

Anesthetic Risk in the Pregnant Surgical Patient

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IT IS ESTIMATED THAT, in this country, at least 50,000 women every year undergo anesthesia and operation at some time during gestation, for indications that are unrelated to pregnancy.¹ Expressed in another way: 1.6 per cent of pregnant women are subjected to surgical procedures during pregnancy.² By far the most common lesions necessitating intervention during the first two trimesters are ovarian cysts. These tumors, which occur with the frequency of approximately 1:2,500 pregnancies, may present a particular anesthetic hazard, as they are more subject to torsion, rupture, or hemorrhage during pregnancy.³ Acute appendicitis is also a common condition, occurring in approximately 0.07 per cent of pregnancies.⁴ Difficulties in diagnosis expose the mother to the complications of perforation, peritonitis, and thrombophlebitis. Mammary tumors are probably equally common. Furthermore, there is a growing number of reports of successful surgical interventions carried out during pregnancy for such critical conditions as intracranial tumors and aneurysms, cardiac valvular disease, pheochromocytoma, and hyperthyroidism. One should also mention the repair of an incompetent cervix (Shirodkar procedure), nowadays not uncommon, which may necessitate anesthesia during the first or second trimester.

The particular hazards of surgical anesthesia during pregnancy are related to the physiologic changes in the mother and to possible adverse effects on the fetus. These are similar to those encountered in obstetric anesthesia, with two important differences. First, while one of the potential side effects of obstetric anesthesia is interference with the course of labor, surgical anesthesia may stimulate uterine activity and precipitate premature labor. Second, obstetrical anesthesia may result in central nervous system depression in the newborn, thus delaying the establishment of spontaneous and sustained breath-

ing. In surgical anesthesia, fetal oxygenation may be compromised through the interference with circulation on which it depends.

In this review we discuss pertinent physiologic changes of pregnancy and the potential effects on the offspring of drugs and techniques used in anesthesia. Finally, we present a brief series of guidelines for safe surgical anesthesia during pregnancy.

Physiologic Changes Associated with Pregnancy

Major alterations in practically every organ system occur in association with pregnancy. They are induced by hormonal secretions from the corpus luteum and the placenta, as well as by the mechanical effects of the gravid uterus in the second and third trimester. Our discussion is limited to the changes of greatest interest to the anesthesiologist, namely, those involving the cardiovascular and respiratory systems, acid-base balance, and the gastrointestinal tract.

CARDIOVASCULAR SYSTEM

Blood Volume and Constituents

Both the plasma volume and the erythrocyte volume begin to increase between the sixth and twelfth weeks of pregnancy, resulting at term in a plasma volume increase of 40 to 50 per cent and a total blood volume increase of 25 to 40 per cent (fig. 1).⁵ It is generally agreed that a decline in plasma volume after the thirty-fourth week, as reported in earlier studies, was an artifact induced by vena caval compression in the supine position.⁶

Since the erythrocyte volume increases by only approximately 20 per cent, there are reductions in the erythrocyte count, hemoglobin, and hematocrit. However, with a proper diet and supplementation with iron and folic acid, the so-called "physiologic anemia" of pregnancy can be largely prevented. The minimum normal hemoglobin value is 11-12 g/dl and the hematocrit value 35 per cent. The leukocyte count remains 8,000-10,000 throughout pregnancy, while the platelet count increases from the mean nonpregnant value of 187,000 per mm³ to 210,000 per mm³ in

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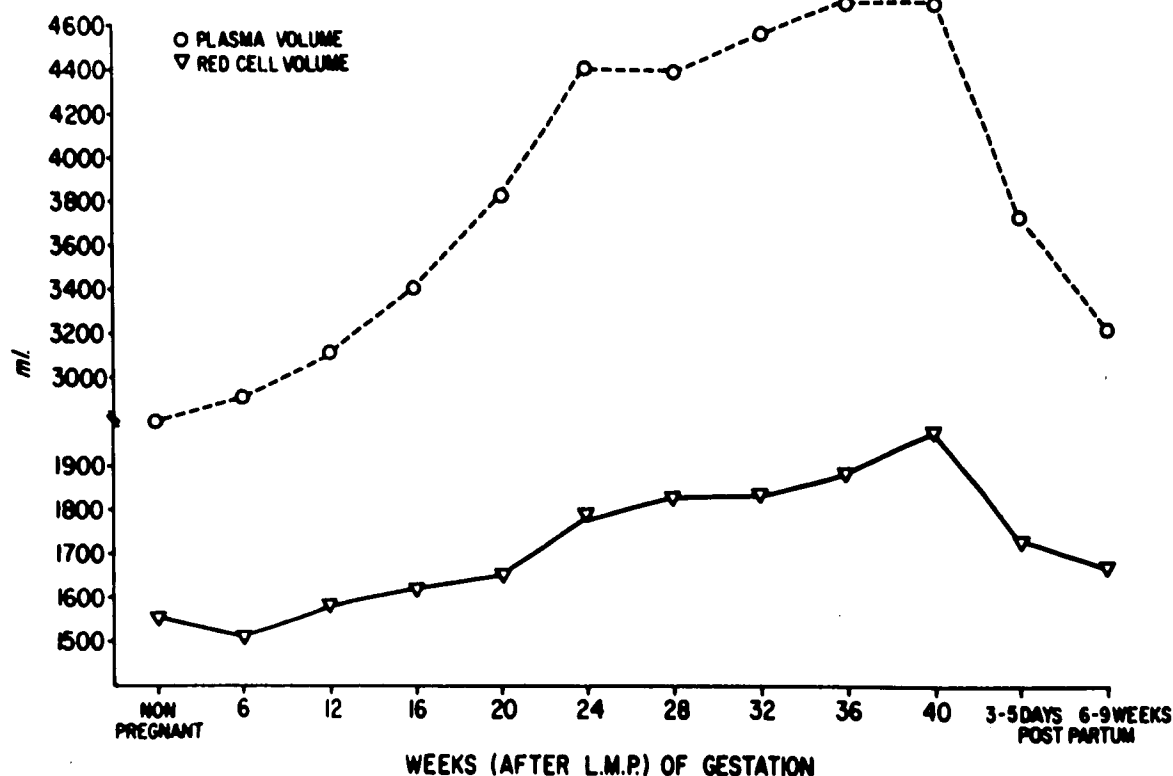


