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REVIEW ARTICLE

A meta-analysis of risk of pregnancy loss and caffeine and coffee consumption during pregnancy

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ABSTRACT

Background: Previous reports of the relationship between pregnancy loss and caffeine/coffee consumption have been inconsistent. *Objectives:* To evaluate the association between pregnancy loss and caffeine and coffee consumption. *Search strategy:* PubMed was searched for reports published before September 2014, with the keywords "caffeine," "coffee," "beverage," "miscarriage," "spontaneous abortion," and "fetal loss." *Selection criteria:* Case-control and cohort studies were included when they had been reported in English, the exposure of interest was caffeine/coffee consumption during pregnancy, the outcome of interest was spontaneous abortion or fetal death, and multivariate-adjusted odds ratios (ORs) or risk ratios were provided or could be calculated. *Data collection and analysis:* Data were extracted and combined ORs calculated. *Main results:* Overall, 26 studies were included (20 of caffeine and eight of coffee). After adjustment for heterogeneity, caffeine consumption was associated with an increased risk of pregnancy loss (OR 1.32, 95% confidence interval [CI] 1.24–1.40), as was coffee consumption (OR 1.11, 95% CI 1.02–1.21). A dose–response analysis suggested that risk of pregnancy loss rose by 19% for every increase in caffeine intake of 150 mg/day and by 8% for every increase in coffee intake of two cups per day. *Conclusions:* Consumption of caffeine and coffee during pregnancy seems to increase the risk of pregnancy loss.

1. Introduction

Pregnancy loss through spontaneous abortion (an unintended termination of pregnancy before 20 weeks) or fetal death (fetal demise after 20 weeks) is not uncommon in the general population [1]. Despite decades of research, the causes of such pregnancy losses are unclear. Fernandes et al. [2] suggested that the process might be multifactorial, with the possible involvement of environmental factors such as caffeine consumption.

Caffeine increases cellular cyclic adenosine monophosphate levels by inhibiting phosphodiesterases [3], which can affect cell growth and fetal development [4]. Moreover, the structure of caffeine is similar to that of adenine and guanine, so it might be incorporated into the DNA macromolecule during mitosis, causing chromosomal anomalies [5]. A fetus can be exposed to caffeine through the amniotic fluid or umbilical cord, but has little ability to metabolize the compound [6]. Additionally, clearance of caffeine from the mother's body slows down during pregnancy [7], Furuhashi et al. [8] showed high rates of chromosomal anomalies and spontaneous abortion among pregnant women who consumed many caffeinated drinks.

However, the results of epidemiological studies into the association between caffeine/coffee consumption during pregnancy and pregnancy loss are inconsistent. Although the risk estimates about the association between caffeine consumption during pregnancy and spontaneous abortion were pooled by Fernandes et al. [2], their inclusion criteria were not overly stringent. Additionally, it seems that the dose–response relationship between caffeine/coffee consumption and pregnancy loss has not yet been investigated in a meta-analysis. Thus, the aim of the present review was to elucidate potential associations between pregnancy loss and caffeine and coffee consumption.

2. Materials and methods

2.1. Search strategy

PubMed was searched for reports published before September 1, 2014, with the keywords "caffeine," "coffee," "beverage," "miscarriage," "spontaneous abortion," and "fetal loss." The references of identified

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publications (including reviews) were also searched to identify additional studies.

2.2. Selection criteria

All identified studies were independently reviewed by two investigators (J.L. and H.Z.). Studies were included in the present meta-analysis if they had been reported in English, were case-control or cohort investigations, the exposure of interest was caffeine or coffee consumption during pregnancy, the outcome of interest was spontaneous abortion or fetal death, and multivariate-adjusted odds ratios (ORs) or risk ratios (RRs) with 95% confidence intervals (CIs) were provided (or data provided allowed their calculation). If data were duplicated in more than one study, the largest study was preferred. Reports were excluded before full-text assessment if they were of animal studies or were reviews, systematic reviews, or meta-analyses.

2.3. Data extraction

Data were extracted from each study by two investigators (J.L. and H.Z.) independently. The first author's last name, year of publication, location, study period, number of cases and controls or sample size, level of maternal caffeine and/or coffee consumption during pregnancy, estimates with 95% CIs, and details of adjustment for potential confounding factors were recorded.

2.4. Statistical analyses

If ORs or RRs and 95% CIs were not provided, they were calculated using the Mantel–Haenszel method. If the incidence of disease is low, RRs are approximately equal to ORs [9]. Therefore, combined ORs were used to estimate the combined effects. The combined ORs were calculated by combining logarithmic risk estimates weighted by the inverse of their variances to evaluate the strength of association between caffeine/coffee consumption during pregnancy and risk of pregnancy loss.

