Pregnancy Topic Update

Overview

Early pregnancy is often associated with the onset of nausea, vomiting and appetite loss (this is often referred to as the 'pregnancy signal'), which in turn may cause a reduction in coffee consumption, and hence, caffeine intake from coffee[1-4]. Research suggests that women experiencing viable pregnancies are more likely to reduce their caffeine intake in response to the pregnancy signal than women who have a miscarriage[1]. Therefore, reduced caffeine consumption may be a consequence of pregnancy viability[4].

The European Food Safety Authority (EFSA) in its Scientific Opinion on Caffeine concluded that pregnant women should limit their caffeine intake from all sources to 200mg per day during pregnancy[5]. Research suggests that moderate caffeine consumption of 200mg/day* does not increase the risk of any reproductive or perinatal complication[5]. This conclusion is based on prospective cohort studies showing a dose-dependent positive association between caffeine intakes during pregnancy and the risk of adverse birth weight-related outcomes (i.e. fetal growth retardation, small for gestational age)[5]. It is nevertheless difficult to define the association between caffeine and reproductive health as confounding factors such as changes in diet, smoking, and incorrect or imprecise assessment of the duration of exposure to caffeine may limit the ability to draw clear conclusions[1].

Research suggests that coffee consumption is not associated with reduced fertility[1,6-10], pre-term labour[11,12], or fetal death[1]; or significantly associated with congenital malformations[13-19], although further investigation is needed to confirm any suggested association with congenital malformations. Research on pregnancy loss[20-28] and fetal growth[1,13,29,30] gives some conflicting results and further work is required. While one paper suggests that moderate (i.e. less than 200mg/day) caffeine intake does not appear to be a major contributing factor in miscarriage[23], another suggests that caffeine intakes of 300mg/day or more are associated with increases in late miscarriage, although the authors note remaining uncertainty in the strength of association[24] .A Cochrane Review concluded that there is insufficient data to confirm or refute the effectiveness of caffeine avoidance on birthweight or other pregnancy outcomes[31]

The content in this Overview was last edited in August 2018. Papers in the Latest Research section and further resources are added regularly.

* A typical cup of coffee contains approximately 75-100mg caffeine.

Background information

It is widely accepted that any effects of coffee consumption on reproductive health are likely to be linked to caffeine rather than to coffee consumption per se. Hence the majority of the published work focuses on the effects of caffeine, not coffee, consumption.

An epidemiological review of the effects of caffeine on reproductive health published in 2010 concluded that the research available did not suggest any adverse effect of caffeine on reproductive or perinatal outcomes[1]. However the authors did highlight a number of confounding factors including the effect of pregnancy symptoms and smoking that could influence results. A further 2011 review of in utero caffeine exposure concluded that moderate intakes of beverages and foods containing caffeine did not increase the risks of congenital malformations, miscarriage or growth retardation[13].

Caffeine intake and fertility

Studies assessing the impact of caffeine on fertility have evaluated a variety of outcomes including time to pregnancy, infertility and semen quality[6-10].

Incorrect, or imprecise, assessments of the duration of exposure are a primary concern for the few studies addressing time to conception and ovulatory infertility[8,9]. Potential recall bias and exposure misclassification may explain the modest association reported for coffee and tea consumption and increased time to pregnancy.

A Danish prospective study evaluated the relation of caffeine, coffee, tea and sodas with time to pregnancy in a cohort of 3,628 women planning a pregnancy. There was little relation between fecundability and caffeine intake of more than 300mg per day compared with less than 100 mg/day or coffee intake of 3 or more servings a day compared with none[8].
No support for an association with infertility due to ovulation disorders was provided, but exposure measurement error was likely introduced as a result of the timing of exposure assessments[8,9].

Additionally, a 2018 population-based cohort study found no association between coffee, tea or total caffeine consumption and the risk of primary infertility in women[10].

