Maternal Indication for Placental Examination: Smoking

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Did you know smoking a single cigarette reduces blood flow to the uterus for 5-15 minutes? Infants of mothers who smoke typically weigh 200 grams less than infants of nonsmoking mothers? These infants are shorter? They are at increased risk for stillbirth and compromise during labor? In the United States today, cigarette smoking is the most common preventable cause of fetal growth retardation? Although over the past 40 years there has been a decreasing incidence of smoking in pregnancy from just under 50% in the 1950's, tobacco use continues in up to 25% of pregnancies, overshadowing the use of illicit drugs, including cocaine. The exact etiologic pathways aren't known, but studies support the deleterious effects of tobacco use during pregnancy on the pregnancy, placenta, fetus, and neonate.

Chemicals In Cigarette Smoke

There are over 300 toxic substances in cigarette smoke, including nicotine and carbon monoxide - the two main chemicals suspected of harming the fetus. Studies have repeatedly shown the strength of the cigarettes, their carbon monoxide content, and the number of cigarettes smoked per day impact the toxic effect, i.e., the higher the dose the greater the affect on the placenta and fetus.

Nicotine is the primary alkaloid in tobacco, is a known vasoconstrictor, and readily gains access to the fetus by crossing the placenta. In fact, fetal concentrations of nicotine are generally 15% higher than maternal levels. In addition, nicotine is present in the amniotic fluid and passes freely into breast milk.

Nicotine exerts its cardiovascular effects through the direct stimulation of acetylcholine receptors of the autonomic ganglion, adrenal medulla, and neuromuscular junctions, causing the release of multiple vasoactive catecholamines and peptides. It moves quickly from the plasma into the intracellular space because it is lipid soluble, has a half life of 1-2 hours, is primarily metabolized by the liver, and is excreted by the kidneys.

Carbon monoxide readily passes through the placenta by simple diffusion. It binds with fetal hemoglobin and therefore decreases the blood's capacity to transport oxygen, thus producing fetal hypoxia.

The physiologically-negative effects of tobacco on fetal growth seem to be due to the vasoconstrictive effects of nicotine on the uterine and placental vessels, absorption of carbon monoxide by the fetal red blood cells in place of oxygen, and the inhibition of oxygen release into the fetal tissue by carboxyhemoglobin (nicotine increases the concentration of carboxyhemoglobin). Theoretically, such hypoxia in the fetuses of smokers could adversely affect fetal growth, with long-term effects on the fetal brain (possibly causing learning deficits and behavioral abnormalities).

In addition, cadmium, present in high concentrations in cigarette smoke, may cause hemorrhagic necrosis of endothelium and fetal zinc deficiency. Extensive accumulation in the placenta is suspected to cause morphological and functional placental impairment.

Cyanide, also present in cigarette smoke, may contribute to fetal growth retardation and increased perinatal mortality. Increased levels of cyanide have been found in the body fluids of cigarette-smoking pregnant women and their fetuses. In addition, vitamin B12 is depleted in smokers, as it is used to break down cyanide.

Polycyclic aromatic hydrocarbons, such as benzopyrene, are present in cigarette smoke. They are known mutagens and carcinogens, and placental concentrations are highly correlated with the amount a pregnant woman smokes. Might these substances increase the risk of cancer or congenital anomalies in progeny exposed in utero?

Studies also suggest smoking more than five cigarettes a day places both mother and fetus at risk for low vitamin C levels and the consequences thereof. Smoking reduces plasma concentrations of serum copper and ascorbic acid, both necessary for the synthesis and maintenance of collagen, an important component of the extraplacental membranes.

In many instances, the chemical effects of tobacco are compounded by the anorexic effects on the mother and a higher incidence of risky behavior (co-abuse of other substances, poor prenatal care, and low socioeconomic status). Of note, low nicotine cigarettes are not thought to be advantageous to the pregnant smoker, as smokers absorb as much nicotine and perhaps as much carbon monoxide and cyanide from the lower-yield cigarettes as do smokers of the higher-yield cigarettes.