FIG. 1. Plasma and erythrocyte volumes during normal pregnancy and the puerperium. Reproduced from Abouleish E: Pain Control in Obstetrics, Philadelphia, J. B. Lippincott, 1978, p 22, with permission.

the first trimester, to 276,000 per mm^3 in the second trimester, and to 316,000 per mm^3 in the third trimester.⁷

The plasma proteins show changes similar to those seen in the erythrocytes, namely, their total concentration declines (to less than 6 g/dl at term), while the total amount in the circulation increases.⁸ The albumin:globulin ratio declines because of a relatively greater reduction in albumin concentration. The fibrinogen content increases throughout pregnancy, both in absolute amounts and in relative concentrations, the latter from 250–300 mg/dl to 450 mg/dl.⁹

In addition to the increases in the amount of plasma fibrinogen and in the number of platelets, there is a marked increase in activity of several clotting factors, rendering the blood hypercoagulable, and predisposing the pregnant woman to thromboembolic phenomena.¹⁰

Pregnancy and the puerperium are associated with a decline in serum cholinesterase activity.^{11,12} It amounts to approximately 21 per cent, and takes place during the first trimester, with cholinesterase remaining fairly stable during the remainder of pregnancy. It is not associated with any structural malformation of the enzyme molecule, as indicated by normal dibucaine, fluoride and chloride numbers.¹¹ It is doubtful,

therefore, that this reduction in activity of the normal enzyme can lead to prolonged apnea in patients given small to moderate doses of succinylcholine (50–400 mg) in the absence of other contributing factors.¹³

Hemodynamic Changes

Some of the changes that occur in the maternal circulation during pregnancy are attributable to hormonal alterations. For example, the administration of various estrogens to nonpregnant ewes leads to an increase in cardiac output and a reduction in vascular resistance.¹⁴ A decrease in vascular resistance occurs within the pregnant uterus, allowing for an increase in blood flow to satisfy the metabolic needs of the fetus. A lowered resistance is also found in the renal and other vascular beds. As a consequence of the decreased vascular resistance in the maternal circulation, the mother's cardiac output increases, as do her heart rate (to 92–95 beats/min at term) and blood volume. Arterial blood pressure decreases slightly because the decrease in peripheral resistance exceeds the increase in cardiac output.

Cardiac output begins to increase during the eighth week of pregnancy, initially through an increase in the stroke volume, and reaches its peak of 30–50 per cent

above normal at 30–34 weeks. Alterations in cardiac output in the remaining six to ten weeks are a subject of controversy. Older studies, performed with the patients in the supine position, indicated that by the thirty-eighth to fortieth weeks cardiac output declines to the nonpregnant level.^{15,16} It was subsequently postulated that the low cardiac output seen in the supine position was due to compression of the inferior vena cava by the enlarged uterus since, when measured in the lateral decubitus position, cardiac output during the last few weeks of pregnancy was no less than that seen in the second trimester.¹⁷ Yet another study indicates that there is a decline in maternal cardiac output after the thirty-second week of pregnancy whether the woman is in the sitting, lateral or supine position (fig. 2).¹⁸ The greatest reduction occurs when the mother is supine; cardiac output measured in this position was less than that found in the nonpregnant state, as determined six to eight weeks post partum. Despite this, in most women, normal or near-normal brachial arterial pressure is maintained by increase of peripheral resistance. The compensatory response seems to involve the uteroplacental vasculature, with harmful effects on the fetus.¹⁹

Vena caval compression can begin to develop during the second trimester and becomes maximal at 36 to 38 weeks. It may decrease thereafter with the descent of the fetal head into the pelvis. It has been known since 1953 to account for the "supine hypotensive syndrome," characterized by arterial hypotension, tachycardia, pallor, and faintness. This occurs in approximately 10 per cent of pregnant women at term, placed in the supine position.²⁰ More recently, a radiographic study revealed that complete obstruction of the inferior vena cava occurs in approximately 90 per cent of pregnant women at term, lying supine.¹⁷ In this circumstance venous blood from the lower part of the body reaches the heart through the superior vena cava, after diversion via the intervertebral venous plexus and the azygos vein. The resulting engorgement of the intervertebral plexus reduces the size of the epidural and subarachnoid spaces, consequently diminishing the drug requirement for regional anesthesia.

The lower aorta may also be compressed in the supine position, as was demonstrated by aortography in 1968.²¹ This phenomenon affects primarily the renal and uteroplacental blood flows. Thus, the supine position should be avoided during the second and third trimesters of pregnancy, even in the absence of maternal arterial hypotension.

