

## First trimester anesthesia exposure and fetal outcome. A review

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**Abstract** : Approximately 0.5-2% of all pregnant women undergo nonobstetric surgery during their pregnancy. This percentage does not include patients who are in the early phase of gestation and are not aware of it at the time of surgery. When pregnancy is diagnosed, the concern raises whether surgery and anesthesia during early gestation pose hazard to the developing fetus, by increasing the risk of congenital anomalies and spontaneous abortion. Literature review suggests that there is no increase in congenital anomalies at birth in women who underwent anesthesia during pregnancy. However, first trimester anesthesia exposure does increase the risk of spontaneous abortion and lower birth weight. This is more likely due to surgical manipulation and the medical condition that necessitates surgery than to the exposure to anesthesia.

**Key words** : Anesthesia ; pregnancy ; nonobstetric surgery ; pregnancy outcome ; congenital abnormalities.

### INTRODUCTION

In our hospital, we recently had two successive cases of women who were pregnant at the time of surgery without being aware of it preoperatively. When pregnancy was diagnosed, both women consulted us because they were concerned about the effect of the former anesthesia on their pregnancy. As a result of this we did a literature review on anesthesia during first trimester pregnancy and its influence on fetal outcome.

The need for nonobstetric surgery and anesthesia occurs in about 0.5-2% (11, 12, 17, 31) of all pregnant women. This percentage does not include a number of patients whose pregnant status is undetected or unsuspected when undergoing elective or emergent surgery. In a prospective study of MANLEY *et al.* (22) the incidence of unrecognized pregnancies in women of childbearing age presenting for elective ambulatory surgery was 0.3%.

When it appears that the patient was pregnant at the time of surgery, the question raises whether this has consequences for the developing fetus. Fetal damage can result from teratogenic effects of drugs administered in the perioperative period,

from alterations in uteroplacental blood flow and from maternal hypoxemia (29).

### PHYSIOLOGIC DERANGEMENTS

Intrauterine asphyxia, resulting from maternal hypoxemia or decreased uterine blood flow, poses the greatest risk to the fetus (3, 11, 26, 32). Therefore it is extremely important to avoid maternal hypotension, hypoxia, hypercapnia and hypocapnia. Maternal hypoxemia induces uteroplacental vasoconstriction and reduced placental perfusion, leading to fetal hypoxemia, acidosis and possibly, if not corrected, fetal death. Maternal hypocapnia and respiratory alkalosis result in fetal acidosis through placental hypoperfusion. Maternal hypercapnia leads directly to fetal respiratory acidosis. Severe fetal acidosis may produce myocardial depression. These conditions can result from the underlying surgical disease or from perioperative complications.

Maternal stress is frequently considered an important risk factor for spontaneous abortion. NEPOMNASCHY *et al.* (25) examined the association between maternal cortisol, a physiological marker of stress, and spontaneous abortion during the first 3 weeks of pregnancy. They found that 90% of the increased cortisol pregnancies resulted in spontaneous abortion, a significant difference with the normal cortisol pregnancies. As other studies could not demonstrate such an association later during gestation, those first 3 weeks of conception, the placentation period, seem to be the most vulnerable

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period for maternal stress.

#### TERATOGENICITY OF ANESTHETIC AGENTS

Fewer than 30 drugs are teratogenic in humans when used in a clinically effective dose, including thalidomide, diethylstilbestrol, angiotensin-converting-enzyme inhibitors, carbamazepine, cyclophosphamide, tetracycline, lithium, systemic retinoids, warfarin, etc. (5, 16).

