International Journal of Medical and Health Research
ISSN: 2454-9142
Received: 21-08-2018; Accepted: 23-09-2018
www.medicalsciencejournal.com
Volume 4; Issue 10; October 2018; Page No. 163-167

The effects of maternal caffeine consumption during pregnancy (A meta-analysis study conducted among Saudi Women)

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Abstract
Many studies have shown inconsistent results in term of the effect of caffeine intake during pregnancy on the risk of low birth weight (LBW). In this study, we performed a linear-dose response analysis and meta-analysis examining the association between caffeine consumption during pregnancy and risk of LBW among Saudi women. We found that high caffeine intake during pregnancy is associated with a significant increase in the risk of LBW among Saudi women, and this risk appears to increase linearly as caffeine intake increases.

Keywords: caffeine, young women, coffee, soda, Saudi Arabia, low birth weight (LBW)

Introduction
Caffeine is a substance that belongs to a group of compounds called methylxanthines which is currently the most popular drug available to humans and found in nonprescription drugs like pain relievers, diet pills, cold and allergy medicines and diuretics. It is normally found in the leaves, seeds and products of more than 60 unique plants and a constituent of espresso, tea, some soda pops, chocolate and espresso enhanced items, for example, yogurt, dessert, hot cocoa, confections, cakes, treats and biscuits. The amount of caffeine in foods and beverages varies widely due to differences in food and beverage preparations. In general, brewed coffee contains the highest amounts of caffeine, with an average of 137milligrams (mg) per 8-ounce cup. Instant coffee contains about 76mg per 8-ounce cup. A 12-ounce can of caffeinated soda contains about 37 mg. Chocolate for the most part contains low measures of caffeine [1]. A large number of individuals expend caffeine and for most, it has turned into a piece of their everyday diet. In the United State, four out of every five Americans consume caffeine each day in some form or another. Numerous individuals consume caffeine to enable them to remain alert since it is absorbed in the body quickly and inside 30-a hour of utilization, the level of caffeine in the circulation system achieve a high point and takes the body roughly three hours to dispose of a large portion of the measure of caffeine expended. It is set up that caffeine influences the human body in various ways [2]. It invigorates cardiovascular muscles, loosens up smooth muscles, animates the focal sensory system, goes about as a diuretic, starts the discharge of gastric corrosive and furthermore builds the centralizations of plasma glucose and free unsaturated fats [3]. Considering the sum that is devoured regularly, the impact of caffeine on wellbeing turns into a critical subject. Zones of concern are the physiological impacts of caffeine on the body, its effect on pregnancy and the job it plays in bone thickness. Ladies of youngster bearing age are a legitimate target crowd for messages about potential teratogenic impacts of caffeine. During the first trimester of pregnancy, however, the half-life of caffeine increasesto5.6 hours and continues to increase to a high of 18hours by the 35th week of pregnancy. The sheltered pharmacokinetics may be due to changing hormone levels during pregnancy. Changing levels and the efficacy of particular enzymes may also be involved in altered caffeine half-life [4]. The half-life of caffeine in newborns can be as long as 40-130hours because of the immature metabolic pathways utilized in caffeine excretion. Animal studies have shown an increased incidence of birth defects when caffeine is administered to rodents in alargebolus, usually 250 mg or more. Such high caffeine doses are typically associated with delayed skeletal ossification, palate malformation and missing digits. Caffeine metabolism differs in animals and humans. In rodents, 40% of caffeine is metabolized in totrimethyl derivatives such as methyl xanthine; this pathway accounts for only 6% of caffeine metabolism in humans. In humans, between 72 and 80% of caffeine undergoes 3-methyl demethylation resulting in paraxanthanine formation. This difference makes the applicability of animal studies to humans questionable The Food and Drug Administration (FDA) completed a safety review of caffeine that focused on potential teratogenic effects of caffeine and advised pregnant women either to avoid or to use sparingly foods and drugs that contain caffeine . The March of Dimes also advised pregnant women as well as those who may become pregnant to limit their caffeine consumption to 444milligrams (mg) per day. Since these warnings, numerous studies have examined the effects of caffeine intake on fertility and pregnancy and its association with miscarriages, spontaneous abortion, stillbirth birth defects and low birth weight. Some studies have found that low levels of caffeine consumption probably don't increase the risk of miscarriage. Other studies have found that women who consume large amounts of caffeine may be twice as