Electrocardiogram. Changes in the electrocardiogram are attributable to the shift in the position of the heart (left axis deviation) resulting from the up-

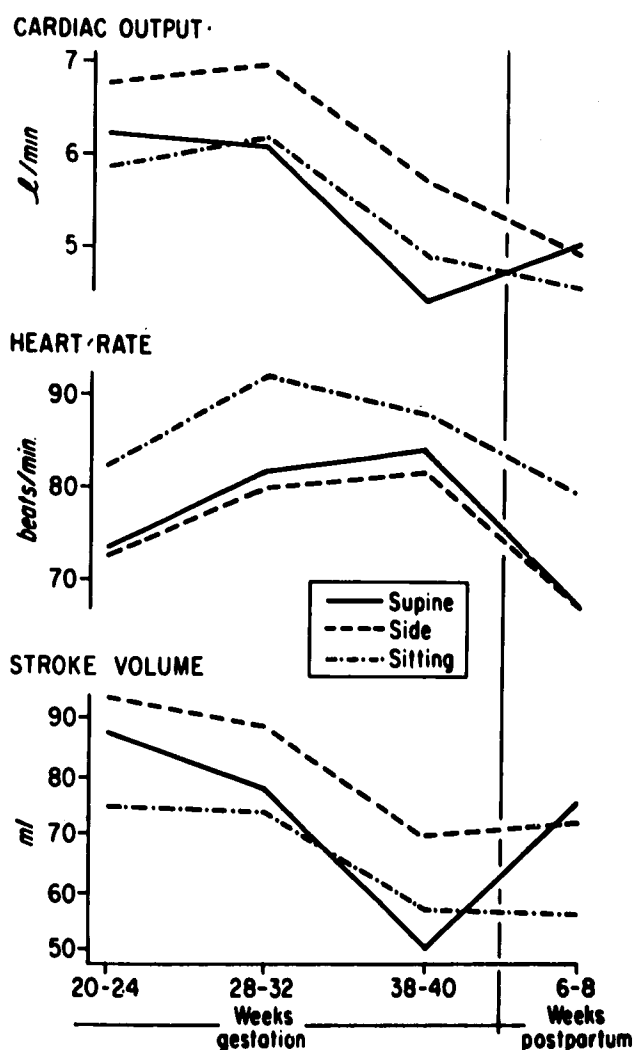


FIG. 2. The effects of posture on maternal cardiac output, heart rate and stroke volume during different periods of gestation. Reproduced from Ueland K, Novy MJ, Peterson EN, et al,¹⁸ with permission.

ward displacement of the diaphragm by the gravid uterus. There is also an increased tendency toward premature contractions, sinus tachycardia, and paroxysmal supraventricular tachycardia, the cause of which is unknown. In the absence of organic heart disease these arrhythmias do not ordinarily alter the normal course of pregnancy, and there is no significant maternal hazard.²²

RESPIRATORY SYSTEM

Anatomic Changes

Capillary engorgement throughout the respiratory tract occurs in the majority of pregnant women.²³ Swelling in the area of the nasopharynx makes nasal

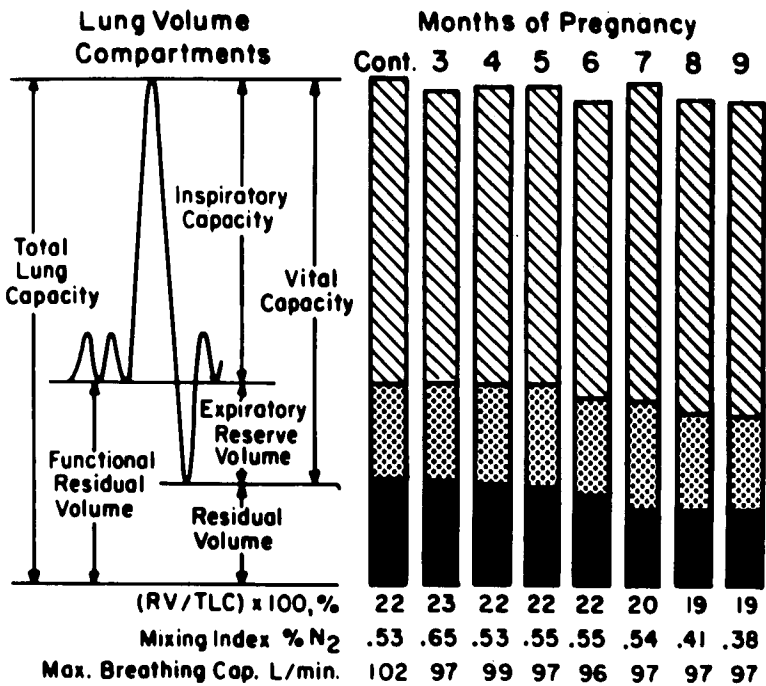


FIG. 3. Values obtained by serial measurements of lung-volume compartments, pulmonary mixing index (the percentage of nitrogen remaining in the alveolar air after 7 min of breathing oxygen), and maximum breathing capacity during normal pregnancy. Control values were obtained from the same women four to nine months post partum. Reproduced from Bonica JJ: Maternal respiratory changes during pregnancy and parturition, Parturition and Perinatology, edited by G Marx. Philadelphia, F. A. Davis, 1973, p 5, with permission.

breathing difficult for some women, and increases the risk of bleeding following nasotracheal intubation. The level of the diaphragm rises by a maximum of approximately 4 cm, but diaphragmatic breathing remains unimpeded. As a matter of fact, breathing in pregnancy is more diaphragmatic than costal.²⁴ The upward shift of the diaphragm is counterbalanced by an increase in the anteroposterior and transverse diameters of the thoracic cage, and by flaring of the ribs. These changes result in important modifications of lung volumes during pregnancy.

Lung Volumes and Dynamics

As can be seen in figure 3, lung volumes undergo progressive changes beginning in the fifth month of pregnancy. There are decreases in expiratory reserve volume, residual volume, and functional residual capacity.²⁵ At term, functional residual capacity is approximately 1,350 ml, or 20 per cent less than that in the nonpregnant state. There is a concomitant increase in inspiratory capacity and inspiratory reserve volume so that total lung capacity remains unchanged.

