



**TOURO COLLEGE &
UNIVERSITY SYSTEM**

The Science Journal of the Lander
College of Arts and Sciences


Volume 11
Number 2 *Spring 2018*

2018

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Recommended Citation

Kahan, J. (2018). The Effects of Maternal Caffeine Intake on a Fetus. *The Science Journal of the Lander College of Arts and Sciences*, 11(2). Retrieved from <https://touro scholar.touro.edu/sjlcas/vol11/iss2/8>

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The Effects of Maternal Caffeine Intake on a Fetus

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Abstract

The United States has been noted as the country with the greatest caffeine consumption in the world. More than half of all Americans are said to consume caffeine on a daily basis. Caffeine is easily available in a variety of dietary products including coffee, tea, soft drinks, and chocolate. Many pregnant women are unaware of the potential risk that excessive caffeine consumption can have on their unborn child. The purpose of this paper is to explore the ramifications of caffeine intake on a fetus. The studies reviewed propose that heavy maternal caffeine consumption, that of more than 300 mg daily, is associated with increased risk of spontaneous abortion or delivery of an infant of low birth weight. Most researchers agreed that caffeine does cause preterm labor and delivery, nor does it act as a human teratogen.

Acronyms

LBW- Low Birth Weight

SGA- Small for Gestational Age

IUGR-Intrauterine Growth Retardation

Introduction

Caffeine (1,3,7-trimethylxanthine) is a naturally occurring compound. Its pharmacological and physiological effects include stimulation of the central nervous system and cardiac muscle, and relaxation of smooth muscle. Caffeine has been shown to have effects on physical and cognitive performance, as well as mood, memory, and alertness. Caffeine is the most widely used stimulant for the central nervous system. Clinically, caffeine is useful for relaxing the bronchial muscle in asthmatic patients, increasing secretion of gastric acid, and the concentrations of plasma free fatty acids, and glucose (Institute of Medicine, 2001).

Sources of Caffeine

Coffee, tea, and soft drinks are the main sources of caffeine in the diet of the average American adult. Other dietary sources include chocolate and cocoa, sugars and sweets, and flavored dairy products. Tea also contains a significant amount of theophylline (1,3-dimethylxanthine), as cocoa also contains theobromine (3,7-dimethylxanthine), both being derivatives of caffeine that have not been as widely researched (Frary, 2005). Many classes of nonprescription medications including analgesics, cold/allergy products, diuretic products, stimulants, and weight control agents have some caffeine content. All medications have a suggested dose, but consistent usage may lead to the medication becoming a significant source of caffeine consumption.

Absorption, Distribution, and Elimination of Caffeine Absorption

Caffeine and the other methylxanthines are quickly absorbed in humans. As much as 99 percent is absorbed within the 45 minutes after ingestion. Oral, rectal, and parenteral administration is possible, with the oral route being most common. When consumed in a beverage, the caffeine is quickly absorbed from the gastrointestinal tract and distributed throughout body water. Caffeine in preparations that allow absorption through oral mucosa, such as caffeinated chewing gum, are absorbed even more rapidly. Depending on the source of the caffeine and the individual's metabolism, caffeine's peak plasma levels appear between 15 and 120 minutes after ingestion or administration (Institute of Medicine, 2001).

Distribution

The distribution volume of caffeine within the body is 0.7 L/kg, demonstrating caffeine's hydrophilic quality and ability to distribute freely into intracellular tissue water (Arnaud, 1993). Caffeine can also pass through all biological membranes and freely crosses the blood-brain barrier, demonstrating its lipophilic quality (Institute of Medicine, 2001). In pregnant women, the caffeine can cross the placenta to the fetus, and as early as 7-8 weeks gestation, maternal and fetal plasma can achieve an equilibrium (Goldstein, Warren, 1962). A fetus swallows approximately 500 mL of amniotic fluid daily, and studies suggest that several milligrams of caffeine can be ingested along with the fluids. Additionally, by week 12 of gestation the fetal liver is able to methylate theophylline to caffeine (Brazier, 1981). Both caffeine and theophylline are eliminated in the amniotic fluid, with caffeine's fetal elimination half-life at approximately 150 hours, while theophylline's is 30 hours.