Virtually every drug can have teratogenic characteristics in a certain species, when administered in a sufficient amount during a particular gestational period for a substantial period of time and when crossing the placenta (29). This also applies for anesthetic agents and their adjuvants (3, 18), though the anesthetic exposure is mostly single and short-term. Most medications used for sedation, analgesia or anesthesia have properties in favor of placental diffusion: low molecular weight, high lipid solubility, low degree of ionisation and low protein binding (33). When a drug crosses the placenta, its teratogenicity depends on the stage of fetal development. Between conception and implantation, insults to the embryo can result in its death and miscarriage or in intact survival. At this "all or none" stage, the embryo is undifferentiated and repair is possible through multiplication of the still omnipotent cells. Organogenesis, from 18 to 58 days after conception, is the period of maximum sensitivity to teratogenicity. Tissues are differentiating rapidly and damage to them becomes irreparable, resulting in structural anomalies. When organogenesis is completed, teratogen exposure will affect fetal growth, organ size or organ function (7, 32).

So far, no anesthetic agent has been identified as a definite human teratogen (3, 11, 19, 21, 26, 29).

#### *Inhalation Anesthetics*

Clinical concentrations of volatile anesthetics have wide-ranging cellular effects, but so far, no clinical data link these cellular actions with teratogenic outcomes (11, 12, 29).

There has been a lot of controversy about nitrous oxide. Nitrous oxide (N<sub>2</sub>O) inhibits methionine synthetase activity through oxidation of vitamin B12, leading to interference with DNA synthesis and myelin deposition (17, 21). Current evidence shows however, that although DNA production is affected by nitrous oxide, it does not impair fetal outcome after brief maternal exposure.

Sevoflurane and desflurane are considered safe products. No teratogenic effects have been observed in animal studies. However, there are no adequate and well-controlled studies in pregnant women (20).

The reports on halothane have been conflicting. One study demonstrated an increased incidence of aberrant skeletal development and fetal death when pregnant rats, in various gestational periods, were exposed to halothane for 12 hours. Other investigators could not validate this teratogenic effect when exposing rats, rabbits and mice to halothane (1).

Pregnant mice exposed to enflurane or isoflurane showed an increased incidence of cleft palate. But cleft palate readily develops in mice and the fact that it occurred as an isolated finding, suggests a species-specific response. To clarify the previous findings, rats were exposed to halothane, isoflurane, enflurane or a known teratogen. No major abnormalities occurred in any of the anesthetic-exposed groups (1). None of these teratogenic findings have been reported in humans despite worldwide use of these products (20).

#### *Induction Agents*

Neither propofol, etomidate, thiopental or ketamine is known to be a teratogen in clinically effective doses (1, 12, 13, 20, 34). But there is lack of adequate and well-controlled studies in pregnant women. Reproduction studies with propofol have been performed on rats and rabbits and revealed no evidence of adverse fetal effects. Animal studies showed no birth defects after administration of etomidate and ketamine. Ketamine however can cause uterine contractions during early pregnancy and should therefore be avoided (31).

#### *Analgesics*

Literature review yields little information on analgesic agents used in human pregnancy. Some well-documented case reports demonstrate the safe use of opioids for acute and chronic pain (33). In addition, the lack of adverse neonatal outcomes in pregnant women seeking recovery from addiction by means of morphine or methadone, illustrates the safety of opioid-use during pregnancy (33).

Some animal studies reported developmental toxicity of codeine, but a study of EINARSON *et al.* (9) showed no increase in the rate of major malformations when dextrometorphan, the d-isomer of the codeine analogue levorphanol, was used during pregnancy.

Paracetamol can be used without danger for the developing fetus if the daily dose of 60 mg/kg is not exceeded (20).

Non-steroidal anti-inflammatory drugs (NSAID's) can cause premature constriction of the ductus arteriosus and are therefore contraindicated in late pregnancy (21). Relatively little is known however about possible teratogenic effects. First trimester use has been considered safe, but other studies seem to refute this. Aspirin and ibuprofen have been shown to increase the risk for gastroschisis (33). In a prospective study of ERICSON and KALLEN (10), early pregnancy use of NSAID's did not increase total malformation rate. First trimester NSAID use was however associated with an excess of rather mild cardiac defects, notably ventricular and atrial septum defects or a combination of both. Furthermore, the use of naproxen was specifically associated with orofacial clefts. NØRGÅRD *et al.* (27) conducted a large case-control study and found no association between early pregnancy use of aspirin and neural tube defects, exomphalos/gastroschisis, cleft lip ± palate or posterior cleft palate.