The closing capacity (residual volume plus closing volume) of the lung is defined as the pulmonary gas volume below which airways begin to close, resulting in trapping of gas in pulmonary alveoli. These may rapidly become atelectatic and thereby augment the pulmonary shunt. Closing capacity in the young, healthy nonpregnant woman is well below functional residual capacity (FRC). The first study carried out in pregnant women indicated that the closing volume

exceeded FRC in 30 per cent of subjects lying supine.²⁶ However, these subjects had been admitted to hospital for various medical reasons and, therefore, could not be considered healthy. The study also lacked postpartum or nonpregnant controls. Three more recent investigations in which normal women were studied sequentially during pregnancy and two days to eight weeks postpartum have shown no significant change in closing lung volume and $PA_{O_2} - Pa_{O_2}$.²⁷⁻²⁹ In only two of 43 patients studied in the supine position did the closing volume exceed FRC.

Pulmonary compliance is also unchanged, but total pulmonary resistance is diminished, primarily because of progesterone-induced relaxation of bronchiolar smooth muscle resulting in decreased airway resistance.³⁰

Ventilation

Ventilation increases early in pregnancy, approaching maximum in the second or third month.³¹ At term, tidal volume is increased by 40 per cent and respiratory rate by 15 per cent, with a net minute ventilation of approximately 50 per cent above the nonpregnant level. As dead space does not change significantly, alveolar ventilation at term is approximately 70 per cent more than that in the nonpregnant state.

Acid-Base Balance

Basal oxygen consumption increases during pregnancy but is compensated by hyperventilation, so that

there is an increase in maternal PaO_2 to a mean of 106 torr and a decrease in the mean PaCO_2 to 32 torr. At the same time, the plasma buffer base decreases from an average of 47 to 42 mEq/l; thus, pH remains practically unchanged. All of these changes occur early in pregnancy, as indicated in table 1.

Increased alveolar ventilation along with decreased FRC enhances maternal uptake and elimination of inhalational anesthetics.³² On the other hand, decreased FRC and increased metabolic rate predispose the mother to hypoxemia, even during a brief period of airway obstruction or the apnea of intubation.³³

GASTROINTESTINAL TRACT

During the course of pregnancy, the stomach and intestines are gradually pushed upward by the enlarging uterus. Eventually, the stomach assumes a horizontal position, with the pylorus displaced upward and posteriorly, thus slowing the evacuation of gastric contents. It has been found, indeed, that gastric emptying time of a watery meal is prolonged by approximately 60 per cent from the thirty-fourth week onward.³⁴ Pain, anxiety, and administration of narcotics and belladonna alkaloids may further delay gastric emptying. Toward term, there is an increase in intragastric pressure, particularly in the lithotomy and Trendelenburg position. In most women, this is exceeded by the increase in the opening pressure of the

gastroesophageal sphincter,³⁵ so that in most unanesthetized patients the risk of regurgitation is not enhanced by pregnancy. Women who have heartburn appear to be an exception. In this group, the sphincter tone has been found to be greatly reduced. The administration of general anesthesia and of muscle relaxants obviously enhances the risk of regurgitation and aspiration in all pregnant patients by obtunding the protective reflexes, increasing intra-abdominal pressure (succinylcholine-induced fasciculations) and relaxing the cricopharyngeal sphincter, the "last line of defense" against regurgitation.

Effects of Anesthesia on the Embryo and Fetus

DIRECT EFFECTS

In the last twenty years, evidence about the cellular effects of anesthetics and their metabolic products has been accumulating. It has been recognized that anesthetics depress cell growth and slow cell division. Recent studies indicate that anesthetics may also produce abnormal products of cell division,³⁶ and at least one anesthetic, halothane, in concentrations of 0.7 per cent or higher, has been shown to interfere with the synthesis of DNA.^{37,38} This evidence, along with the recognition that biotransformation of an inhalational anesthetic begins almost immediately upon its administration, thus introducing the potential hazard of accumu-

TABLE 1. Maternal Arterial Blood Oxygen and Acid-Base Status during Pregnancy

	Gestation (Trimester)			All Patients
	First	Second	Third	
PaO_2 (torr)				
Number of patients	20	25	34	79
Mean \pm SD	107.7 \pm 8.5	107.0 \pm 8.6	104.0 \pm 6.2	106.1 \pm 7.7
PaCO_2 (torr)				
Number of patients	18	26	26	70
Mean \pm SD	31.9 \pm 1.2	32.9 \pm 1.7	31.7 \pm 2.3	31.9 \pm 1.8
pH				
Number of patients	18	26	26	70
Mean \pm SD	7.400 \pm 0.007	7.404 \pm 0.007	7.413 \pm 0.013	7.405 \pm 0.012
Standard bicarbonate (mEq/l plasma)				
Number of patients	18	26	26	70
Mean \pm SD	20.6 \pm 0.6	20.8 \pm 1.0	21.2 \pm 1.0	20.9 \pm 0.9
Buffer base (mEq/l blood)				
Number of patients	18	26	26	70
Mean \pm SD	42.3 \pm 0.9	42.6 \pm 1.4	43.1 \pm 1.1	42.8 \pm 1.4
Base excess (mEq/l blood)				
Number of patients	18	26	26	70
Mean \pm SD	-3.6 \pm 0.9	-3.4 \pm 1.2	-2.8 \pm 1.2	-3.2 \pm 1.1

* (Modified from Andersen GJ, et al: J Obstet Gynaecol Br Commonw 76:16, 1969. Reprinted with permission from Bonica JJ: Maternal respiratory changes during pregnancy and parturition,

Parturition and Perinatology, edited by G. Marx Philadelphia, F. A. Davis, 1973, p 11.)

lated toxic metabolites, has contributed to the growing interest regarding mechanisms by which cytotoxicity, including mutagenic, teratogenic and carcinogenic effects, may occur. More indirectly, the similarities in structure between methoxyflurane, enflurane and isoflurane and certain known carcinogens such as chloromethyl-methyl ether lend circumstantial support to the theory that anesthetics have a potential for teratogenicity.³⁹

Acute Exposure

The idea that surgical anesthesia, though deemed necessary for the patient, might have detrimental effects on the growth and development of the human fetus has led to a great deal of investigation, both *in vitro* and in experimental animals. These studies present difficulties in interpretation because the concentrations of anesthetics and durations of exposure are frequently far in excess of what is used clinically, and also because most studies were performed in lower animals. The first test of embryotoxicity of an anesthetic agent (nitrous oxide) was made in the chick embryo.⁴⁰ Most subsequent studies have employed mammalian models, such as the rat, where pregnancy lasts for a few weeks, and organogenesis only for a few days.