Elimination

The small fraction of caffeine that is excreted unchanged in urine indicates that caffeine metabolism is the rate-limiting factor in its plasma clearance. Its limited appearance in urine is due to caffeine being readily reabsorbed by the renal tubules and filtered by the glomeruli (Arnaud, 1993). Frequent caffeine ingestion has not been shown to affect its absorption or metabolism in healthy humans. The bulk of caffeine metabolism takes place in the liver, catalyzed by hepatic microsomal enzyme systems (Grant et. al., 1987). In the liver, caffeine is metabolized to dimethylxanthines, uric acids, di- and trimethylallantoin, and uracil derivatives. 3-ethyl demethylation to paraxanthine is shown to be the most frequent route for caffeine metabolism in humans (Arnaud, 1987). This is the first step in caffeine metabolism and accounts for approximately 75-80 percent of the process. Being the chief metabolite in humans, paraxanthine is found to have a plasma concentration ten times higher than those of theophylline and theobromine. Eight to ten hours after ingestion, plasma levels of paraxanthine surpass those of caffeine, as caffeine is cleared more rapidly than paraxanthine (Arnaud, 1993). During the second and third trimesters of pregnancy, maternal caffeine elimination rates drop due to changes in progesterone and estrogen levels, with the half-life of caffeine changing from 5.3 hours to 18.1 hours. Maternal clearance of caffeine during pregnancy can be decreased further by other factors, including smoking and long-term use of oral contraceptives, as well as age

and disease. Within a couple of weeks of giving birth, a woman's caffeine metabolism rate returns to the same rate as prior to pregnancy (Aldridge et al., 1981).

Methods

Critical analysis of peer reviewed journal articles and original clinical research papers was used to write this review. The articles and papers were obtained with access to online publications through the Touro College library. Additional references were obtained through Pubmed and Google Scholar.

Effects of Caffeine Consumption on Birth Weight

A low birth weight (LBW) infant is one who weighs less than 2,500 g (5 lbs, 8 oz) at birth. Prematurity due to a shortened gestational period can cause low birth weight, but LBW can also be the consequence of intrauterine growth retardation (IUGR), which results in a small for gestational age (SGA) infant. Intrauterine growth retardation is classified as less than the 10th percentile of birth weight for gestational age in comparison to an external standard of birth weight for gestational age, adjusted for gender and ethnicity, that was developed from all 1999 singleton births in the United States, and updated in 2014 (Talge et al., 2014). Many studies have shown a strong correlation between caffeine intake during pregnancy and reduced birth weights. For pregnant women who consume more than 300 mg of caffeine daily, a high risk of SGA and IUGR has been found. Intake between 150 mg and 300 mg daily has also been linked to such risks; however, the data is not as consistent.

From 2003-2006, a perspective cohort study following pregnant women between the ages of 18 and 45 with singleton pregnancies was implemented. The caffeine intake of these women was monitored, and the relationship between caffeine and fetal growth was evaluated. At any level of caffeine intake there was an associated risk of fetal growth retardation found, and this risk was maintained throughout pregnancy. They found that after adjustment for smoking and alcohol intake, an average caffeine consumption of more than 100 mg per day was correlated with a reduction in birth weight of 34-59 g in the first trimester, 24-74 g in the second, and 66-89 g in the third. An extra 60-70 g may seem insignificant, but it can make all the difference for an already compromised fetus, and can help avoid perinatal morbidity and mortality. The study did observe a large decline in risk for a daily caffeine intake of less than 30 mg, but this may be due to unmeasured confounding, or simply because lower caffeine intake is probably more common among women who have healthier diets and habits in general (CARE Study Group, 2008).

A second prospective study observed the caffeine intake of 9,921 healthy pregnant women throughout their third trimester. Fifty-three of the women reportedly consumed more than five cups of coffee daily, and they were found to have a 13.2% higher prevalence of fetuses who were SGA (Fuhurhashi et al., 1985).

The Norwegian Mother and Child Cohort Study conducted by the Norwegian Institute of Public Health followed 59,123 women with uncomplicated singleton pregnancies. At weeks 17, 22, and 30, the women reported their caffeine intakes from different sources. SGA was defined according to ultrasound-based, population-based, and customized growth curves. Based on the three scales, an average of 25 g weight reduction was associated with every additional 100 mg of maternal caffeine intake per day for a baby with an expected birth weight of 3,600 g. Coinciding results for caffeine sources, time of survey, and different definitions of SGA were found for this, substantiating its results. Even caffeine consumption below the recommended maximum such as 200 mg per day, compared to the recommended 300 mg per day, was consistently associated with increased risk for SGA (Sengpiel, 2013).

Gestational age was not linked to caffeine intake in these studies, suggesting that the effect maternal caffeine consumption has on fetal birth weight occurs through IUGR. Possible mechanisms responsible for this effect include caffeine's similar structure to adenine and guanine which may allow it to interfere with cell division and metabolism. Additionally, caffeine has a vasoconstrictive effect on placental intervillous blood flow, which may be a factor to increase the risk of IUGR (Kirkinen, 1983).

