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Caffeine During Pregnancy: A Systematic Review of the Risks for Miscarriage and Stillbirths

Emily L. Schwantke

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Caffeine During Pregnancy: A Systematic Review of the Risks for Miscarriage and Stillbirths

Abstract

Background: Maternal caffeine consumption during pregnancy directly affects the developing fetus as caffeine is rapidly absorbed in the maternal gastrointestinal tract and freely passes across the placenta. There is much concern about the affect of caffeine on reproductive outcomes prior to pregnancy and increased rates of fetal death. Since the 1980s, numerous studies have been published on caffeine intake during pregnancy and the risk of miscarriage and stillbirths. However, a clear consensus on whether caffeine posses these risks has yet to be determined. A systematic review of the literature using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool developed by the GRADE Working Group will be conducted to determine an accepted conclusion to this topic.

Method: An exhaustive search of available medical literature was conducted using the following databases; Medline, PubMed, Cochrane Systematic Reviews, and CINAHL.

Results: A total of five studies, four cohort and one case-control, were reviewed in their entirety. These studies looked at the relationship between caffeine intake during pregnancy and its proposed associations to an increase risk of miscarriage and stillbirth rates.

Conclusion: Based on the combined results there is still much uncertainty. Four studies, all demonstrate a dose-response related effect on caffeine and negative pregnancy outcomes. Only one study did not show a relationship between caffeine and miscarriages or stillbirths. The final GRADE for this review is moderate.

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Miscarriage, spontaneous abortion, caffeine

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Caffeine During Pregnancy: A Systematic Review of the Risks for Miscarriage and
Stillbirths

Emily Schwantke



A course paper presented to the College of Health Professions
in partial fulfillment of the requirements of the degree of
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Biography

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ABSTRACT

Background: Maternal caffeine consumption during pregnancy directly affects the developing fetus as caffeine is rapidly absorbed in the maternal gastrointestinal tract and freely passes across the placenta. There is much concern about the affect of caffeine on reproductive outcomes prior to pregnancy and increased rates of fetal death. Since the 1980s, numerous studies have been published on caffeine intake during pregnancy and the risk of miscarriage and stillbirths. However, a clear consensus on whether caffeine posses these risks has yet to be determined. A systematic review of the literature using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool developed by the GRADE Working Group will be conducted to determine an accepted conclusion to this topic.

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Keywords: Miscarriage, spontaneous abortion, caffeine

TABLE OF CONTENTS

INTRODUCTION	4
Background.....	4
Purpose of the Study	8
METHOD	8
RESULTS	9
DISCUSSION	21
REFERENCES	31
APPENDIXES	33
A. Table 1: Late miscarriage and stillbirth rates based on caffeine intake over first trimester	34
Table 2: Risk of miscarriage occurring at or before 20 weeks’ gestation based on caffeine intake.....	34
Table 3: Risk of miscarriage occurring at or before 20 weeks’ gestation based on caffeine consumption.....	34
B. Table 4: Fetal death rates based on coffee consumption	35
Table 5: Fetal death rates based on differing amounts of caffeine consumption	35
C. Table 6: GRADE Table.....	36

INTRODUCTION

Background

Caffeine (1,3,7-Trimethylxanthine) is the most widely consumed pharmacologically active substance in the world (Weng, Odouli, & Li, 2008). Due to these high consumption rates, caffeine is one of the most commonly researched topics drawing much attention to its affects on human health. The US Food and Drug Administration (FDA) first claimed caffeine to be potentially harmful for pregnant females on September 5, 1980. The FDA issued its warning, which was based primarily on animal studies, to avoid or restrict caffeine intake during pregnancy (Giannelli, Doyle, Roman, Pelerin & Hermon, 2003). Many people today believe that caffeine is linked to various health conditions and is perceived by many to be harmful to health. There is much concern about the affect of caffeine on reproductive outcomes such as; increased rates of miscarriage, congenital malformations, fetal growth restrictions, stillbirths, long-term behavioral issues, and decreased fertility (Norman & Nisenblat, 2011). Epidemiological studies on this topic have produced conflicting results. Currently, few studies report no association between caffeine consumption and negative fetal outcomes while numerous studies show either weak or strong associations (Greenwood et al. 2010).

