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Caffeine and Pregnancy Outcome

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Since caffeine is a readily consumed non-nutritive component of numerous foods and beverages, many of its physiological mechanisms and effects have been studied. It is known to be completely absorbed by the gastrointestinal tract, and easily crosses the blood-brain, placental, and other membranes to permeate all fluids and tissues (1). A few of the known biological effects of caffeine include central nervous system stimulation, increased secretion of catecholamines, relaxation of smooth muscle, and increased heart rate. In normal adults, caffeine reaches a peak concentration in the blood within 30 to 60 min after ingestion and its half-life averages 2.5-4.5 h (2). Consequently, upon repeated consumption plasma caffeine concentration and its biological effects are additive.

In pregnant women this additive effect is enhanced due to hindered caffeine metabolism. Elevated estrogen levels have been implicated as the cause for the increase in half-life to 7 h in mid-pregnancy and to 10.5 h during the last few weeks of pregnancy (1). In addition to the higher caffeine blood levels in the mother and the fetus, the fetus also lacks the enzymes necessary to metabolize caffeine (3). This compounds the fetus' exposure to caffeine. Thus it appears that caffeine could affect the outcome of pregnancy.

Since pregnant women commonly consume caffeine, it has been the subject of scrutiny regarding its possible reproductive adverse effects. Some of the outcomes elucidated from animal models include fetal resorption, lower birth weight, and congenital malformation in association with exposure to caffeine (4). Mainly based on these animal studies, in 1980 the US Food and Drug Administration cautioned pregnant women to limit their caffeine intake (5). As a result, many women reduce their caffeine consumption once they know they are pregnant; however, 70 to 80% of pregnant women still consume significant amounts of caffeine. Since 1980, numerous human epidemiological studies have investigated the impact of caffeine on reproduction. I will focus on the current knowledge regarding the association between caffeine use during pregnancy and birth outcome; specifically, fetal loss, congenital malformation, and issues related to fetal growth.

In most studies coffee, tea, soda and chocolate are the main sources of caffeine in an individual's diet. In order to assess the actual levels of caffeine intake, these studies had to approximate the caffeine content of these sources. The typical caffeine content of brewed coffee is 85 to 100 mg per 6-oz cup and of instant coffee is 65 mg per 6-oz cup. By comparison, there are 40 mg of caffeine in a cup of tea and 45 mg in 350 ml (12-oz) of caffeinated soda (2). A chocolate bar (average weight of 50g) has 56 mg of caffeine and a piece of chocolate has 16 mg of caffeine (3).

Several studies have examined the relationship of maternal caffeine use during pregnancy to increased risk of spontaneous abortion or fetal loss. The results have been inconsistent; some studies have found an association between caffeine consumption and spontaneous abortion, while others have not. For example, two different studies in 1993 reported somewhat conflicting conclusions. Mills et al., in a prospective cohort, closely monitored 460 nondiabetic women starting soon after conception (6). They found that the mean first-trimester caffeine consumption was not significantly higher in women who aborted than in women who delivered liveborn infants. First-trimester caffeine consumption was

studied because virtually all spontaneous abortions occurred in the first trimester. Therefore, they concluded that moderate caffeine consumption of less than 300 mg/day did not increase the risk of spontaneous abortion. Whereas Infante-Rivard et al., in a case control study, demonstrated a two fold increased risk of fetal loss associated with caffeine consumption as low as 163 mg/day during the first trimester (5). Furthermore, high caffeine consumption (321 mg/day) even in the month before pregnancy nearly doubled the risk. The disparity of these two studies may in part be explained by differences in assessing exposure; in addition to other differences in experimental design (7). In the Mills et al. study, women were interviewed seven times including four times in the first trimester. They were asked to report their average consumption of coffee, tea, cocoa, and sodas so that average daily exposure to caffeine could be quantified for the time period of interest (6). While in the study by Infante-Rivard et al., both the cases and controls were interviewed only once and were asked to report the average consumption for coffee, tea, and colas for the previous 3 months. As a result they may have reported caffeine consumption less accurately than women in the cohort study by Mills et al. Although these two studies' conclusions conflict, they reflect the current understanding of this issue (7). In addition to the possibility that caffeine may effect the pregnancy outcome of fetal loss, caffeine has also been implicated in congenital malformation and negative effects on the growth of fetuses that are liveborn.