likely tom is carry as women who consume less. The studies prior to the FDA statement were often thought to be fraught with methodological flaws and the latter studies were judged to be inadequate because they did not consider other lifestyle factors that could contribute to infertility or miscarriages [2, 3]. On a latest study that is unlike most past research as it looked at women in early pregnancy when most miscarriages happen and tried to account for a separate risk from genetic defects in fetuses and a possible risk from smoking. The research team found that the equivalent of one to three cups of American coffee increases the risk of miscarriage by 30 percent and that three to five cups raises the risk by 40 percent. They conclude that the ingestion of caffeine may increase the risk of an early spontaneous abortion among non-smoking women carrying fetuses with normal karyotypes. The problem with reporting on caffeine's relationship with health has been the myriad of conflicting reports that verify and commend caffeine. Simply put, there are difficulties interpreting caffeine's effects on the human body and its health. Not only are caffeine's effects difficult to isolate from the other substances that often accompany in food and drink, but, the method preparation, the differences between types of coffee beans, different methods of roasting and consumption canal so have varying effects on human health. Further compounding this difficulty is that there exist individual differences in sensitivity to caffeine [5]. It is difficult to hold for all variables involved, therefore it must be emphasized that the results of any study should be treated with a critical eye. Despite these cautionary words, some conclusions have been formed about caffeine in relation to human health and young women in particular. The Organization of Teratology Information Services (OTIS) recommends that pregnant and nursing women drink plenty of water, milk and juice and not substitute those fluids with caffeinated beverages and the American Academy of Pediatrics recommends that nursing women limit caffeine intake. Finally, most experts agree that high caffeine intake may increase the risk of miscarriage and of having a low-birth weight baby [6].

Results

The results of our meta-analysis suggest that consuming 100 mg of caffeine per day may lead to a small, but significant, increase in the risk of LBW among Saudi women. It is important that Saudi women are aware of the effects that caffeine may have on their infants' health and make appropriate adjustments to their levels of consumption. The searching scheme resulted in a total of 30 studies. A total of 13 studies, nine cohort and four case-control studies, were included with a total of 4,919 cases. Of these, three cohort and one case-control studies had not been incorporated in the recent meta-analysis. Mill *et al*. [7], was not included for meta-analysis since it did not have desired outcomes as defined by our inclusion criteria. For dose-response analysis, ten studies, seven cohort and three case-control studies with a total of 4,499 cases, met the eligibility criteria. The pooled estimate of the twelve studies presented that maternal caffeine consumption during pregnancy was associated with increased risk of LBW (pooled OR: 1.38, 95% CI: 1.10, 1.73). The linear dose-response analysis showed that one additional cup of coffee or two additional cups of tea per day during pregnancy was associated with a 3.0% increase in the OR for LBW (pooled OR: 1.03, 95% CI: 1.01, 1.05). The test of heterogeneity resulted in a moderate level of heterogeneity ($P = 0.01$, $I^2 = 55\%$, 95% CI: 13, 76%). The meta-regression tests showed that none of the study characteristics, including study design, proportion of women aged 35 and older, region, exposure assessment, sources of caffeine, timing of the exposure, publication year, and confounders adjustment status, significantly modified the pooled estimate for the effect of maternal caffeine intake on the risk of LBW [8].

The sensitivity analysis showed that there were no changes in directionality and significance of the pooled ORs of high vs low meta-analysis after excluding studies with manually calculated effect estimate, Eskenazi *et al*. [9], (pooled OR = 1.41, 95% CI: 1.07, 1.85) and Linn *et al*. (pooled OR = 1.43, 95% CI: 1.10, 1.87)), and most influential study (Martin *et al*. (pooled OR = 1.27, 95% CI: 1.05, 1.52). Similarly, removing Linn *et al*. did not change the directionality and significance of the OR for the linear dose-response meta-analysis (OR = 1.03 95% CI: 1.02, 1.05). However, after removing Martin *et al*, the OR was no longer significant (OR = 1.07 95% CI = 0.18, 6.19).