Caffeine can be found in numerous beverages and foods including; coffee, tea, cola, soft drinks, energy drinks, and chocolate. Caffeine is also added to certain prescriptions and over-the-counter medications, such as cold, flu, allergy, and headache treatments, diet pills, diuretics, and stimulants. Coffee which contains fifty to seventy percent more caffeine than other products, is the main source of caffeine intake (Norman & Nisenblat, 2011). In the United States' general population, the prevalence of caffeine

exposure is greater than 80%. In 2005, the United States Department of Agriculture reported that 89% of women ages 18 to 34 consume caffeine with an average daily intake of 164 mg per day. Even though most women reduce their caffeine consumption during pregnancy, average daily intake among pregnant females still remains at 125 mg. (Bakker, Steegersw, Obradov, and Raat, 2010; Norman & Nisenblat, 2011; Anderson, Juliano & Schulkin, 2009).

Animal studies looking at caffeine's effect on birth outcomes, have confirmed that caffeine intake is associated with increased rates of malformations and decreased fetal weights in rodents, as well as increased rates of miscarriages and stillbirths in monkeys. The relevance of these animal studies is unclear as the pharmacokinetics of caffeine differs between animals and humans (Fenster et al. 1997). However, previous studies looking at the effects of caffeine on pregnancy outcomes in humans, have linked high maternal caffeine intake to small for gestational age or low birth weight infants. (Bech et al., 2007).

Controversy on the link between caffeine intake and miscarriage or stillbirths still remains as prior studies show varying results. These inconsistent results could possibly be due to differing factors in the study design, number of subjects, methods of obtaining accurate caffeine intake, and adjustment for potential confounders (Bakker et al. 2010). Numerous studies have shown a correlation between women with high caffeine consumption during pregnancy and those with higher levels of smoking and alcohol intake, and lower educational levels (Bech et al. 2007). This association further complicates the study outcomes as results can be distorted by these confounding factors.

Many studies are now taking into account several potential confounders and effect modifiers. Even so, the effect of caffeine intake during pregnancy still remains unclear.

Maternal caffeine consumption during pregnancy directly affects fetal caffeine levels as caffeine is rapidly absorbed in the maternal gastrointestinal tract and freely passes across the placental barrier as well as the blood brain barrier (Bech et al. 2007; Giannelli et al. 2003). Bech et al, (2007), reports that caffeine's effects include an increase in catecholamine levels and cyclic adenosine monophosphate, cAMP. This increase in the release of circulating catecholamines from the renal medulla has been associated with uteroplacental vasoconstriction and fetal hypoxia which can lead to altered fetal growth and possible death. The authors also report that caffeine prevents cyclic nucleotide phosphodiesterases which results in an increase in cAMP. High levels of cellular cAMP may interfere and influence fetal cell development and growth. Caffeine also has an effect on the fetal cardiovascular system which can lead to tachycardia and other arrhythmias (Wisborg et al., 2003). Increased fetal breathing activity has also been identified (Bech et al., 2007). Some evidence points to caffeine producing chromosomal aberrations in human cells but no studies have confirmed this (Giannelli et al. 2003; Norman and Nisenblat, 2011). As a result, most guidelines recommend limiting caffeine intake immediately before and during pregnancy as a precaution (Greenwood et al., 2010).

Caffeine is metabolized in the liver by the cytochrome P450 family of enzymes, with cytochrome P450 1A2 being the predominant enzyme. CYP1A2 metabolizes caffeine through a demethylation process (Norman & Nisenblat, 2011). The half life of caffeine ranges from 4.1 to 6.4 hours in a non-pregnant female but during pregnancy this

half life increases due to hormonal changes. In the first trimester, caffeine's half life increases to approximately 10 hours and again increases to 18 hours during the third trimester. This can lead to elevated caffeine levels among women who maintain their usual caffeine intake or even slightly decrease their consumption. Elevated levels of caffeine in pregnant females can produce intoxication symptoms such as nervousness, jitteriness, and cardiac arrhythmias. An increase in fetal exposure to caffeine may also occur (Anderson, Juliano & Schulkin, 2009; Bech, Obel, Henriksen, & Olsen, 2007; Norman & Nisenblat, 2011). Caffeine metabolism in fetuses and neonates is exceedingly slow with an 80 to 100 hour half life due to a lack of CYP1A2 enzymes. This is due to the immature liver systems in the fetus and neonate which do not fully develop until 6 to 8 months after delivery (Anderson, Juliano & Schulkin, 2009). Therefore, even low maternal caffeine consumption will lead to increased and prolonged levels of fetal exposure (Bakker et al., 2010; Giannelli et al., 2003; Norman & Nisenblat, 2011).