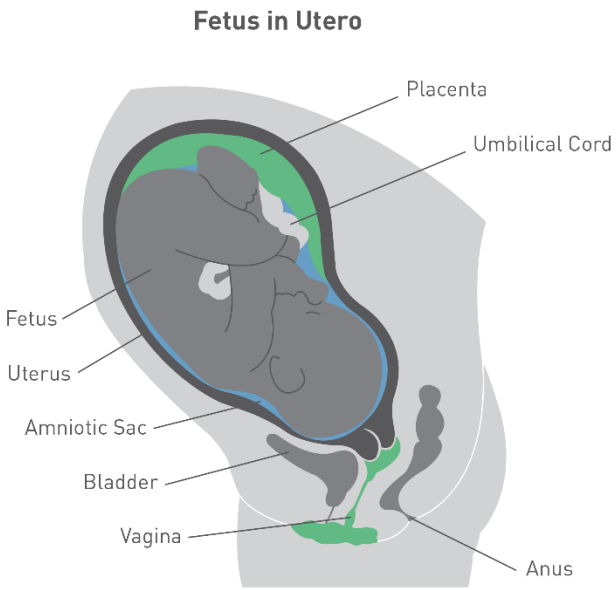
Evaluations of semen quality have consistently failed to observe adverse effects associated with caffeine intake[1], as suggested by a Danish study[6]. However, a systematic literature review including 19,697 men concluded that whilst the literature suggests that caffeine intake, possibly through sperm DNA damage, may negatively

affect male reproductive function, data from epidemiological studies on semen parameters and fertility is inconsistent and inconclusive[7].

As stated by an Australian review paper, research results are unclear and insufficient to provide coffee consumption guidelines for preconception advice[9].

In summary, consistent relationships between caffeine intake and measures of sub-fecundity have not been observed.

Caffeine intake and gestation



Caffeine intake in early pregnancy

A critical aspect of caffeine exposure includes the importance of measuring exposure to caffeine during the relevant time window and the need to capture changing intake patterns throughout pregnancy. Caffeine consumption tends to decrease during the early weeks of pregnancy, coinciding with increasing pregnancy symptoms and aversions[1].

Pregnancy symptoms, including aversions to tastes and smells, nausea and vomiting are common in healthy pregnancies that result in live births, and occur less frequently among women whose pregnancies end in miscarriages. This relationship has been attributed to a stronger pregnancy signal linked to higher concentrations of pregnancy hormones in viable pregnancies[4].

Caffeine consumption has been shown to decrease with increasing pregnancy symptoms during the early weeks of pregnancy[1]. For example, research from a group of pregnant women suggested that the mean onset of nausea, vomiting and appetite loss occurred between 5 and 6 weeks from the last menstrual period, and was accompanied by a 59% decrease in caffeine intake from coffee between weeks 4 and 6[2].

It may be that women experiencing healthy pregnancies are more likely to reduce their caffeine intake in response to pregnancy symptoms than women who will have a miscarriage. As a result, reduced caffeine consumption may be a consequence of pregnancy viability as opposed to increased consumption causing any reproductive complication ("reverse causation").

One study describes patterns of dietary caffeine consumption before and after pregnancy recognition in a cohort of 8,347 American women who had recently given birth[3]. Maternal self-reported consumption of beverages (caffeinated coffee, tea, and soda) and chocolate the year before pregnancy was used to estimate caffeine intake. About 97% of mothers reported caffeine consumption (average intake of 129.9 mg/day the year before pregnancy); soda was the primary source of caffeine. The proportion of mothers reporting dietary caffeine intake of more than 300mg/day was significantly higher among those who smoked cigarettes or drank alcohol. Most mothers stopped or decreased their caffeinated beverage consumption during pregnancy. A high level of caffeine intake was associated with risk factors for adverse reproductive outcomes. The authors recommend further studies which may improve the maternal caffeine exposure assessment by acquiring additional information regarding the timing and amount of change in caffeine consumption after pregnancy recognition.

Data from the UK Caffeine and Reproductive Health (CARE) study were used to explore the relationship between maternal caffeine intake and nausea, vomiting and fetal growth restriction in pregnancy[32]. No suggestion of a relationship could be found. The strength of this study is the thorough assessment of caffeine exposure, however the extremely low response rate (20%) is a concern and a selection bias cannot be excluded.

