



# NUTRITIONAL PERSPECTIVES

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# The Deleterious Affects of Caffeine on Pregnancy

Brian K. Applebee, DC, MS, DICCP, DACBN, CCEP

Caffeine is an ever present and socially neutral drug in our society that seems to only be gaining in popularity with the dramatic increase in consumption of caffeine-laden sports beverages such as Red Bull. Many women wonder if they should alter their caffeine consumption either before or during their pregnancy and if so by how much? Can their daily cup(s) of coffee or sports drink(s) cause their pregnancy to end or their future baby to be developmentally affected? This review is designed to discern answers to these questions based on current human and animal studies.

One study performed on fetal sheep demonstrated that although "fetal brain (cerebral) oxygenation may be affected" by caffeine this did not "affect (sic) systemic oxygenation."<sup>1</sup> This is an example of the apparent complexity of what appears to be a simple question about the extent and type of effect seen by caffeine consumption.

According to another study "caffeine intake in pregnancy has been linked to adverse outcome, but evidence from non-experimental studies on impaired fetal growth remains equivocal."<sup>2</sup> This study checked both the effect of reducing caffeine intake on birth weight and the length of gestation. They found "no differences in mean birth weight or mean length of gestation between women randomized to caffeinated coffee and women randomized to decaffeinated coffee."<sup>2</sup> "A moderate reduction in caffeine intake in the second half of pregnancy has no effect on birth weight or the length of gestation."<sup>2</sup>

Another study looked at Gestational Diabetes since "coffee consumption has been associated with a decreased risk of type 2 diabetes mellitus."<sup>3</sup> Their conclusions were: "moderate pre-pregnancy caffeinated coffee consumption may have a protective association with Gestational Diabetes Mellitus."<sup>3</sup>

There may also be different susceptibilities in different populations, such as a study conducted to "determine whether the cytochrome P450 1B1 (CYP1B1) Val432Leu polymorphism is associated with risk of miscarriage."<sup>4</sup> The conclusion was: "CYP1B1 Val432Leu polymorphism is associated with first-trimester miscarriage, and it may also modify the risk among coffee drinkers."<sup>4</sup>

There are concomitant behaviors that can further complicate analysis of caffeine's ill effects. As an example, there also seems to be mounting evidence that smoking and caffeine have a link that can be challenging to differentiate, as in a study "among non-smoking women with high caffeine intake", which demonstrated "an increased risk of repeated miscarriage, whereas there was no such association among smokers."<sup>5</sup>

When the amount of caffeine is taken into account we see results like: "mean caffeine intake of  $>$  or  $=$  300 mg/day showing (sic) a significantly increased risk of fetal death (OR 2.33 [1.23; 4.41]) compared with no caffeine consumption during pregnancy."<sup>6</sup>

So, what about people who never consume coffee being used as the control group? "High levels of coffee consumption were associated with an increased risk of fetal death relative to non-consumers of coffee", specifically demonstrating that "consumption of coffee during pregnancy was associated with a higher risk of fetal death, especially losses occurring after 20 completed weeks of gestation."<sup>7</sup>

A systematic review points out some potential methodological problems such as: "selection and recall bias, confounding, several issues pertaining to exposure measurement, and the failure to account for fetal karyotype, caffeine metabolism, the timing of fetal demise, and the possibility that an effect of caffeine may be gestational age-specific."<sup>8</sup>

The dose relationship is taken into account in a study that looked at "women with a pre-pregnancy intake of  $<$ 75 mg caffeine per day", with a conclusion that a "high intake of caffeine prior to pregnancy seems to be associated with an increased risk of spontaneous abortion, whereas a low-to-moderate alcohol intake does not influence the risk."<sup>9</sup> Adding the viable of alcohol in another study demonstrated that "consumption of 5 or more units of alcohol per week and 375 mg or more caffeine per day during pregnancy may increase the risk of spontaneous abortion."<sup>10</sup>

The effect of cigarette smoking adds another level of complexity to analysis. Cigarette smoking seems to be "over-represented among those who drink the most coffee/caffeine."<sup>11</sup> Potentially, "women underreport socially undesirable behaviors (e.g. smoking) while accurately reporting socially neutral behaviors (e.g. coffee and caffeine consumption)."<sup>11</sup> Could this be a factor that is usually not accounted for? Especially in light of current social stigma of smoking while pregnant. In another study, "the authors conclude that maternal third-trimester serum paraxanthine concentration, which reflects caffeine consumption, was associated with a higher risk of reduced fetal growth, particularly among women who smoked."<sup>12</sup>

Caffeine consumption timing in the pregnancy and nausea may play an interesting role. "Maternal caffeine consumption before pregnancy, or in women without nausea, did not increase the risk of spontaneous abortion, whereas maternal caffeine consumption during the first

trimester after nausea started might increase risk of spontaneous abortion (risk ratio = 5.4, 95% confidence interval = 2.0-14.6 for caffeine consumption  $\geq$  or = 300 mg per day compared with  $<$  20 mg per day). These results suggest that maternal caffeine consumption during pregnancy may influence fetal viability in women with nausea.<sup>13</sup>

A well controlled study that looked at karyotyping and smoking combined with caffeine determined that when the analyses were stratified according to the results of karyotyping, the ingestion of moderate or high levels of caffeine was found to be associated with an excess risk of spontaneous abortion when the fetus had a normal or unknown karyotype but not when the fetal karyotype was abnormal.<sup>14</sup>