Maternal exposure to caffeine is not based solely on intake but also on the rate of caffeine metabolism and clearance from the body. Individuals are classified as either slow or fast metabolizers with caffeine metabolism rates depending on various genetic and environmental factors. The main factors are CYP1A2 activity, cigarette smoking, pregnancy, oral contraceptives, liver disorders, various medications, and ethnicity. The variation in metabolism rates among pregnant women could be a factor in determining the fetus's susceptibility to the effects of caffeine. Further studies and data on these factors are needed in order to validate their influence on the risk of pregnancy loss and

other negative pregnancy outcomes (Anderson, Juliano & Schulkin, 2009; Signorello et al., 2001).

Since the 1980s, a number of studies have been published on maternal caffeine intake during pregnancy and the risk of miscarriage and stillbirths. However, a clear consensus on whether caffeine poses these risks has yet been determined (Signorello & McLaughlin, 2004).

Purpose of the Study

The purpose of this systematic review is to summarize the epidemiological evidence and results found in five separate cohort and case-control studies in order to come to an accepted conclusion on this topic of great interest and importance. In addition the methodological issues that have impaired the interpretation of previous studies will also be discussed in order to determine how future studies can be improved to gain additional information on this topic of immense controversy and debate. A systematic review of the literature looking at the effects of caffeine consumption in pregnant women and the risk of miscarriage or stillbirth using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool developed by the GRADE Working Group will be performed (Guyatt et al., 2008).

METHOD

An extensive literature search was performed using Medline, PubMed, Cochrane Systematic Reviews, and CINAHL. These databases were accessed through the Pacific University Library system. The following keywords were searched individually and in

combination: miscarriage, spontaneous abortion, and caffeine. This initially resulted in 1,013 articles. The search was limited to human studies, English language, and articles published since 2005. This resulted in 135 articles to be reviewed, the CINAHL database alone identified 102 articles of the total 135. After hand searching through the articles in the CINAHL database, it was determined that one article was relevant for the systematic review. The remaining 33 articles were also hand-searched. Articles that did not investigate caffeine's effect on miscarriage and stillbirth rates were excluded. This resulted in five studies, four cohort and one case-control, for the final systematic review which were retrieved from Medline, PubMed, CINAHL, and Cochrane Systematic Reviews.

RESULTS

Caffeine Intake During Pregnancy, Late Miscarriage and Stillbirth, Written by
Greenwood et al., (2010)

The purpose of this cohort study was to examine the relationship between caffeine consumption and miscarriage or stillbirth rates. This study was performed in two separate maternity units in the United Kingdom between September 2003 and June 2006. Study participants included 2,643 women ages 18 through 45 with singleton pregnancies. These women entered the study between 8 and 12 weeks of gestation. Women with prior chronic disease, psychiatric illness, HIV, or hepatitis B infections were excluded from this study.

The authors used a validated and highly detailed caffeine assessment tool to calculate total caffeine consumption. Women were given this caffeine assessment to track their caffeine intake at specific time periods throughout their pregnancy: 4 weeks before pregnancy, weeks 1 through 4, 5 through 12, 13 through 28, 28 through 36, and finally at the end of their pregnancy. The questionnaire looked at all possible dietary sources of caffeine; food, drink, and over-the-counter medications. Specific brand names, portion sizes, methods of preparation, quantity and frequency of intake were all obtained. Caffeine intake was then calculated based on the published caffeine content for each item and from information provided by manufacturers and coffee houses. This study tried to correct for potentially important confounders by including alcohol intake, tobacco use, nausea, and vomiting in their questionnaire.

The primary outcomes were defined as spontaneous pregnancy loss, occurring between 12 and 24 weeks of gestation, and stillbirth, occurring at or after 24 weeks. Caffeine intake was measured in milligrams per day, mg/day. The authors examined caffeine consumption during each trimester in order to determine when caffeine consumption has the largest effect on pregnancy outcomes. Caffeine consumption during the second and third trimester was too small to investigate any associations. The first trimester was divided into (1) 4 weeks prior to the pregnancy (2) weeks 1-4, and (3) weeks 5-12. Median caffeine intake during the 4 weeks prior was 217 mg/day (104-366). Median caffeine intake over the first 4 weeks was 183mg/day (74-321). Median caffeine intake over weeks 5-12 was 92 mg/day (22-217). Over the entire first trimester, the median caffeine intake was 132mg/day (58-241).