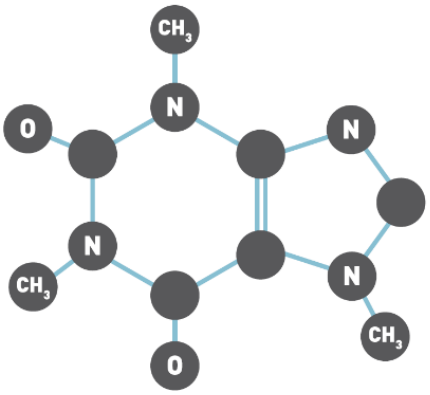
Coffee and Gestational Diabetes Mellitus

Gestational diabetes (or gestational diabetes mellitus, GDM) is a condition in which women without previously diagnosed diabetes exhibit high blood glucose levels during pregnancy (especially during their third trimester).

A population-based cohort of 71,239 women taking part in the Danish National Birth Cohort examined the relation between first trimester coffee and tea consumption and gestational diabetes mellitus (GDM) risk[33]. Coffee or tea intake was reported in 81.2% of the women (n = 57 882). 1.3% (n = 912) of pregnancies were complicated by GDM, and among non-consumers, 1.5% of pregnancies were complicated by GDM. After

adjustment for age, socio-occupational status, parity, pre-pregnancy body mass index, smoking, and cola intake, there was suggestion of a protective, but non-significant association with increasing coffee and tea intakes. Results were similar by smoking status, except a non-significant 1.45-fold increased risk with ≥8 coffee cups/day for non-smokers. There was a non-significant reduced GDM risk with increasing total caffeine. These results suggest that moderate first trimester coffee and tea intake is not associated with GDM increased risk; it may even have a protective effect[33].

Caffeine and miscarriage



The epidemiological studies evaluating the risk of miscarriage, also known as spontaneous abortion, from caffeine exposure have been inconsistent[1,13] . However, many of these studies failed to evaluate the pregnancy signal.

A study of maternal caffeine consumption, nausea and spontaneous abortion suggests that an increased risk of miscarriage was only observed for caffeine consumed after nausea onset, but not for caffeine consumed before nausea onset, or among those without nausea[20].

Other persistent problems with the validity of studies of caffeine and miscarriage include confounding by smoking and potential recall bias, as suggested in a 2008 cohort study[21]. This study is characterised by incomplete control for confounding by the daily number of cigarettes smoked or the duration of nausea and vomiting (only yes/no answers). In addition, this study was only stratified for two levels of caffeine intake, lower or higher than 200mg daily and the latter group includes very high levels of caffeine intake.

In 2010, a Chinese case-control study[22] and a small US prospective cohort study[23] did not find any association between caffeine consumption and the risk of miscarriage. In contrast, a UK study reported that greater caffeine intake is associated with an increase in late miscarriage and stillbirth. However, they identified small numbers of late

miscarriages and stillbirths, hence limiting the power to detect small associations and leading to considerable uncertainty in the size of the association[24].

The 2010 Committee Opinion of the American College of Obstetricians and Gynecologists stated that "Moderate caffeine consumption (less than 200mg per day) does not appear to be a major contributing factor in miscarriage; … a final conclusion cannot be made as to whether there is a correlation between high caffeine intake and miscarriage"[34].

A dose response meta-analysis of 130,456 individuals suggested that higher maternal caffeine intake was associated with a higher risk of pregnancy loss, although adjustment for smoking and pregnancy symptoms may have been incomplete. The authors also advised that adherence to guidelines to avoid high caffeine intake during pregnancy appears prudent[25].

However, a prospective cohort study of 5,921 women suggested that pre-conceptional caffeine consumption was not associated with an increased risk of spontaneous abortion. The authors did note that consumption during early pregnancy was associated with a small increased risk, although the relation was not linear[26].

A further systematic review and meta-analysis suggested that coffee and caffeine consumption was associated with an increased risk of spontaneous abortion at intakes of 300mg and 600mg a day[27]. The authors expressed their support for advice to limit caffeine intakes during pregnancy in line with the EFSA recommendations of a maximum of 200mg of caffeine per day[5].