#### *Neuromuscular Blocking Agents*

The commonly used depolarizing and nondepolarizing muscle relaxants do not reach fetal circulation in clinically significant amounts. They are water soluble, positively charged and have high molecular weights, which keeps them from crossing the placenta. As expected, no teratogenic effect has been reported after administration of neuromuscular blocking agents to pregnant women (11, 12, 20, 29).

#### *Local Anaesthetics*

Spinal anesthesia offers the least placental drug transfer for the degree of anesthesia achieved. Epidural anesthesia or plexus block bring along higher blood levels of local anesthetic and thus more fetal exposure. For clinical concentrations of local anesthetics, there has been no indication of teratogenicity in humans. Recent animal studies seem to confirm this (1, 17, 20). When using spinal anesthesia however, attention to maternal fluid volume and blood pressure is critical. Maternal hypotension has to be avoided or treated promptly (3, 17).

#### *Benzodiazepines*

Some retrospective studies reported an association between maternal diazepam use and oral

clefts. More recent studies do not validate these results (16, 26).

#### FETAL OUTCOME

This is a survey of the most important studies and reviews published on anesthesia and surgery during early pregnancy from 1980 to 2005, chronologically ordered.

BRODSKY *et al.* (2) examined a population of 287 women who received anesthesia for surgery during their pregnancy, 187 during the first and 100 women during the second trimester. Eight thousand six hundred and fifty-four women who neither underwent surgery during their pregnancy nor were occupationally exposed to waste anesthetic gasses served as a control group. The authors found no association between surgery and anesthesia during early pregnancy and congenital anomalies. They did find however an increase in the rate of spontaneous abortion in women who had anesthesia and surgery during the first trimester of pregnancy. The incidence of miscarriage in the first trimester was 8.0% in the anesthesia group and 5.1% in the control group, which was statistically significant. The data for this rather small study were obtained through questionnaires. Some limitations such as the absence of information on the type of anesthesia used and the operation performed, makes interpretation of these findings rather difficult.

DUNCAN *et al.* (8) explored the incidence of congenital anomalies and spontaneous abortion in 2565 women who had anesthesia for surgery during their pregnancy, comparing them with a similar number of pregnant women not exposed to anesthesia. Statistical analysis showed no significant difference in the number of congenital anomalies between the study and the control group. There was no overall increase in spontaneous abortions in the study group, but the subgroup of women who received a general anesthetic appeared to be at high risk for spontaneous abortion.

In one of the largest studies on surgery and anesthesia during pregnancy, MAZZE and KALLEN (23) linked data from three Swedish health care registries to investigate the pregnancy outcome of 5405 women who underwent nonobstetric surgery while being pregnant. Two thousand two hundred and fifty-two women were operated on in the first trimester and 65% of this study group received general anesthesia, almost all including nitrous oxide. Analysis showed an increased incidence of very low (less than 1500 g) and low (less than 2500 g)

birth weight infants, but no higher rates of congenital malformations. The low birth weights were not associated with any specific type of anesthesia or surgery and the authors concluded that the condition which necessitated surgery may have played the most significant role in determining this result.

In a subsequent study, KALLEN and MAZZE (15) explored the relationship between neural tube defects (NTD ; i.e. anencephaly, encephalocele and spina bifida) and first trimester anesthesia. As earlier described, the total malformation rate among the 5405 investigated women was not increased, but in the subgroup of 572 women who underwent surgery during gestational weeks 4-5, the period of neural tube formation, four infants were diagnosed with NTD (expected number : 0.6). Three of them had general anesthesia with nitrous oxide (two laparoscopies and one breast biopsy), but these data do not define a causal relation, since 63% of the study group received nitrous oxide. One had spinal anesthesia for hemorrhoidectomy.

In order to investigate whether this increased incidence of NTD was a random finding or a significant fact, the authors carried out a supplemental study on 194 women who had an infant with an NTD. The finding that none of these 194 women had undergone surgery during pregnancy, supported the authors idea that their previous result was a random association.