Work in animals exposed to toxic substances and several anesthetics shows a dose-related response, the first observable changes being decreased fertility and increased fetal death. With increasing doses, the number of surviving fetuses with anomalies begins to increase, the peak incidence of anomalies being at a dose that causes 50 per cent fetal deaths.⁴¹ The variability of teratogenic effects among species, and also among animals of greater genetic susceptibility within the same species, is very marked. The stage of development is also important in teratogenic effects. There may be dramatic sensitivity to exposure during certain days of gestation, and little or no effect later.^{41,42} While it is true that the most critical period of exposure is during organogenesis in the first trimester (15–56 days in man), there may be a particular sensitivity of the central nervous system to external factors, during the period of myelination. This is chiefly due to the high metabolic stability of constituents of myelin sheets. ¹⁴C-labeled cholesterol is known to persist in the white matter of the rabbit for a year when administered in the newborn period. It is probable that there is similar stability for other substances of the brain, such as DNA. Thus, exposure to agents exerting an untoward effect upon formation of myelin could have long-lasting sequelae. Extrapolation from animal data to man would place the vulnerable period of the human

brain from the seventh intrauterine month to the first few months after birth.⁴³ However, there is no evidence to date that intrauterine exposure to anesthetics has long-term effects on the newborn.

Other possible age-dependent effects of anesthetics have been discussed in a recent editorial, which brings out the importance of appreciating the differences in physiologic and pharmacologic responses between immature and adult brains.⁴⁴ Studies *in vitro* indicate that there is an increase with maturation in the brain's capacity to increase energy metabolism in response to acute physiologic demands.⁴⁵ These developmental increases in the enzymatic pathways involved in aerobic metabolism may result in age-dependent differences in the fetal brain's responses, both to anesthetic agents that act directly on the enzyme systems, and to the systemic effects, such as hypotension and acidemia, that these agents may produce in the mother.

In man, many of the common congenital malformations show a pattern of multifactorial inheritance. In this mode of inheritance a teratogen may influence a developmental threshold in an individual who already has a hereditary predisposition to produce a certain defect. Thus, maldevelopment may result from a combination of factors within one individual, such as hereditary predisposition, sensitivity to a given drug, and exposure at a vulnerable time in development.

Stressing the caution with which animal experimental data must be interpreted, specific agents and premedicants commonly used by anesthesiologists are considered.

Nitrous oxide. It was first observed in 1955 that leukocytopenia developed in patients with tetanus after several days of exposure to nitrous oxide. It was later shown that nitrous oxide inhibits hematopoiesis in rats,⁴⁶ and this has led to widespread investigations showing that nearly all anesthetics and hypnotics are inhibitors of cell division, and that the inhibition is concentration-dependent.⁴⁷

Nitrous oxide remains the most extensively studied anesthetic agent from the point of view of cellular depression and teratogenicity. One study demonstrated that inhalation of 50 per cent nitrous oxide in oxygen and nitrogen by pregnant rats for one or two days, beginning on day 8 of gestation, produced profound effects on the offspring. There was a high incidence of intrauterine deaths, a significant frequency of skeletal and rib deformities, and a decrease in size of the embryos, compared with controls.⁴⁸ Similar effects on growth and death rates were found after exposure of incubating chicks to nitrous oxide, 80 per cent, for six hours on the third day of incubation.⁴⁹

Halothane. The exposure of pregnant rats for 12

hours to halothane, 0.8 per cent, at various times during gestation increased the incidences of anomalous skeletal development and fetal death.⁵⁰ Briefer administration of halothane, 0.6 per cent, for three hours to pregnant hamsters on day 11 of gestation led to reduced fetal weight and size, and increased the number of abortions.⁵¹ Other studies have failed to show these teratologic effects in rats, rabbits, and mice exposed for brief periods to anesthetic concentrations of this agent.^{52,53}

Diethyl ether. Concentrations of ether in the blood of chick embryos (90 mg/dl) not dissimilar to those used in mammalian surgical anesthesia, maintained for five hours on the fourth day of incubation, caused a death rate of 40 per cent, and an incidence of anomalies among survivors of 21 per cent.⁵⁴

Methoxyflurane. Again in chick embryos, increased death rate and anomalies occurred with exposures to concentrations of 0.5 per cent and higher on days 3 and 4.⁵⁵ The known nephrotoxic effects of fluoride have led to investigation of the fluoride content of fetal bone in rats exposed to methoxyflurane, 0.2 per cent, and also enflurane, 1.5 per cent.⁵⁶ There was a marked increase in fluoride only when exposure to methoxyflurane took place after twelve days of gestation, *i.e.*, when ossification of many parts of the fetal skeleton was in progress. It was postulated that the source of fluoride might be maternal defluorination and/or fetal metabolism following placental transfer.