Effects on Pregnancy in General

Smoking reduces the fecundity rate, a woman's ability to become pregnant, in a dose-dependent fashion. If a woman stops smoking, her fecundity rate returns to that of a nonsmoker.

Women who smoke are at increased risk for first trimester spontaneous abortion. Nicotine is metabolized to cotinine, which is known to activate placental phospholipase-A2-like enzymes, which may activate prostaglandin formation and trigger spontaneous abortions in pregnant smokers.

Women who smoke have a dose-dependent, increased risk for placenta previa and increased risk for placental abruption. An estimated 10% of neonatal deaths are attributed to these conditions in pregnant smokers; in other words, these deaths are preventable. Women who smoke during pregnancy are at increased risk for pre-eclampsia. Although smoking does decrease the risk of pregnancy-induced hypertension (PIH), this "benefit" is offset by the increased risk for low birth weight babies and the higher perinatal death rate in women

who do develop pre-eclampsia. Pregnancies of smokers are also at an increased risk for premature rupture of membranes (perhaps due to impaired collagen synthesis related to decreased serum copper and ascorbic acid levels in smokers) and preterm labor. There is a higher incidence of infection and chorioamnionitis (perhaps related to impaired maternal immunity, more common among smokers).

Effects on the Fetus/Neonate

Maternal cigarette smoking during pregnancy causes a decrease in the fetal growth rate in a dose-dependent fashion. The decrease ranges from 70 to greater than 400 grams, with an average reduction in birth weight of about 200 grams. Two hundred grams doesn't sound like much when considering a term infant, but think about the preterm infants. In fact, smokers produce twice as many neonates weighing less than 2500 grams, and are estimated to account for about 30% of all low birth weight infants. This is compounded by the fact the infants of mothers who smoke during pregnancy do not appear to exhibit the "catch-up phenomenon" of accelerated postnatal growth.

The decreased birth weight is primarily due to a reduction in lean body mass, while deposition of subcutaneous fat is relatively unaffected. This appears to be a third trimester phenomenon, as smokers who give up cigarettes prior to the sixth month of pregnancy have been shown to give birth to infants of similar birth weight as nonsmokers. The growth retardation is thought to result primarily from fetal hypoxia and under-nutrition due to placental abnormalities.

Maternal smoking also induces a number of cardiorespiratory changes in the fetus, including increased heart rate, decreased fetal heart rate variability, clustered breathing movements (the total number of movements does not change, but they become more clustered), and an increased chance a non-stress test will be positive.

Nicotine readily crosses the placenta and is known to release the primary neurotransmitters norepinephrine and acetylcholine, which may trigger the release of enkephalin, which, in turn, may depress fetal respiration and induce apnea, causing the well documented decreases in fetal breathing movements. Studies have found the maximum reduction in fetal breathing movements occurs about thirty minutes after tobacco smoking by the mother, with recovery at ninety minutes. When the mother smoked herbal cigarettes (i.e., no nicotine), these changes did not occur.

These infants are also shorter, and some studies have shown they have significantly-decreased head circumferences, while others have not. During childhood, these children are at known increased risk for respiratory morbidity, such as asthma and upper respiratory infections. Animal studies suggest the following. Nicotine interferes with the integrity of the fetal alveolar type II pneumocyte and significantly decreases the number of type I pneumocytes. It also seems to interfere with the surfactant synthesis necessary to decrease the alveolar membrane surface tension required to make the transition to neonatal respiration. Nicotine irreversibly inhibits the glycolytic pathway in the neonatal lung, reducing the cellular capacity to derive ATP for glycolysis. Nicotine interferes with elastic tissue formation, with subsequent development of emphysema-like damage in the neonatal lung.

In addition, smoking during pregnancy has been implicated to be related to long-term deficits in mental development during infancy and behavioral problems, such as attention deficit disorder, in these children. These children consistently score lower in expressive language and conceptual comprehension, and have lower IQs. Researchers admit such relationships are difficult to measure and sort out from other compounding variables, like socioeconomic factors. However, repeated research suggests the magnitude of such long-term developmental outcomes between the infants of smokers and nonsmokers is small but measurable. Animal studies support the effects of nicotine on the developing brain, namely arterial vasoconstriction potentially leading to reduced cerebral perfusion; and nicotine is known to freely cross the blood-brain barrier.