Caffeine was once believed to have a teratogenic effect. Adverse developmental consequences of caffeine were seen in several species including mice, rats, and rabbits. For example, mice are susceptible to cleft palate and abnormalities of digits at doses of caffeine of greater than 50 mg/kg per day (8). This corresponds to about 25 cups of coffee per day which well exceeds the highest consumption of any pregnant woman. Possibly as a result of differences in dosage and differences in the metabolism of caffeine by humans and other animal models, most epidemiological studies do not support the animal data that caffeine may be a human teratogen (4). For example, of 12,205 pregnant women interviewed in the Boston area from 1 to 2 days after delivery, major malformations were documented in 2.5% of the women who reported no coffee or tea use during pregnancy and in 2.0% of women who reported being heavy coffee drinkers (8). There seems to be very little evidence to implicate caffeine as a cause of human congenital malformations.

The other possible effect on pregnancy outcome involves three main issues related to fetal growth: low birth weight, preterm birth, and intrauterine growth retardation. Birth weight is frequently studied because it provides an accurate and predictive indicator of infant health; lower birth weight may indicate poorer health. The definition of low birth weight is a weight of less than 2500 grams at birth (8). Most studies report that, after controlling for smoking, the birth weight of infants born to women who consumed large amounts of caffeine (more than 300 mg/day) were lower than that of those born to women who consumed little or no caffeine (4). However, there are also a few studies that show no effect of caffeine. Larroque et al. examined the consequence of prenatal alcohol, smoking, and caffeine consumption on birthweight on a sample of 628 French women who delivered between 1985 and 1986 (4). They found that alcohol and smoking resulted in lowered birth weight, but the relationship between caffeine intake and birthweight

disappeared after adjusting for smoking. The consumption of caffeine in this study was also very large. Very few women (6 percent) consumed no caffeine at all during pregnancy; 27 percent consumed more than 400 mg/day and 7 percent consumed more than 800 mg/day (4).

Preterm birth or prematurity is defined as delivery at less than 37 weeks of gestational age calculated from the first day of the last menstrual period. Pasture and colleagues evaluated the relationship between caffeine consumption and preterm delivery by conducting a case-control study on infants born to women in selected North Carolina counties from September 1988 through April 1991 (9). After assessing the consumption of a variety of caffeinated beverages and calculating the intake of caffeine, overall, their results did not support an association between caffeinated beverage consumption and preterm delivery. This is consistent with a majority of the studies involved with preterm delivery.

Since preterm delivery has been shown to be unrelated to caffeine consumption, it is possible that caffeine exerts its influence on low birth weight through intrauterine fetal growth retardation. Growth retardation is considered to occur when the birth weight is less than the 10th percentile for sex and gestational age (3). Forteir et al. evaluated the relationship between prenatal caffeine intake and intrauterine growth retardation based on data from 7025 Canadian women who had given birth between January and October 1989 (3). They found that for each step increase of average daily caffeine consumption (0-10, 11-150, 151-300, and 300 mg) there was a corresponding increase in the risk of intrauterine growth retardation. However, the results disagreed with the Mills et al. investigation of moderate caffeine use (300 mg/day or less) which found no evidence of increased risk of intrauterine growth retardation (6). Hatch and Bracken argue that Mills' et al. result of no association is misleading because none of the previous studies had found effects of caffeine on fetal growth at these low levels; however, most studies suggest some effect of higher levels of caffeine (most often over 300 mg/day) (10). Mills et al. could not draw conclusions at these higher levels because too few women consumed this amount. Unlike the issue of preterm birth, the association of maternal caffeine consumption during pregnancy on low birth weight and intrauterine growth retardation are still unresolved.

Although numerous epidemiological studies have been conducted to assess the effects of caffeine use on pregnancy outcomes of humans, no overall conclusion has emerged. Most studies agree that there is no association between caffeine intake and congenital malformation or preterm delivery. However, the picture is less clear regarding fetal loss, low birth weight and intrauterine growth retardation. Often these studies are plagued with problems, resulting in inclusive findings. I believe there needs to be further research in these areas because there are a number of biological mechanisms that could explain caffeine's adverse effect on birth outcome. For example, the longer half life of caffeine and the resulting higher blood caffeine levels cause vasoconstriction and a reduction in placental blood flow resulting in a reduction in the transmission of nutrients to the fetus (3). Until the results reach a consensus, I believe women should still be advised to eliminate caffeine when they become pregnant. However, it appears that low to moderate

levels of caffeine consumption, below 300 mg/day (equivalent to 3 cups of coffee a day), are relatively safe in relationship to pregnancy outcome.

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