Fluroxene. Fluroxene, 2.5 per cent, in air produced an increase, which was statistically significant, in external anomalies in the chick embryo exposed at three and four days of gestation.⁵⁵ In recent years the *in-vitro* system of bacterial assay developed by Ames *et al.*⁵⁷ for testing metagens has been used to examine volatile anesthetics. In their original assay system, the suspect mutagen and bacteria were combined and poured onto an agar plate. This system, however, could not identify promutagens, *i.e.*, compounds that require metabolic activation before they are mutagenic. Therefore, later on, metabolically active mammalian cell fractions, such as postmitochondrial supernatant, or hepatic microsomes, were combined with bacterial tester strains. Fluroxene was mutagenic in the presence of a metabolic activation system prepared from the livers of rats that had been pretreated with a potent inducer of the mixed-function oxidase system. It was not mutagenic in the absence of the hepatic activation system, suggesting that a metabolic product of fluroxene was the mutagen.⁵⁸

Cyclopropane. Incubation of four-day chick embryos for six hours in cyclopropane, 20–65 per cent, in oxygen has resulted in a significant number of abnor-

mal birds. Both lethality and the incidence of anomalies increased directly with increasing concentration.⁴⁷

Enflurane. An assay system similar to the one described above for fluroxene failed to demonstrate mutagenicity.⁵⁸

Barbiturates. There is considerable disagreement about the possible teratogenic effects of the barbiturates. A wide spectrum of congenital malformations after the use of pentobarbital and phenobarbital in mice has been reported, but much evidence denies these effects.⁴² Possibly a more relevant practical aspect for the anesthesiologist is the likely protective effect of high doses of pentobarbital against asphyxial brain damage in the fetus. This has been demonstrated in both the monkey and the rat.^{59,60} On the other hand, chronic use of phenobarbital by the mother exposes her infant to the risk of hemorrhagic disease, as described by Wilson.⁶¹

Narcotics. There have been several recent investigations of the teratogenic capabilities of morphine, meperidine, and other related narcotics. Central nervous system malformations arose following maternal administration of several narcotics in hamsters.⁶² Groups of these animals were given different doses of a drug by single subcutaneous injection on day 8 of gestation, and were killed on day 12. To investigate the results of relatively prolonged exposure of the fetus, certain narcotics were given to yet other groups of hamsters on days 8, 9 and 10 of gestation, and they were subsequently killed on day 12. The number of abnormal fetuses from females given heroin and methadone increased with maternal doses of the compounds, whereas multiple maternal doses of morphine and meperidine failed to produce a further increase in anomalies above a certain dose level. Another interesting feature of this study was the finding that narcotic antagonists such as nalorphine and naloxone, injected 20–30 min prior to the narcotic compound, blocked the teratogenic effects of both single and multiple doses. Methadone, administered by subcutaneous injection to pregnant mice (22 mg/kg on day 9), produced central nervous system malformations in embryos,⁶³ but it did not seem to be teratogenic in rats or rabbits.⁶⁴ However, rats appear to be sensitive to morphine. Growth retardation,⁶⁵ alterations in locomotor activity and neonatal mortality,⁶⁶ and tolerance to morphine-induced analgesia⁶⁷ have all been shown in their offspring following maternal exposure. Indeed, the increasing numbers of pregnant patients who are narcotic addicts or who are in narcotic-dependent treatment programs has focused attention on long-term effects of morphine, heroin and methadone on the fetus. In human studies so far

carried out, the offspring of such mothers have not shown abnormalities other than low birth weight.^{68,69}

Tranquilizers. Phenothiazine derivatives, as well as other tranquilizers, are frequently used in preoperative medication or as antiemetics in the postoperative period. Several of these drugs have been found to have teratogenic properties in rats and rabbits (sometimes only in very large doses), but there has been no confirmation of such effects in man. Decreased size of offspring, reduced learning ability, and teratogenic properties in rats have been reported for both chlorpromazine (Thorazine) and prochlorperazine (Compazine).⁷⁰ Imipramine (Tofranil) has been shown to be teratogenic in rabbits in high doses, but not in man.⁷¹ Promethazine (Phenergan) has not been shown to be teratogenic in man.⁷² A prospective study of more than 50,000 human pregnancies, where more than 1,300 mothers had been exposed to various doses of phenothiazines during the first four months of pregnancy, has shown no evidence of adverse effects on perinatal mortality, birth weight, congenital abnormalities or intelligence scores at 4 years of age.⁷³

Diazepam (Valium) is probably the most commonly used tranquilizer today. It is also popular as a premedicant and as an adjunct to general and regional anesthesia. Although a prospective study failed to correlate the use of the drug during pregnancy with congenital anomalies,⁷⁴ several reports of a specific relationship between diazepam and oral clefts have been published.^{75,76}

Muscle relaxants. The attention of teratologists was drawn to this group of drugs when it was demonstrated that infusion of *d*-tubocurarine in the chick embryo between the seventh and fifteenth days of incubation caused deformities involving the joints.⁷⁷ This was thought to be due to paralysis at a time of skeletal development. Although all the commonly used muscle relaxants cross the placenta to some extent, there is no trace of evidence that the normal clinical dose of such a drug used during a surgical procedure has any adverse effect on human fetal development.

Local anesthetics. In clinical practice, blood levels of local anesthetics that reach the fetus during maternal anesthesia are very low after subarachnoid injection. However, when peridural or caudal anesthesia is used, or when there is an accidental intravascular injection in the mother, significant amounts may lead to effects on the fetal central nervous system and/or myocardium. Direct infusion of large doses of lidocaine into fetal lambs has shown an age-dependent sensitivity of the fetal central nervous system in producing epileptiform discharges.⁷⁸ This phenomenon may be related to changes in responsiveness of the

central nervous system. Local anesthetics are also known to stabilize the cell membrane, and may play an important part in cellular mitosis at certain stages of development. However, no evidence is available to define the teratogenic effects of these drugs, if any.