Discussion

This meta-analysis of twelve studies identified an overall 37.8% increase in the odds of LBW among women in the highest caffeine intake group compared to those in the lowest group. A dose-response analysis based on ten studies found a 3.0% increase in the odds of LBW for every 100 mg of caffeine consumed per day during pregnancy, which is equivalent to about one cup of coffee or two cups of tea. The effect size of our high vs low meta-analysis is relatively small compared to well recognized risk factors of LBW, such as active maternal smoking [9, 17]. Jaddoe *et al*. [18] and Horta *et al*. [19] found active maternal smoking during pregnancy increased the risk of LBW incidence by 75% and 59%, respectively. However, the OR of LBW among pregnant women exposed to environmental tobacco smoke (ETS) is similar to our result [20] Salmasi *et al*. [21] and Leonardi-Bee [22] reported ETS exposure increased the risk of LBW births by 16% and 22%, respectively. Although the effect size is small in our dose-response analysis, the result is more precisely estimated, compared to conventional analysis, by using pooling data from ten studies and indicated that there is a significant association even with very small dose of exposure. Since there is no evidence of threshold effect or plateau in the linear dose-response curve, recommendations to pregnant women regarding caffeine intake should consider the absolute risk of increasing maternal caffeine consumption [23, 24].

Our findings are in agreement with a meta-analysis conducted by Fernandes *et al*. [25] in 1998, which reported an increased risk of LBW among pregnant women who consumed more than 150 mg of caffeine per day. Also, Sengpiel *et al*. [26] reported a 21–28 g decrease in birth weight for each additional 100 mg of caffeine consumed per day. Similar results have been reported in several recent studies [27], while others have not found a significant association to exist [28].

The effect of caffeine consumption during pregnancy is of public health concern because caffeine passes through placental barriers [29]. The cytochrome P450 1A2 enzyme

(CYP1A2) predominantly metabolizes caffeine [30]. Tsutsumi *et al*. [31]. Reported that CYP1A2 activity in early (8–16 weeks) and late (32–39 weeks) pregnancy is reduced by 35% and 52%, respectively. During pregnancy, the half-life of caffeine increases, which causes caffeine to be retained in the body longer [32]. Caffeine can then cross the placenta and be present in the plasma of newborns [33]. Since the levels of CYP1A2 are believed to be low in the placenta and fetus [31, 33], the fetus can be exposed to caffeine for a long period of time. The pharmacological effects of caffeine related to fetal growth are the blockade of adenosine receptors and the inhibition of cyclic nucleotide phosphodiesterase (PDE) [27, 30]. When caffeine acts as an antagonist of adenosine receptor, adenosine is unable to regulate the local blood flow during hypoxia [30]. The acute maternal hypoxia can negatively impact the fetal cardiovascular function and fetal growth [31]. Also, when PDE is inhibited by caffeine, the levels of cyclic adenosine monophosphate (cAMP) will be increased because PDE degrades cAMP, which may interfere with fetal growth. For example, Bistoletti *et al* [23] explained that fetal asphyxia is associated with higher cyclic AMP levels.

Of the studies included in this meta-analysis, four reported a significant positive association between caffeine intake and LBW while eight found no significant association [9, 11, 13, 20]. In case-control studies, mothers with an LBW outcome are more likely to report their caffeine consumption to be less than true amount, which may attenuate the effect estimate towards the null or bias it towards inverse association [17]. Attenuated linear dose-response line was shown rather than strong linear line when mothers who consumed high levels of caffeine under-reported their actual consumption. This could explain why we observed different results for case-control and cohort studies in our high vs low meta-analysis. Among the cohort studies, there was a significant increase in risk of LBW among mothers who consumed higher amounts of caffeine. Among the case-control studies, the effect was no longer significant, although the directionality of the association was consistent.

