the procedural risks from risks associated with the anesthesia exposure, even in animal studies, it remains difficult to determine if the observed effect is due to the anesthetic or to the physiological changes caused by anesthesia. Variations in genetic susceptibility also make it difficult to generalize these studies to humans because of interspecies variation.

Most human studies have not found a significant difference in the overall rate of congenital anomalies among women receiving general anesthesia while undergoing surgery (Knill Jones, 1972; Duncan et al., 1986; Mazze et al., 1989). Further analysis of the Mazze et al. study did note a significant increase in the incidence of neural tube defects (NTDs); six NTDs were observed while only 2.5 were expected. There were no indications that any one anesthetic was the cause of the NTDs, and researchers could not rule out other factors such as the underlying disease, the neuroendocrine events associated with the stress of surgery, or the trauma of the operation as the cause of the increased incidence NTDs. The authors report that the association could be a random finding because the observation developed as a result of searching a large data base, rather than as a consequence of testing a hypothesis regarding the effect of surgeries on NTDs. No other studies have found similar increases in NTD incidence, and as such, the association between NTDs and maternal surgery during the period of neural tube formation must be regarded as unproven (Kallen et al., 1990).

For women undergoing general anesthesia and surgery during pregnancy, aside from malformations, several studies have noted an increase in spontaneous abortions (Brodsky et al. 1980; Duncan et al.,

1986), in infants with very low (<1500 gm) or low (<2500 gm) birth weights and in infant mortality (Mazze et al., 1989).

Occupational exposure to anesthetic agents

Not unlike the confounding factors associated with surgery, occupational exposure studies are confounded by a number of factors, particularly that the control groups in these studies often consisted of non-working women. One study found that employed women had higher levels of education and income, earlier prenatal care, greater weight gain during pregnancy, and they were slightly less likely to be heavy smokers. Employed women were also had fewer previous births and more spontaneous abortions and stillbirths than their unemployed counterparts (Savitz et al., 1990). Factors such as standing, heavy lifting, long work hours and changing shift work may also contribute to the confounding biases of these studies.

Finally, it is important to note that these studies were performed in the 1970's, when ventilation and scavenger systems in hospitals and dental operating rooms were not as efficient as those produced today; women in these studies were probably exposed to significantly higher levels of anesthetic gas than current workers. Nevertheless, a report in 1994, warning exposed workers of the potential harmful effects of nitrous oxide, was published by the United States National Institute for Occupational Safety and Health (NIOSH) (Boivin, 1997).

Common General Anesthetic Agents

Most human data available on individual anesthetic agents comes from the Collaborative Perinatal Project (Heinonen et al., 1977). Data are reported individually for each agent despite the fact that women in this study were probably given more than one anesthetic at surgery in every case. Consequently, the information available is difficult to interpret. Unfortunately, for many of these agents reproductive risk assessment is limited to this retrospective human data, coupled with minimal animal data. Friedman (1988) provides a comprehensive review of the available literature on a larger number of anesthetic agents.

Parenteral anesthesia

Thiopental

Thiopental is a rapidly acting barbiturate that has been used since the 1930s. In studies with rats and mice treated with 1.5-3 times the human dose, thiopental was not found to be teratogenic (Persaud, 1965). In a retrospective study of 152 women treated with thiopental during the first four months of pregnancy, there was no increase in congenital anomalies (Heinonen et al., 1977).

Methohexital

Methohexital is a short acting barbiturate. A manufacturer study using pregnant rabbits and rats found no increase in fetal abnormalities. Forty-one women treated with methohexital during the first four months of pregnancy did not result in a significant increase in the number of congenital anomalies (Heinonen et al., 1977).

Thiamylal

Thiamylal is an ultra-short acting barbiturate, similar to Thiopental. Treating pregnant mice with thiamylal resulted in an increase in limb anomalies, which sometimes are a sign of maternal toxicity (Friedman, 1988). Among the children of 21 women treated with this agent during the first four months of pregnancy, the frequency of congenital anomalies was not increased (Heinonen et al., 1977).

Etomidate

Etomidate is an imidazole hypnotic used for the induction of general anesthesia. In rats exposed to up

to forty times the recommended human dose, the frequency of malformations was no greater than expected (Friedman, 1988). No epidemiological studies have been reported of women treated with etomidate during pregnancy having children with congenital anomalies, and therefore the risk associated with etomidate in human pregnancy remains unknown.

Ketamine

Rats exposed to ketamine at doses more than ten times those used in humans were not found to have an increased incidence of malformations (Friedman, 1988). No epidemiological studies have been reported of congenital anomalies in children born to women treated with ketamine during pregnancy, and therefore the risk associated with ketamine in human pregnancy remains unknown.