Data from the Nurses' Health Study of 15,590 pregnancies concluded that pre-pregnancy coffee consumption at levels above 4 cups of coffee per day was associated with an increased risk of spontaneous abortion, particularly at weeks 8-19[28].

Caffeine and pre-term birth

Large studies considering total caffeine intake have consistently reported no increased risk of delivery before 37 weeks of gestation[1]. This was confirmed by a meta-analysis, including 15 cohort studies and 7 case-control studies, where no important association between caffeine intake during pregnancy and the risk of preterm birth was observed[11].

In addition, the 2010 Committee Opinion of the American College of Obstetricians and Gynecologists stated that "Moderate caffeine consumption (less than 200mg per day) does not appear to be a major contributing factor in preterm birth"[34].

A Polish study published in 2012 had the objective of estimating maternal caffeine intake during pregnancy and its influence on pregnancy duration, birthweight and the

Apgar score of the newborn[12]. It concluded that caffeine intake of no more than 300mg per day during pregnancy does not affect pregnancy duration and the condition of the newborn. Black tea was the major source of caffeine, whereas 26% of women gave up coffee during pregnancy. An underestimation of maternal caffeine intake during pregnancy could not be excluded, since the questionnaire was carried out on the last day before delivery[12].

Caffeine intake and fetal health

Caffeine and fetal growth

Studies of caffeine and fetal growth restriction are equivocal. Some studies showed no effects on growth, whilst others demonstrated a risk of growth retardation with increased exposure to caffeine, although with the inability to determine the role of confounding factors[1,13].

One of the larger studies was the Dutch Generation R Study, a prospective cohort study which included 7,346 pregnant women. Inconsistent associations were observed between caffeine intake and fetal head circumference, or estimated fetal weight. Higher caffeine intake (over 540mg caffeine daily) was associated with shorter birth length, suggesting that fetal growth may be impaired by caffeine[35]. However, further studies are needed to assess these associations in non-European populations and the possible postnatal consequences of the observed fetal growth restriction. Results from a large prospective cohort in which the main caffeine source was coffee, showed that coffee but not caffeine, was associated with marginally increased gestational length but not with spontaneous preterm delivery[29]. However, caffeine intake was consistently associated with decreased birth weight and increased odds of the baby being small for its gestational age[29].

The 2010 Committee Opinion of the American College of Obstetricians and Gynecologists stated that the relationship between caffeine and growth restriction remains undetermined[34] .

A 2015 meta-analysis reviewing the associations between caffeine consumption and risk of low birth weight concluded that for every additional 100mg of caffeine per day the risk of low birth weight increased by 3%[36].

A further 2015 Cochrane review of the effect of restricting caffeine intake by mothers concluded that there is insufficient data to confirm or refute the effectiveness of caffeine avoidance on birthweight or other pregnancy outcomes[31].

Caffeine and congenital malformations

Brent et al. concluded in their risk analyses that it is very unlikely that regular or even high exposures to dietary caffeine increase the risk of birth defects for pregnant mothers exposed to caffeine[13]. With a few exceptions, studies have not reported an increased risk of malformations with greater caffeine consumption.

One paper reported weak positive associations between maternal caffeine consumption and spina bifida (neural tube defects), but without a dose-effect relationship and with a negative association for tea. However, the control for confounding by smoking and alcohol (both yes/no answers only) was insufficient[14]. A further case-control study, with 776 cases and 8,756 controls, looked at the risk of spina bifida and maternal cigarette, alcohol, and coffee use during the first month of pregnancy. It found that levels of cigarette smoking (1-9 and ≥ 10/day), alcohol intake (average ≥4 drinks/day) and caffeine intake (<1, 1, and ≥2 cups/day) were not likely to be associated with increased risk of spina bifida[15]. The same research group raised the issue that gene variants like slow/fast caffeine metabolisers may run different risks[16].

A further meta-analysis published in 2015 considering maternal coffee consumption and the incidence of neural tube defects (NTD), suggested that maternal coffee consumption during pregnancy was not significantly associated with the occurrence of total NTD or the spina bifida subtype of NTD[17].