Overall, there was a moderate level of heterogeneity between the studies, but we were not able to identify significant sources of heterogeneity after performing meta-regression tests based on different study characteristics. However, removing the most influential study, Martin *et al* [32], reduced the level of heterogeneity from I-squared of 55% to 34%. After reviewing its study design and adjusted confounders, we were not able to identify characteristics of this study [20] that may have caused it to be particularly influential. Removing another study that did not provide an adjusted OR, Eskenazi *et al*. [13] Linn *et al*. [17], did not change the directionality or significance of the results.

This meta-analysis also considered possible confounders of the relationship between caffeine intake and LBW by using adjusted ORs reported by the studies. The most common confounders adjusted for were smoking status, parity, alcohol use, and ethnicity. Maternal age, weight, and trimester were also adjusted for in many studies. Levels of smoking, alcohol use, and maternal age have previously been found to have a positive correlation with levels of caffeine consumption [30].

This meta-analysis has a few limitations. Frequency, quantity, and sources of caffeine intake during pregnancy were self-reported by the mothers or expectant mothers in all accepted studies. Thus, recall bias might have occurred in terms of exposure assessment, especially for the seven retrospective studies [6, 7, 8]. Most of the studies did not conduct exposure measurement validation. However, Fenster *et al*. [12] and Bracken *et al*. [16] reported that retrospective data was reliable. Fenster *et al*. [12] found that 77% of the respondents could reproduce their caffeine consumption record from 6 months earlier within one cup of coffee. Bracken *et al*. [16] observed that prospective data collected at 28 and 36 weeks of pregnancy were similar to respective data gathered retrospectively. It is not possible to perform individual exposure quality assessment, but misclassification of exposure would have likely occurred randomly, causing non-differential bias. Exposure validation was not found to be a source of heterogeneity in our pooled estimates.

Another limitation is that studies differed in the units used to measure caffeine intake. The amount of caffeine consumption was measured in cups per day by four studies [17, 19], while the other studies reported milligrams per day. To make these estimates comparable for dose-response analysis, we used conversion factors of 100mg/day for 1 cup of coffee and 50mg/day for 1 cup of tea. Since each study had different conversion factors, exposure levels may have been slightly under- or overestimated. For example, Fenster *et al*. [13] assumed a caffeine content of 107mg/cup of coffee and 34mg/cup of tea, and Bakker *et al*. [5] estimated that 1 cup of caffeinated coffee contains 90mg caffeine However, we believe that an approximate difference of 10mg for estimating one cup of coffee or tea would not lead to clinically relevant differences in the results.

A strength of this meta-analysis is the extensiveness of the literature search; all studies ever conducted prior to March 2014 were considered for inclusion. Our findings not only reaffirm the recent meta-analysis results [11] that identified an inverse relationship between caffeine consumption and birth weight, but also induce a comprehensive conclusion by including more studies. The quality of outcome measurement in all studies was reliable as they were collected by birth certificate, from hospitals, or were confirmed by physicians. Furthermore, evaluation of the funnel plot and Egger's test found no evidence of publication bias.

The results of our meta-analysis suggest that consuming 100 mg of caffeine per day may lead to a small, but significant, increase in the risk of LBW. It is important that women are aware of the effects that caffeine may have on their infants' health and make appropriate adjustments to their levels of consumption [32].

Conclusion

In conclusion, the findings of this study represent the first report from Saudi Arabia of the prevalence of HRP among Saudi pregnant mothers (63.3%) and the identification of putative risk factors such as older Maternal age 30-40 years (84%), obesity (60%), multigravida, multipara (47%), habitual abortion (23%) and 68.7% of them complained of different medical associated conditions during their current pregnancies such as: anemia (25.3%), gestational diabetes (16.2%), pregnancy induced hypertension, 40% of them reported exposure to smoking. Consequently, in the future, the

implantation of routine screening for HRP during the antenatal visits to primary health care centers in Saudi Arabia must be addressed.

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