Administration of the local anesthetic, prilocaine, may produce methemoglobinemia in both mother and fetus, and indeed, the fetal erythrocytes are known to have increased susceptibility to a number of oxidants.⁴³

Hypoxia, hypercarbia and other factors. Numerous other factors contribute to the potential teratogenicity of anesthesia. As already mentioned, the cytotoxicity of anesthetic agents is closely associated with biodegradation, which, in turn, is influenced by oxygenation and hepatic blood flow. Thus, the complications associated with anesthesia, maternal hypoxia, hypotension, administration of vasopressors, hypercarbia, hypocarbia, electrolyte disturbances, etc., may possibly be a greater cause for concern as regards teratogenesis than the use of the agents themselves. Certainly hypoxia is a well-documented teratogen in the incubating chick embryo.⁷⁹ The role of maternal carbohydrate metabolism on embryonic development is also very important. For example, the effects of 48 hours of fasting, and administration of insulin to pregnant rats on days 7, 9, or 11 of gestation, have included a large number of skeletal deformities.⁸⁰

Chronic Exposure

An entirely different body of evidence has been growing in recent years regarding the possible carcinogenic and teratogenic effects of chronic exposure to trace concentrations of anesthetic agents, affecting not patients, but the operating room personnel and their offspring. It has come from large epidemiologic surveys. The first report came in 1967, from Russia, where there was reported to be an unusually large number of spontaneous abortions among anesthesiologists.⁸¹ Studies in Denmark, Finland, the United Kingdom, and the United States followed. A nationwide survey conducted by the American Society of Anesthesiologists found a higher incidence of cancer among female anesthesia personnel, as well as increased abortion rates, and increased rates of congenital abnormalities in their infants.³⁶ It also showed that the last of these misfortunes applied, though in lesser degree, to the infants of unexposed wives of male operating room personnel. Another study, involving nurse anesthetists, suggested a higher than expected incidence of cancer.⁸² All these studies have been the subject of some dispute.^{83,84} Criticism has included possible statistical inaccuracies and inappropriate choices of control groups.

The experimental evidence with regard to trace concentrations of inhalational agents administered chronically to laboratory animals is contradictory. There was an increase in fetal death rate in pregnant rats breathing 1,000 and 100 ppm of nitrous oxide, eight hours a day, for four days.⁸⁵ On the other hand, exposure of mice to halothane for seven hours a day, five days a week for six weeks, at a concentration known to exist in the operating room (16 ppm), had no deleterious effect on reproduction.⁸⁶ Most recently, mice chronically exposed to halothane did show decreases in fetal weight, pregnancy rate, and fetal survival, but only at concentrations very much higher than those present in unscavenged operating rooms.⁵³

Human Implications

To our knowledge, only two studies have attempted to relate operation and anesthesia during human pregnancy to fetal outcome, as regards congenital anomalies, premature labor, or abortion.^{2,87} Both failed to correlate congenital anomalies with anesthesia and surgical exposure. Fetal mortality in one study was quoted at 7.5 per cent, compared with 2 per cent in patients not subjected to operation. Mothers in the surgical group had a higher percentage (15.6 per cent) of babies of birth weights of less than 2,500 g than those in the control group (9.9 per cent).² However, when analysis was made according to type of operation and anesthesia, it was found that premature labor was more related to the disease necessitating the surgical procedure than to other factors, *e.g.*, incidence was higher after appendectomy, or where there was pelvic surgery, than after other procedures. No particular anesthetic agent or technique seemed superior. A large prospective study, attempting to determine whether associations between maternal drug exposure and abnormalities in offspring exist, highlights the difficulties in establishing such causal relationships.⁸⁸ Among the complicating factors are the frequency of maternal exposure to a multiplicity of drugs; the difficulty in separating the effects of the underlying disease and surgical treatment from those of the drug administered; the differing risks at different stages of gestation; and the variety, rather than the consistency, of anomalies that appear in association with one agent.

INDIRECT EFFECTS

The adequacy of the uteroplacental circulation, so vital to the well-being of the fetus, is easily affected by drugs and anesthetic procedures.

Figure 4 is a schematic representation of factors determining placental and nonplacental (myometrial

and endometrial) blood flow.⁸⁹ It shows that placental blood flow is directly proportional to the net perfusion pressure across the intervillous space ($UABP - IUP - UVBP$), and inversely proportional to the resistance of the spiral arterioles supplying the intervillous space (R_{iPL}), as well as the resistance imparted to the blood vessels by the myometrial tension (R_e). Thus, any anesthetic procedure or agent that would tend to decrease the perfusion pressure and/or increase vascular resistance may result in placental hypoperfusion and fetal asphyxia.

Perfusion pressure across the intervillous space may be diminished consequent to maternal systemic hypotension, which, in turn, may be due to the use of epidural or spinal anesthesia, to aortocaval compression in the supine position, or to hemorrhage. It has been proposed that, in normal circumstances, the placental vasculature is maximally dilated, so that the perfusion pressure is the major determinant of uterine blood flow.⁹⁰ However, a recent study indicated that in pregnant ewes, under conditions of light, or moderately deep, general anesthesia (1.0 or 1.5 MAC) with halothane or isoflurane, uterine vascular resistance was diminished, resulting in increased uterine blood flow, even in the face of mild to moderate maternal hypotension.⁹¹ These changes were attributed to the relaxing effect of the anesthetic on the myometrium.

Conversely, increased uterine activity may result in reduced placental perfusion. Thus, the use of alpha-adrenergic drugs such as methoxamine to correct maternal hypotension,⁹² and anesthetics such as ketamine (in doses of more than 1 mg/kg), may increase uterine tone sufficiently to endanger the fetus.⁹³

Hyperventilation of the mother, when severe, may also reduce uterine blood flow. This was originally attributed to hypocapnia or respiratory alkalosis. More recently, a study performed in pregnant sheep has established that placental hypoperfusion results from the mechanical effect of hyperventilation, since it could not be corrected by restoring Pa_{CO_2} to normal, or above normal, levels.⁹⁴

Finally, it has been shown in experimental animals that epinephrine and norepinephrine infusion results in a decrease in uterine blood flow, and deterioration of fetal condition.^{95,96} Administration of local anesthetic solutions containing epinephrine, or maternal pain and apprehension, may similarly affect the fetus.