During the first trimester of pregnancy, the embryo first starts developing its organs, heartbeat, brain waves, and the rest of its body parts. As this is such a crucial time of development, caffeine intake should be limited especially then. In fact, a greater reduction in risk for IUGR and delivering LBW infants was found among women who reduced their caffeine intake to less than 300 mg within 6 days of their last menstrual period, compared to those who reduced their intake later in pregnancy (Fenster et al., 1991).

There is a steady negative correlation between LBW infants and daily maternal caffeine intake above 300 mg. In many studies, a daily caffeine consumption between 151 and 300 mg, and occasionally even 150 mg or lower has been associated with risks of low birth weight. Pregnant women should be sure to limit their caffeine intake as much as possible to lessen the probability of reductions in infant birth weight. The seemingly slight decrease in weight can be very harmful for premature infants or infants who are otherwise compromised. Further research is needed to clarify the mechanisms by which caffeine exercises an effect on fetal growth.

Effects of Caffeine Consumption on Preterm Labor and Delivery

Caffeine has not been found to be a strong factor in increasing the risks of preterm labor and delivery. In 1996-2000, 2,291 mothers with singleton pregnancies in Connecticut and Massachusetts were questioned about caffeine consumption and other important confounding factors after their first

prenatal visit. Urine samples were taken to analyze urinary caffeine, cotinine, and creatinine levels. The mothers were followed throughout pregnancy to monitor changes in consumption, and medical records were obtained to confirm pregnancy outcomes. While mean birth weight was found to be reduced by 28 g per 100 mg of daily caffeine intake, mean gestational age was not found to be affected at all (CARE Study Group, 2008).

In the Norwegian Mother and Child Cohort Study, spontaneous preterm delivery was defined as "spontaneous onset of delivery between 22+0 and 36+6 weeks (n = 1,451)". Caffeine from coffee, but not from other sources, was actually associated with prolonged gestation, but no association of increased risk of spontaneous preterm delivery was found with caffeine consumption (Sengpeil et al., 2013).

Other studies as well found no effect on gestational age, indicating that caffeine influences fetal growth, not gestational age at delivery. Pastor et al performed a case control study of 408 preterm (less than 37 weeks gestation) infants, and analysis of caffeine intake in the third trimester showed a nonsignificant relationship with preterm delivery (Pastore, Savotz, 1995).

Alternatively, in a population-based study of 7,855 livebirths, increased preterm birth among women who drank caffeinated coffee was found compared with women who drank neither decaffeinated nor caffeinated coffee. Those who consumed only decaffeinated coffee showed no increased odds of SGA birth, LBW, or preterm delivery, while women who consumed caffeinated coffee alone had a higher association with preterm delivery (Eskenzai et al., 1999). This study has not been replicated, and other analyses did not support it.

Gestational age is difficult to calculate and assess, making this topic more difficult to analyze accurately. Generally, there appears to be no relationship between caffeine consumption during pregnancy and premature labor and delivery in humans.

Effects of Caffeine Consumption on Spontaneous Abortion

Most studies report effects of caffeine on spontaneous abortion, however, there are some who suggest otherwise. In one study, 2,967 pregnant women who delivered at Yale-New Haven hospital between 1988 and 1992 were evaluated for caffeine intake during the first month of pregnancy. After studying the effect of the caffeine on pregnancy outcomes, it was concluded that increased risk of spontaneous abortions was linked to drinking more than 3 cups of tea or coffee daily. The association of risk with tea and coffee intake was shown to be stronger than with caffeine in general, and was primarily correlated with abortions which took place in later trimesters (Dlugosz et al., 1996).

A prospective cohort study of 3,135 pregnant women found that those who consumed more than 151 mg of caffeine daily were more likely to spontaneously abort in the second or third trimester, in comparison to those who had a daily intake of less

than 150 mg of caffeine (Srisuphan, Bracken, 1986).

A study of healthy, pregnant women, all of whom were beyond 24 weeks of gestation revealed that caffeine consumption of more than 600 mg daily was significantly associated with impending abortion, with a higher prevalence of 17% found (Fuhurhashi et al., 1985).

Another study of 1,324 women demonstrated associations between caffeine intake prior to and during pregnancy with spontaneous abortions in 331 of the 1,324 women. The risk of fetal loss increased for each 100 mg of caffeine ingested daily during pregnancy, as well as smaller increases in risk for each 100 mg of caffeine ingested daily prior to becoming pregnant (Infante-Rivard, 1993).

Dominguez-Rojas et al conducted a retrospective cohort study of 711 pregnant women, monitoring their caffeine intake, and found caffeine to be a clear risk factor for spontaneous abortion. They determined that the adjusted odds ratio (a measure of association between exposure and outcome) of spontaneous abortion by caffeine consumption was significant for 141-280 mg daily, doubled for 281-420 mg daily, and then almost tripled for intake of greater than 421 mg daily (Dominguez-Rojas et al., 1994).

