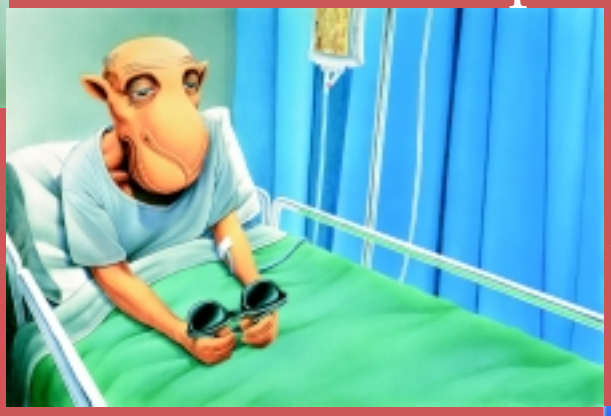
Cigarette Smoking, Pregnancy and the Developing Fetus



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Cigarette smoke contains over 1000 different compounds including carbon monoxide, hydrogen cyanide, carcinogens and trace elements such as lead, nickel and cadium. The two main compounds suspected of causing the harmful effects on the developing fetus during pregnancy are carbon monoxide and nicotine.

Carbon monoxide has a higher affinity for hemoglobin than oxygen, quickly forming the compound carboxyhemoglobin which is unable to carry oxygen. The formation of this molecule leads to a potential for decreased oxygen delivery to the fetus and fetal hypoxia.

Nicotine is generally regarded as the pharmacologically active ingredient in tobacco responsible for the majority of its effects. It has both cardiovascular and central nervous system effects. Nicotine activates the adrenergic system through the release of catecholamines from the adrenal medulla, autonomic ganglia and neuromuscular junctions. Two separate types of central nervous system stimulation account for the positive stimulation responsible for the addictive properties of nicotine. Nicotine has a half life of 1 to 2 hours and it is metabolized by the liver and eliminated by the kidney. Cotinine, its metabolite, has a half life of 15 to 20 hours and significantly higher levels and thus provides an accurate assay for nicotine exposure. Nicotine is known to cross the placenta reaching levels in the amniotic fluid and fetus that exceed those of the mother.[1] Nicotine is also measurable in the breast milk of smoking mothers as well as mothers passively exposed to cigarette smoke.[2]

The effects of cigarettes on the pregnant woman and developing fetus are numerous with a wide range of sequelae that will remain with the fetus for the rest of her life. A large body of medical research has focused on smoking in pregnancy and its far-reaching effects on the fetus which I will attempt to review.

Fertility

Several studies have suggested that smoking may be associated with decreased fertility among both women and men. In men, smoking has been shown to cause decreased sperm motility; abstinence from smoking leads to return of motility.[3] In women, numerous studies have confirmed a decreased fertility among women who smoke, documenting adverse effects on several crucial processes such as ovulation, tubal transport and implantation.[4]

Spontaneous Abortion

Nicotine has been shown to be a potent vasoconstrictor reducing uterine and placental blood flow.[5] These properties may account for the increase in spontaneous abortions seen in smoking women. This knowledge is not new; Ballantyne in 1902 noted that miscarriages were more common in female tobacco factory workers. A study published in 1999 studied the association between cocaine and tobacco use and spontaneous abortions among pregnant women.[6] Both cocaine and cigarette use were measured using urine analysis. The presence of cotinine, a nicotine metabolite with a long half-life, was independently and significantly related to an increased risk of spontaneous abortion. Among those women with spontaneous abortion, 28.9% used cocaine and 34.6% smoked cigarettes based on urine analysis.

Placental Problems

Placental abruption, the premature detachment of the normally implanted placenta, accounts for 15 to 25% of all perinatal mortality due to complications such as preterm delivery, fetal distress, maternal coagulopathy and ischemic injury to other organs. Placenta previa, the implantation of the placenta in the lower part of the lower uterine segment in advance of the fetal presenting part can be complicated by prematurity, placenta accreta, vasa previa and hemorrhage

among others. Placenta previa is responsible for an increase in perinatal mortality as high as 81 in 1,000 births as compared with a rate of 10 in 1,000 births for the general obstetric population.

The Ontario Perinatal Mortality Study was the first to report the association of cigarette smoking with both placental abruption and placenta previa.[7] This study was performed between 1960 and 1961 in 10 Ontario hospitals. Mothers were interviewed in the early postpartum period about smoking during pregnancy and separated into 3 groups; nonsmokers, less than 1 pack per day smokers, and greater than 1 pack per day smokers. The overall perinatal mortality was increased from 23.3 in 1,000 births in non-smokers to 33.4 in 1,000 births in women smoking greater than 1 pack per day. Placental abruption and placenta previa were responsible for 50% of the increase in perinatal mortality seen in smoking women.