Interestingly, infants of smokers have a lesser incidence of respiratory distress syndrome, presumably due to smoking-induced chronic fetal stress that is thought to cause accelerated fetal pulmonary maturation. However, this "advantage" is offset by the increased incidence of fetal hypoxia.

In addition to the morbidity associated with fetal hypoxia (primarily growth retardation), maternal smoking is also associated with an increased incidence of stillbirths (61% in smokers compared to 10% of controls in one study) thought to be due to hypoxia, and increased perinatal morbidity primarily related to preterm delivery. Preterm delivery occurs in 8-9% of all births but accounts for 85% of all perinatal deaths excluding those due to congenital anomalies. Smoking less than one pack of cigarettes per day (ppd) leads to a 20% increase in preterm deliveries and a 35-50% increase if mothers smoke more than one ppd. The relative differences in perinatal mortality of infants of mothers who smoked and those who didn't smoke during pregnancy were about double in early gestation, and were increased by about 33% from the 20th week of pregnancy to the end of the first year of life.

Maternal smoking has also been shown to increase the risk of meconium aspiration and there was an increased risk for mild-grade intracranial hemorrhage in the latter half of pregnancy of infants whose mothers smoked more than ten cigarettes/day during the pregnancy. The relationship between maternal smoking and SIDS is well documented, although the etiology is unknown. Most women who smoke during pregnancy also smoke after birth. Is SIDS related to smoking during pregnancy or exposure after birth?

Effects on the Placenta

Grossly, the placenta may show abruption, placenta extrachorialis (circumvallate type), thin umbilical cord, velamentously-inserted cord, single umbilical artery, chorioamnionitis, fetal stem vessel lesions, large infarcts, and the changes associated with placenta previa.

Smoking one cigarette has been shown to decrease blood flow through the placenta for up to fifteen minutes. Tobacco smoke induces changes in the production of thromboxane and causes platelet activation, which may influence the production or effect of other vasoactive substances in the placenta, disturbing the delicate balance of blood flow regulation. Fetal blood flow is controlled by the interactions of paracrine, autocrine and endocrine factors, derived from the endothelium, placental syncytiotrophoblast, and maternal and fetal circulations. In addition, a variety of vasoactive agents are present in placental tissue (such as endothelin I, the concentration of which is increased in smokers), and their production may be altered in smokers because of

(Continued on page 12)

(Continued from page 11)

tobacco's toxic components. Such changes may compromise fetal-placental blood flow, contributing to the lower birth weights seen among infants born to mothers who smoke.

Maternal smoking also leads to significant alterations in placental morphology, including: increased number of abnormal trophoblasts with increased syncytial knots, decreased intervillous space, presence of syncytial buds, ischemic necrosis, retroplacental hematomas, infarcts, and abnormal uteroplacental vessels. These placentas also show characteristics of decreased maternal perfusion, such as obliterative endarteritis, cytotrophoblastic hyperplasia, and marginal decidual necrosis.

The placentas of mothers who smoke during pregnancy also show vascular damage, such as reduced number of capillaries of the placental bed, increased endothelial cell turnover rate resulting in a thickened basement membrane, and degenerative changes of the endothelium with subsequent opening of endothelial junctions and formation of subendothelial edema. These changes suggest placental under-perfusion plays a role in the hypoxic process, predisposing the fetus to growth retardation and the placenta to many of the discussed abnormalities, such as abruption.

The umbilical cord vessels are also affected. In culture, they are significantly less able to grow and have a significantly-reduced ability to produce prostacyclin. The umbilical artery endothelium is a major source of prostacyclin, involved in placental-fetal circulation due to its anti-thrombotic and vasodilating properties. Its reduction in smokers may play a role in the decreased placental perfusion.

Friesen and Fox (1986) remind us ***"Each of us is entitled by law to select nonsmoking accommodations on airplanes and trains. Shouldn't the fetus be afforded the same protection on its significantly longer and more perilous journey?"***

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