Alternatively, different studies found no association between maternal caffeine intake and spontaneous abortions. Four hundred and thirty-one women were enrolled in a multicenter study within 21 days of conception. Throughout pregnancy, they were monitored for caffeine intake, and exposure to other risk factors, and the effects on pregnancy outcome. The investigators found no connection between caffeine intake, neither above or below 30 mg daily, and increased risk of spontaneous abortions (Mills, 1993).

Determining a definite causal connection between caffeine intake and occurrence of spontaneous abortions is difficult, as many of the studies that have been done did not control properly for other factors such as smoking, parity, or alcohol intake. There seems to be a strong association between caffeine consumption and fetal loss, but more research must be done before unambiguous statements can be made.

Effects of Caffeine Consumption on Congenital Malformations

Caffeine can perhaps act as a teratogen due to its chemical structure as a purine, one of the components of DNA. After maternal consumption, caffeine can cross the placenta to the developing embryo. If the molecule were to become incorporated into DNA, there is a possibility that it could induce the production of abnormal proteins (Goldstein, 1962). The literature reviewed showed no significant evidence linking human maternal caffeine intake during pregnancy to major congenital malformations.

In a study performed to analyze information from the Finnish Registry of Congenital Malformation, mothers who had given

birth to infants with the same defects were matched according to place and time of birth. One mother in each pair consumed coffee during pregnancy, while the other did not. To evaluate the hypothesis that coffee consumption during pregnancy is teratogenic, the 706 pairs of mothers of malformed children and their controls were interviewed soon after delivery. The subjects of the study included 112 mothers of children with defects of the central nervous system, 241 mothers of children with orofacial clefts, 210 mothers of children with structural defects of the skeleton, and 143 mothers of children with cardiovascular malformations. The study determined that coffee intake does not appear to increase risk for any of the defects that were studied. Even mothers who consumed more than six cups of coffee per day had no higher risk of giving birth to an infant with congenital malformations. The study also paired these mothers with women who gave birth to non-defective infants, in the same time and place, and who consumed an equivalent amount of caffeine daily during pregnancy. The amount of coffee consumed during pregnancy was similar for the mothers of malformed and non-malformed children, with the broad range of maternal intake being 0-10 cups daily, demonstrating that excessive coffee intake does not increase risk of congenital malformations (Kurppa et al., 1983).

McDonald et al. investigated the relationships between smoking, alcohol intake, and caffeine consumption, and congenital malformations using data from a survey conducted in Montreal from 1982-1984. A weak association between caffeine consumption and heart defects was found, but the evidence was not strong. There was no connection found between caffeine intake and club foot, clefts, neural tube defects, or musculoskeletal renal/urinary, gastrointestinal, or respiratory abnormalities (McDonald et al., 1992).

Similarly, a study was performed to determine the possible effects of different chemical and physical factors during pregnancy on the occurrence of cardiovascular malformations, specifically hypoplastic left heart syndrome. Using a standard questionnaire, 573 cases and 1,055 controls were interviewed approximately 3 months after delivery. An increased risk of cardiovascular malformations was not found to be associated with coffee, tea, or cola consumption (Tikkanen, Heinonen, 1994)

One study did show an increased risk for malformations due to caffeine. A retrospective case-control study was executed in which 558 women in England who had delivered an anencephalic stillbirth were matched with 2,232 control women based on maternal age, parity, and date of delivery. Based on a structured questionnaire completed by the cases and controls, it was shown that the women who drank 3 or more cups of tea daily were more likely to give birth an anencephalic stillborn (Fedrick, 1974). However, the results of this study may not be completely accurate, and the authors themselves wrote that caution should be taken when interpreting their results.

Most studies agree that there is no connection between caffeine intake during pregnancy and congenital abnormalities. Any connections that were found have been deemed weak at best.

Conclusion

Maternal caffeine intake during pregnancy should be limited to between 150 mg and 300 mg per day, to mitigate negative effect caffeine has been shown to have on birth weight, risk of IUGR, and risk of spontaneous abortion. More studies must be done to confirm correlation between caffeine and spontaneous abortion, and based on current data, there does not seem to be a significant risk of preterm labor or congenital malformations related to caffeine intake.

Pregnancy is a time when motherly instincts begin to kick in, and women are likely to be receptive to counseling about lifestyle changes. Many women are unaware of the real risk that their caffeine intake can create for their unborn child. Doctors and prenatal counselors should be sure to discuss the matter with soon-to-be mothers so they can make informed decisions when consuming caffeine during pregnancy. In addition, having a health care provider monitor caffeine intake may help establish the degree of risk for use of other drugs or high-risk behaviors during pregnancy.

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