Considering possible between-study heterogeneity, the I^2 statistic was used to assess heterogeneity. The random effects model was used as the pooling method if an obvious between-study heterogeneity ($I^2 > 50\%$) was found [10]; otherwise, the fixed effects model was used [11]. Sensitivity analysis was performed when between-study heterogeneity was present: studies contributing the most to the heterogeneity were sequentially removed until homogeneity was obtained [12].

A cumulative meta-analysis was performed by chronologically ordering studies by publication year to find the starting point of a risk estimate becoming statistically significant and the trend in estimated risk effect [13]. Subgroup analyses were conducted of region (Europe, North/South America, or Asia), design (cohort or case–control), adjusted (yes or no) and publication year (<2000 or ≥2000). The Egger quantitative test was used to estimate evidence for potential publication bias [14].

A dose–response meta-analysis was also conducted to explore the pooled dose–response relationship between caffeine/coffee consumption during pregnancy and pregnancy loss. Because caffeine consumption was reported in various scales, exposure data were converted into a uniform measurement (mg/day). The median of a range of caffeine or coffee consumption was considered as the corresponding exposure dose; if the median consumption was not reported, the midpoint between the upper and lower range was used. If the lowest category was open-ended, its lower boundary was set to zero. When the highest category was unrestricted for caffeine, it was assumed to be the same size as the next highest category [15]. When the highest category was unrestricted for coffee, the exposure dose was defined by the lower end value of the category multiplied by 1.5. Caffeine consumption was divided into three groups: light (<150 mg/day), moderate (150–300 mg/day), and heavy (≥301 mg/day). Coffee drinkers were also classified into three levels: light (<2 cups per day), moderate (2–3 cups per day), and heavy (≥4 cups per day) drinkers. Nondrinkers and individuals with the lowest consumption were regarded as the reference group for both caffeine and coffee.

Nonlinearity in the relationship between caffeine and coffee consumption and risk of pregnancy loss was assumed. Taking into account the heterogeneity among studies, a two-stage random effects dose–response meta-analysis was performed to compute the trend from the correlated log OR estimates across levels of caffeine and coffee consumption [16]. A restricted cubic spline model was estimated using generalized least square regression with four knots at the fifth, 35th, 65th, and 95th percentiles of the levels of caffeine and coffee consumption, taking into account the correlation within each set of published ORs. A fixed or random effects restricted cubic spline model according to heterogeneity combined the study-specific estimates using the method proposed by Greenland and Longnecker to estimate the covariances of the OR [17]. If the P value was less than 0.05, the nonlinearity dose-response relationship was considered to exist. All statistical analyses were performed with STATA version 12.0 (Stata Corp, College Station, TX, USA).

3. Results

3.1. Literature search and study characteristics

A total of 26 studies were included (Fig. 1, Supplementary Material S1): 13 were case-control studies [18–30] and 13 were cohort studies [31–43]. Twenty studies [18–27,31–40] were of caffeine and eight studies [28–30,36,39,41–43] were of coffee consumption. Among the studies about caffeine consumption, seven were conducted in Europe [21–24,27,34,40], 11 in North/South America [18,19,25,31–33,35–39], and two in Asia [20,26]. Among the studies about coffee consumption, four were conducted in Europe [28,30,42,43], three in North/South America [36,39,41], and one in Asia [29].

3.2. Caffeine consumption and risk of pregnancy loss

Overall, caffeine consumption was associated with risk of pregnancy loss (OR 1.47, 95% CI 1.31–1.66; $I^2 = 70.9\%$). The association remained after two outlying studies [27,34] were excluded in the sensitivity analysis (OR 1.32, 95% CI 1.24–1.40), although the heterogeneity was no longer significant ($I^2 = 48.8\%$).

The association remained for moderate and heavy consumption in the analysis by level of consumption (Fig. 2A). In this analysis, between-study heterogeneity was detected only for heavy consumption. When the two outlying studies [27,34] were excluded from the analyses of moderate and heavy consumption, the associations remained significant (moderate: OR 1.28, 95% CI 1.16–1.42; heavy: 1.60, 1.46–1.76). No between-study heterogeneity was detected (moderate: $I^2 = 8.6\%$; heavy: $I^2 = 44.8\%$). No association was recorded for light consumption in the sensitivity analysis (OR 1.04, 95% CI 0.94–1.16; $I^2 = 0.0\%$).

Caffeine consumption during pregnancy was significantly associated with increased risk of pregnancy loss in both cohort and case-control studies (Table 1). The association was not recorded for either type of study when light consumption was considered; moderate and heavy caffeine consumption during pregnancy were associated with pregnancy loss in both study types, although the association was not significant for moderate consumption in cohort studies after adjustment (Table 1). Caffeine consumption during pregnancy was also significantly associated with increased risk of pregnancy loss in other subgroups (Table 1). No association was recorded for light consumption in the other subgroups; however, moderate and heavy caffeine consumptions during pregnancy were associated with pregnancy loss in all the other subgroups (Table 1).