Inhaled anesthetics

Nitrous oxide

Growth retardation and malformations have been observed in the offspring of pregnant rats exposed to high or chronic doses of nitric oxide (Mazze et al., 1984). In contrast, other studies found that increased rates of resorptions (analogous to spontaneous abortion) but no increase in malformations in exposed rats (Mazze et al., 1982; 1984; 1986). The incidence of congenital anomalies among children of 76 women anesthetized with nitrous oxide during the first four months of pregnancy was no greater than expected (Heinonen et al., 1977). One study reports an association between use of this agent during the first trimester and an increased incidence of spontaneous abortion (Brotsky et al. 1980). A subsequent larger study did not confirm an increased incidence of spontaneous abortion among women treated with nitrous oxide (Mazze et al. 1989).

Halothane

Halothane is a halogenated hydrocarbon. Rodent studies initially found exposure to high or prolonged halothane concentrations to be associated with an increase in birth defects specifically involving the skeleton (Basford et al., 1968). Subsequent studies have not found an association between moderate doses of halothane in pregnant rodents and birth defects (Mazze et al 1986), and it is possible the malformations noted by Basford were due to maternal toxicity. The Collaborative Perinatal Project found that the frequency of congenital anomalies was not significantly increased among children of 25 women who received halothane during the first 4 months of pregnancy (Heinonen et al., 1977).

Enflurane

Among the offspring of rabbits treated with enflurane during pregnancy, limb and abdominal wall defects were observed more often than expected (Freidman, 1988). Pregnant mice exposed to anesthetic concentrations of enflurane had an increased frequency of cleft palate, ventriculomegaly, and hydronephrosis (Wharton et al., 1979). Other studies have not found enflurane during pregnancy to be associated with increased risk for birth defects (Mazze et al., 1986; Freidman, 1988). There are no epidemiological studies of congenital anomalies in children of women treated with enflurane during pregnancy, and therefore the risk associated with enflurane in human pregnancy remains uncertain.

Isoflurane

Pregnant mice exposed to light doses of isoflurane were found to have an increased frequency of cleft palate, skeletal variations and fetal growth retardation (Mazze et al., 1985). At doses similar to those used in humans, other investigators have not observed teratogenic effects among the offspring of pregnant rats or rabbits treated repeatedly with isoflurane (Kennedy et al., 1977; Mazze et al., 1986). There are no epidemiological studies reporting congenital anomalies in children born to women exposed to isoflurane during pregnancy. Therefore, its risk in human pregnancy remains undetermined.

Methoxyflurane

Offspring of rats and mice treated with methoxyflurane had an increase in skeletal anomalies in one study (Schwetz 1970). A subsequent study found no increase in the number of malformations among the offspring of mice treated with this agent during pregnancy, although fetal growth retardation and delayed skeletal development occurred (Wharton, 1980). No epidemiological studies of congenital anomalies in children born to women exposed to methoxyflurane during pregnancy have been reported, and its risk remains undetermined.

Local Anesthetics

Because local anesthetics are used by topical application or injection, their systemic absorption is often limited. In situations where systemic absorption by the mother is virtually absent, no significant teratogenic effect would be expected regardless of the potential teratogenic activity of the agent. The Collaborative Perinatal Project is the primary source of epidemiological data on possible teratogenic effects of local anesthetic agents. In addition to the previously discussed limitations, this study does not distinguish medications by route of exposure. Therefore, topical application, local injection, regional infiltration and spinal infusion are all considered together. This study evaluated the possible teratogenicity of several local anesthetic agents including procaine, lidocaine, mepivacaine, benzocaine, propoxycaine, and tetracaine. Based on the limited information available, it seems unlikely that these topical agents are associated with a high risk of teratogenic effects in humans (Friedman, 1988).

Summary

Information regarding the safety of anesthesia and surgery during pregnancy is limited and confounded by many factors. In the case of surgery, it is important to weigh the risks and benefits of the procedure against any possible risks. Based on the information reviewed in this newsletter, there does not appear to be an increased risk for congenital malformations associated with anesthetic use. The possible association between anesthesia/surgery and a risk for neural tube defects is unclear and warrants further study. Occupational exposure to anesthetics has been shown to increase the risk of spontaneous abortion by 1.5 to two times the background risk. Given the methodological weakness of these studies, there is a possibility that this increase is coincidental. With all exposures, particularly occupational ones, it is best to limit the exposure as much as possible.

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