So, as was discussed and briefly mentioned about dosing, a "recent meta-analysis suggests that the risks for miscarriage and fetal growth retardation increase only with daily doses of caffeine above 150 mg/d, equivalent to six typical cups of coffee a day."<sup>15</sup> Also, "there is a small but statistically significant increase in the risks for spontaneous abortion and low birth-weight babies in pregnant women consuming  $>$ 150 mg caffeine per day."<sup>16</sup> And, in another study, "drinking  $\geq$  or = 3 cups of tea or coffee was associated with elevated risks of spontaneous abortion."<sup>17</sup>

Caffeine itself does not appear to be teratogenic. But, caffeine can potentiate (sic) the teratogenic effect of other substances, such as tobacco, alcohol, and acts synergistically with ergotamine and propranolol to induce materno-fetal vasoconstrictions leading to malformations induced by ischemia.<sup>18</sup>

Some factors in addition to dosing seem to be; "daily consumption of more than 150 mg of caffeine, abdominal trauma, infection and fever during pregnancy."<sup>19</sup>

Interestingly, rat studies have demonstrated that "as soon as the quantity of caffeine is divided over the day, as is the case for human consumption, the teratogenic effect of caffeine disappears in rodents."<sup>20</sup> In animals, caffeine can "induce long-term consequences on sleep, locomotion, learning abilities, emotivity and anxiety, whereas, in children, the effects of early exposure to coffee and caffeine on behavior are not clearly established."<sup>20</sup> These authors suggest, "pregnant mothers should be advised to limit their coffee and caffeine intake to 300 mg caffeine/day (i.e. 2-3 cups of coffee or 2.5-3 l of coke) especially because of the increase of caffeine half-life during the third trimester of pregnancy and in the neonate."<sup>20</sup> Animal studies are often used to determine safety as in this study that stated: "caffeine intake before and during pregnancy was associated with an increased risk of fetal loss, supporting the US Food and Drug Administration recommendation to pregnant women, largely based on animal studies, to reduce their

caffeine intake."<sup>21</sup>

Still, the human debate continues: "despite (sic) intensive surveillance, we found no evidence that moderate caffeine use increased the risk of spontaneous abortion, intrauterine growth retardation, or microcephaly after accounting for other risk factors."<sup>22</sup> With "heavy caffeine consumers who decreased their caffeine intake early in pregnancy had a risk of spontaneous abortion similar to that of nonconsumers."<sup>23</sup>

We looked at risk in relation to a woman's age, pregnancy history, weight, education, prenatal DES exposure, cigarette smoking, use of caffeinated and alcoholic beverages, marijuana, cigarette smoking by baby's father, and other variables. None of these factors was definitely associated with early pregnancy loss. Still, "the possibility of real effects cannot be excluded and deserves further study."<sup>24</sup> Monkeys are often used to test teratogenic effects including this study that demonstrated: in-utero exposure to methylxanthines (caffeine and/or its major metabolite theophylline) adversely affects pregnancy outcome in the monkey.<sup>25</sup>

Although we see animal studies that point to potential issues such as facial clefts in rats given high dosages of caffeine, there appears to be mixed evidence for human teratogenicity.<sup>26</sup> In a summary of a few large and well done studies: "congenital malformations were examined in studies of 12,000 women at Harvard (coffee and tea only), and smaller studies at Boston University, Finland and Tohoku University in Japan (only 0.5% of Japanese women are heavy coffee drinkers, and tea was not considered). A 2nd group of analyses examined low birth weight, at Loma Linda, Harvard, Ottawa, Seattle and elsewhere. Only 1 study, which controlled for nicotine but not education, weight or alcohol, found significantly lower birth weight in 12 women who consumed 300 mg caffeine daily. Preterm birth was not increased in 2 studies. Spontaneous abortion was more likely in 2 studies, the Japanese study with limitations noted above, and the Yale study, which found a higher probability of 2nd trimester miscarriage for both caffeine and alcohol drinkers. These studies apparently prompted the FDA to issue a new statement clearing caffeine, as currently used in foods, of health risk."<sup>27</sup>

Interestingly, there may also be a correlation to a women's pregnancy history where heavy caffeine use and previous miscarriage may predict future spontaneous abortion.<sup>27</sup> In a quite large study of 9,921 healthy pregnant women with a gestational age after 24 weeks, (sic) the women who drank more than 5 cups of coffee per day had a high incidence of impending abortion, premature labor, and fetuses small for gestational age. The heavy coffee drinkers among the pregnant women had high rates of spontaneous abortion, chromosomal abnormality and con-

genital multi-anomalies. However, we would like to stress that the multiple socioeconomic variables might be more important than any direct effect of caffeine.<sup>28</sup> So, yet again here lies the complexity of a compendium of factors that may contribute to possible teratogenic and/or spontaneous abortion effect of caffeine.

Back, to the high energy drinks and we find a study that states "Red Bull Energy Drink significantly improved aerobic endurance (maintaining 65-75% max. heart rate) and anaerobic performance (maintaining max. speed) on cycle ergometers. Significant improvements in mental performance included choice reaction time, concentration (number cancellation) and memory (immediate recall), which reflected increased subjective alertness. These consistent and wide ranging improvements in performance are interpreted as reflecting the effects of the combination of ingredients."<sup>29</sup>

Humans have had a long association with caffeine for performance enhancement. As we arguably continue to look for additional ways to increase our daily performance we need to beware that caffeine may cause teratogenic effects and spontaneous abortion when used in high doses (above 300 mg). I suggest that pregnant women and women who have the potential of becoming pregnant monitor their caffeine consumption and either eliminate caffeine or limit to less than three cups (150 mg) per day.

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