MAZZE and KALLEN selected 778 women from their previous study population (23) for an additional inquiry (24). In order to exclude the influence of the type of surgery on pregnancy outcome, this subgroup was limited to women who underwent the same surgical procedure during their pregnancy (272 during the first trimester), i.e. open appendectomy. The results were similar to those in the previous study : there was a reduction in mean birth weight, but no increase in congenital anomalies.

As a result of the findings of KALLEN and MAZZE (15), SYLVESTER *et al.* (30) further explored whether first trimester general anesthesia exposure is associated with an increased risk of central nervous system defects. They compared 694 mothers of infants with major central nervous system defects with 2984 mothers of healthy babies. Twelve women from the study group reported first trimester anesthesia exposure, compared to 32 such exposures in the control group. There was no higher incidence of neural tube defects or microcephaly in the anesthesia group, but the study demonstrated a significant association between anesthesia and the combination of hydrocephalus and eye defects. The author admits however that the study has several

limitations, such as the absence of details concerning the circumstances of anesthesia, the type of surgery, the indication for it and the incidence of perioperative complications. Moreover, the study population contains only 44 pregnant women who underwent general anesthesia.

Another large study from REEDY *et al.* (28) compares five fetal outcome variables (birth weight, gestational duration, growth restriction, infant survival and fetal malformations) between 2181 laparoscopies and 1522 laparotomies, performed between the fourth and twentieth week of gestation. The study demonstrates no significant differences between the two study groups. When the outcome data were compared with the total population (all Swedish women with singleton pregnancies who delivered during the study period), the authors found an increased number of premature deliveries and low birth weights, but no higher incidence of congenital anomalies.

CZEIZEL *et al.* (6) examined 20830 pregnant women who had babies with congenital abnormalities and matched them with 35727 women who gave birth to healthy babies. Thirty-one women (0.15%) from the study group had anesthesia for surgery during their pregnancy. This was not significantly different from the control group, of which 73 women (0.20%) had undergone surgery while being pregnant. The study is limited by the absence of information on the type of anesthetic used and by the small number of women (n = 104) who actually underwent anesthesia during pregnancy.

As an addition to the conclusion of KALLEN and MAZZE (15), the authors pointed out that of the 31 women who had babies with a congenital anomaly and were exposed to anesthesia during their pregnancy, only one had a neural tube defect, though there were 1161 cases of neural tube defects in their study group.

In a smaller study, JENKINS *et al.* (14) examined 116 cases of women who underwent non-obstetric surgery during pregnancy, either with general or regional anesthesia. A significantly lower birth-weight was seen with intra-abdominal procedures, general anesthesia and longer surgery time.

Recently COHEN-KEREM *et al.* (4) reviewed 54 papers on nonobstetric surgery under anesthesia during pregnancy. Each paper had to include at least 10 patients and was published between 1968 and 2002. The review contains 4 of the previously discussed large studies and 50 small papers, mainly focusing on surgical aspects. Fetal loss was the most important adverse outcome, especially in patients undergoing appendectomy for acute appendicitis,

increasing even more when peritonitis is present. No increase in major birth defects could be revealed. The review contained no data on the different types of anesthesia.

## CONCLUSION

Literature review suggests that there is no increase in congenital anomalies at birth after anesthesia during pregnancy. Nevertheless these studies do not allow us to conclude that anesthetic agents are not teratogenic in humans, since first trimester anesthesia does increase the risk of spontaneous abortion and low birth weight. However this is more likely the result of a wide range of factors, such as compromised uterine blood flow, surgical manipulation and the medical condition that necessitates surgery rather than the exposure to anesthesia alone. First trimester use of NSAID's has been associated with congenital malformations.

Women of child-bearing age should be asked about their last menstrual period and only if their pregnancy status is uncertain, pregnancy testing should be performed.

Whenever possible, elective surgery should be deferred until after the first trimester to minimize potential fetal loss.

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