A 2011 study, evaluating data from the National Birth Defects Prevention Study, examined the association between maternal caffeine consumption (from coffee, tea, soda and chocolate) and the risk of selected birth defects. The cohort of 3,346 cases was matched with 6,642 controls. The research did not suggest an association between maternal caffeine intake and the birth defects[18]. A further study, also evaluating data from the National Birth Defects Prevention Study, assessed associations between maternal dietary caffeine intake and congenital limb deficiencies. In this study, with 844 cases and 8,069 controls, high soda consumption was associated with an elevated risk for longitudinal limb deficiencies. Coffee and tea consumption was not associated with any limb deficiency subtype[19].

Caffeine and fetal death

Four studies detailed in a review of data gathered between 2000 and 2009 evaluated the relationship between caffeine and fetal death[1]. Three of the studies were conducted by the same research group, in which two reported a moderately positive association and the third found no relationship. The fourth study also noted a positive association. None sufficiently address the concerns regarding confounding by pregnancy symptoms. As with studies of miscarriage, the interpretation of the work on caffeine and fetal death needs to consider that these studies may also share common sources of bias which may explain the observed relationship with caffeine use[1].

Maternal coffee consumption and childhood leukemia

There are limited studies in this area, and while some research suggests an association between consumption of coffee during pregnancy and subsequent increased risk of childhood leukemia, more research is needed to better understand this. Pregnant and breastfeeding women are advised by EFSA to drink no more than 200mg of caffeine per day from all sources, which is equivalent to 2-3 cups of coffee[5].

In 2016 IARC reviewed data on childhood leukemia in relation to coffee consumption and concluded that a lack of consistency amongst studies led to inconclusive and inadequate evidence of any association between coffee consumption and childhood leukemia[37].

- Authors of a 2015 meta-analysis comprising a total of 3,649 cases and 5,705 controls concluded that their findings "confirm the detrimental association between maternal coffee consumption and childhood leukemia risk, and provide indications for a similar role for maternal cola consumption"[38].
- A further study published in 2015 examining parental smoking, maternal alcohol, coffee and tea consumption during pregnancy, and childhood acute leukemia concluded that childhood acute leukemia was not associated with coffee consumption during pregnancy, but an association was seen between coffee consumption and acute lymphoblastic leukemia[39].
- A 2018 review of data on maternal coffee intake in 2,552 cases and 4,876 controls suggested that coffee intake over 2 cups per day during pregnancy may increase risk of childhood acute lymphoblastic leukemia, although the authors acknowledged that there were limitations in the research. They supported current advice to limit caffeine intake during pregnancy[40].

Recommendations for caffeine intake during pregnancy

Limiting caffeine during pregnancy – an intervention study

A review of the literature looked at the clinical basis for restricting the caffeine intake of mothers on fetal, neonatal and pregnancy outcomes[41]. After a thorough search of databases for published or unpublished studies, randomised controlled trials, including quasi-randomised trials and cross over studies, the authors identified a single study that met their criteria, thus highlighting the lack of research in this area. The authors selected one Danish study meeting the criteria for a controlled study: women less than 20 weeks pregnant were randomly assigned to drinking caffeinated instant coffee (568 women) or decaffeinated instant coffee (629 women). The study found that reducing the caffeine intake of regular coffee drinkers during the second and third trimester by an average of 182mg/day (approximately 2 regular cups of coffee) did not affect birth weight or length of gestation. According to the study, there is insufficient data to

confirm or refute the effectiveness of caffeine avoidance on birth weight or other pregnancy outcomes and high-quality, double-blind randomised controlled studies are needed to determine whether caffeine has any effect on pregnancy outcomes[41].

Official recommendations for caffeine intake during pregnancy

EFSA in their 'Scientific Opinion on Caffeine', published in 2015, advised that pregnant women should limit their caffeine intake to 200mg per day[5].

This is in line with the UK's NHS[42] and the March of Dimes in the USA[43], who both advise an upper limit for pregnant women of 200mg of caffeine* per day from all sources.

*A regular cup of coffee contains approximately 75mg caffeine.

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