Practical Recommendations

It is generally agreed that only emergency surgical procedures should be performed during pregnancy. Based on the already described maternal and fetal

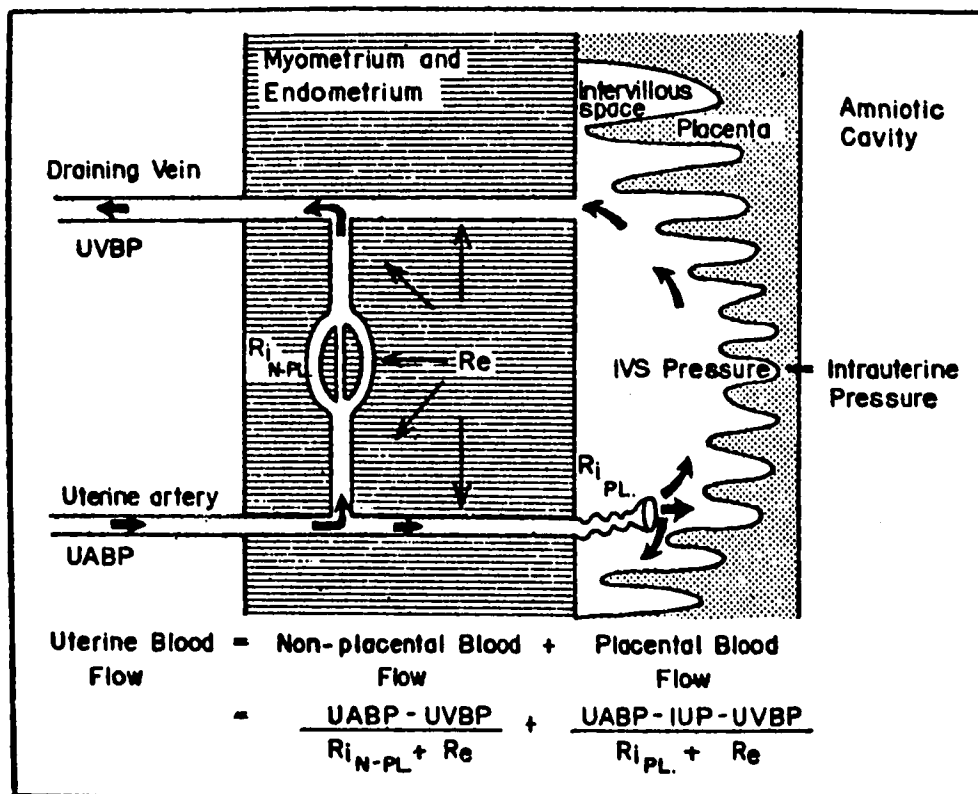


FIG. 4. Schematic representation of factors determining placental and nonplacental uterine blood flow: UABP = uterine arterial pressure; UVBP = uterine venous pressure; IUP = intrauterine (intra-amniotic) pressure; IVS = intervillous space; $R_{i\text{PL}}$ = intrinsic resistance of the spiral arterioles; $R_{i\text{N-PL}}$ = intrinsic resistance of the nonplacental vasculature; R_e = extrinsic vascular resistance imparted by the myometrial tone. Reproduced from Greiss FC Jr.⁹⁰ with permission.

hazards of anesthesia, the following rational approach to anesthesia seems indicated:

1. Apprehension should be allayed as much as possible by personal reassurance and adequate premedication. Barbiturates should be prescribed in preference to benzodiazepines. Belladonna alkaloids may also be used.

2. Pain should be relieved whenever present.

3. Administration of an antacid, 15–30 ml, approximately an hour prior to induction of anesthesia, will usually increase the pH of gastric contents to above the critical level.

4. Beginning in the second trimester, mothers should not be transported or placed on the operating table in the supine position. The lateral decubitus position or left uterine displacement will minimize the risk of vena caval compression.

5. Hypotension related to spinal or epidural anesthesia should be prevented as much as possible by rapid intravenous infusion of at least 1 liter of a crystalloid solution prior to induction. Should maternal blood pressure fall despite this pretreatment, a pre-

dominantly beta-adrenergic vasopressor, such as ephedrine, should be promptly administered intravenously.

6. General anesthesia should be preceded by careful denitrogenation to avoid maternal and fetal hypoxemia during induction and intubation.

7. The risk of aspiration should be minimized by application of cricoid pressure and rapid endotracheal intubation with a cuffed tube.

8. To reduce fetal hazard, particularly during the first trimester, it appears preferable to choose drugs that have histories of safe usage over many years. These would include thiopental, morphine, meperidine, succinylcholine, *d*-tubocurarine and low concentrations of nitrous oxide. However, ketamine, 0.5–0.75 mg/kg, might be preferable to thiopental as an induction agent in the face of severe hypovolemia. In these low doses, ketamine should have minimal effect on uterine tone.⁹⁷ Halothane may offer a specific advantage of relaxing the uterus during procedures involving pelvic organs, particularly the uterus itself, for example, cervical circlage (Shirodkar procedure).

9. In order to avoid maternal hyperventilation, one should monitor arterial blood gases or end-expiratory P_{CO_2} .

10. It is also advisable continuously to monitor the fetal heart rate throughout anesthesia and operation, providing that placement of the transducer does not encroach upon the surgical field.⁹⁸ Using the directional Doppler apparatus, this monitoring is technically feasible from the sixteenth week of pregnancy. Uterine tone may also be monitored with an external tocodynamometer when the uterus has grown enough to reach the umbilicus or above.

11. Special procedures, such as hypothermia and induced hypotension, might be desirable to facilitate operation. Successful fetal outcomes following both procedures for intracranial operations^{99,100} have been reported.

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