The proposed mechanism for development of placental abruption in smoking women is explained by reduction in blood flow to the placenta resulting in decidual necrosis at the periphery of the placenta.[8] The increase in placenta previa in smoking women may be explained by placental enlargement and the greater likelihood that the internal os is covered. Placental enlargement may be a compensatory mechanism for reduction in oxygen transport to the fetus caused by carbon monoxide in cigarette smoke. Placental changes consistent with an impairment in the placenta's ability for gaseous exchange are a thickening of the trophoblastic basal lamina and a reduction in the size of the fetal capillaries.[9]

Birth Weight

A definite, well-established relationship exists between smoking and low birth weight defined as birth weight less than 2500 grams.[10] In general, the average reduction in birth weight seen in smoking women is 200 grams. This results in a doubling of the incidence of low birth weight infants. The risk and magnitude of low birth weight is related to the number of cigarettes smoked during pregnancy. The critical period during which smoking exerts its deleterious influence has not been determined, but it has been shown that if women cease smoking during pregnancy the infant's birth weight will be comparable to a non-smoker.[11]

The exact mechanism for decreased birth weight is unclear. At the present, there is evidence that smokers do not consume fewer calories or have less weight gain during pregnancy so it has been concluded that the decrease in birth weight seen in infants of smokers is not due to nutritional factors.[12] Anthropometric studies comparing the differences in body composition in infants of women who smoke with those of non-smokers have found a decrease in the fat-free mass.[13] Specifically, weight and length were decreased in the infants of smokers, but no differences in skinfold and limb circumference measurements were seen. It is unknown whether the physiological effects of smoking on fetal growth are due to the vasoconstrictive properties of nicotine on uterine blood or the decreased oxygen availablity due to carbon monoxide and the formation of carboxyhemoglobin.

Perinatal Mortality

There is a 33% increase in perinatal (after 20 weeks gestation) and neonatal (in the first 28 days of age) mortality in smoking women.[10] This increase occurs independently of the decrease in birth weight. While the mean length of gestation is only slightly shorter in pregnant smokers, the proportion of preterm births (less than 37 weeks gestation) increases significantly.[7] Analysis of the Ontario Perinatal determined that maternal smoking increases the perinatal death risk for mothers smoking less than one pack per day 20% and 35% for those mothers smoking more than one pack per day. Little further information exists on the other specific causes for increased perinatal mortality.

Congenital Malformations

Studies on the relation between smoking during pregnancy and the incidence of congenital malformations have been inconclusive. Prior retrospective studies have been flawed by small sample size and failure to clearly define specific malformations. Three larger prospective studies found no increase in the prevalence of congenital malformations, but a few malformations were found to be associated with maternal smoking. Data from the Kaiser Permanente Birth Defects Study (33,434 births) and the Collaborative Perinatal Project (53,512 births) were together used to assess the relationship between maternal smoking and congenital malformations.[14] From the Kaiser data, nine malformations were found to be associated with maternal smoking, but only one was confirmed by further testing with the Collaborative Perinatal Project data. The authors concluded that smoking is unlikely to account for an increase in congenital malformations.

Intellectual Function

A wide variety of cognitive, achievement and behavioral deficits such as attention deficit hyperactivity disorder (ADHD) have been identified in the children of women smoking during pregnancy. Whether these findings are a result of other confounding environmental and social factors has been difficult to determine. However, case-controlled studies have continued to identify intellectual impairment as well as a 50% increase in idiopathic mental retardation after controlling for a wide range of variables.[15,16]

Childhood Cancer

Components of cigarette smoke are known to be transported over placental membranes and are able to act as mutagens in fetal tissues. Components of cigarette smoke have been shown in animal studies to be transplacental carcinogens.[17] Numerous studies have investigated the incidence of childhood cancer in the children of women who smoked during pregnancy. An increased risk for all cancers is found as well as an association of acute lymphocytic leukemia and lymphoma with maternal smoking has been confirmed in several studies.[18,19]

Sudden Infant Death Syndrome (SIDS)

Several epidemiological studies have reported a relationship between maternal cigarette smoking and SIDS.[20] Of the various risk factors for SIDS, maternal smoking is one of the most predictive. Decreased ventilatory response to hypoxia is thought to be part of the pathophysiology of SIDS. Recent studies in neonatal lambs have shown that nicotine attenuated the ventilatory response to hypoxia[21] and have led to the speculation that SIDS is related to the effects of nicotine on the central control of breathing.

Our Role as Physicians

The incidence of smoking has decreased significantly from 48%[22] in the 1950's to 16%[23] in 1995. However, it is clear that cigarette smoking remains one of the most common drugs to be used during pregnancy despite the proven adverse effects on the developing fetus. As stated in the 1995 publication "The Future of Children"[24]:

> Cigarette smoking is unequivocally the largest and most important known modifiable risk factor for low birth weight and infant death.

Educational and other interventions to decrease smoking in pregnant women are important services obstetricians and other medical personnel can provide to both the mother and the unborn child. A pregnant woman informed of the possible long term effects of smoking on her child may be more motivated to stop smoking than at other times in her life. Intensified efforts to increase public knowledge regarding the numerous adverse effects of cigarette smoking are still urgently needed so that smoking during pregnancy will become a rare event.

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