Among women who had live births, their average caffeine intake was 103 mg/day (95% CI: 98-108). For women who had stillbirths or miscarriages, their average caffeine intake was 145 mg/day (95% CI: 85-249). The authors reported all findings after adjustments were made for maternal age, parity, alcohol intake, and tobacco use. When compared to caffeine intake of less than 100 mg/day, the odds ratio for miscarriages or stillbirths increased to 2.2 (95% CI: 0.7-7.1) for intakes between 100-199 mg/day, to 1.7 (95% CI: 0.4-7.1) for intakes between 200-299mg/day, and finally to 5.1 (95% CI: 1.6-16.4) for intakes of 300 + mg/day. Results were unchanged after adjusting for nausea, Index of Multiple Deprivation, for previous deliveries, and tobacco use. (Appendix A, Table 1).

This study demonstrates a positive correlation between increased caffeine intake during pregnancy and late miscarriages and stillbirths. Consumption of 300 mg or more of caffeine per day has been shown to increase miscarriage rates up to 5 times that of women with no caffeine consumption. Based on the following results, the authors state that greater caffeine intake is associated with increases in late miscarriage and stillbirth.

Maternal Caffeine Consumption During Pregnancy and the Risk of Miscarriage:
A Prospective Cohort Study, Written by Weng et al., (2008)

This prospective cohort study was conducted to determine the risk association between miscarriage and caffeine intake. The study was performed at the Kaiser Permanente Medical Care Program in San Francisco between the dates of October 1996

and October 1998. Pregnant females residing in the San Francisco area were identified as being potential candidates. Inclusion criteria consisted of intention to carry the pregnancy to term, English speaking, and those who did not return the refusal card to participate. Women who were greater than 15 weeks along in their pregnancy and those already included in the study for one pregnancy were not eligible to be included for subsequent studies. Of the initial 2,729 eligible pregnant females, 1,063 (39% of the total eligible) completed the interview.

Information on exposure to caffeine was gathered during an in-person interview which was conducted soon after the pregnancy was confirmed, with an average of 71 days of gestation. Information on the frequency and amount of intake of coffee, tea, and caffeinated soda consumption since the last menstrual period was collected. Women were also asked if their consumption pattern had changed since becoming pregnant and, if so, information on the new frequency and amount of intake was gathered. The average daily intake was then calculated. Information was also gathered on potential confounders; maternal age, race, education, household income, marital status, alcohol consumption, smoking, hot tub use, exposure to magnetic fields, and symptoms related to pregnancy such as nausea and vomiting. This study only looked at pregnancy outcomes up to 20 weeks of gestation because by definition a miscarriage is a fetal death happening at or before 20 weeks gestation. A fetal death occurring after 20 weeks is defined as a stillbirth. Pregnancy outcomes were obtained by searching through inpatient or outpatient databases, reviewing medical records, or contacting the participant if the outcome could not be determined by using the previous two methods.

The average daily caffeine intake during the pregnancy was categorized as 0, less than 200mg/day, or greater than 200 mg/day. Of the 1,063 women, 264 women (25%) reported no caffeine consumption, 635 women (60%) reported 0-200 mg/day of caffeine intake, and 164 (15%) reported greater than 200 mg/day. Compared to nonusers, women who consumed 0-200 mg daily had an increased risk of miscarriage (15% to 12%) and the risk was much greater (25%) among women who consumed more than 200 mg daily. These results show an increase miscarriage risk with increased caffeine consumption. After adjustment was made for potential confounders, the hazard ratio of miscarriage was 1.42 (95% CI, 0.93 to 2.15) for daily caffeine consumption of 0-200 mg and 2.23 (95% CI, 1.34 to 3.69) for consumption of 200 mg or more, p for trend < .01. Similar results were seen among women with and without nausea and, or vomiting. The effect of caffeine consumption on miscarriage was higher in the nonsmoker group (adjusted hazard ratio[aHR] 2.04, 95% CI, 1.35 to 3.09) than the smoker group (aHR 1.49, 95% CI, 0.36 to 6.08). In addition, caffeine's effect on the risk of miscarriage was stronger among women without a history of miscarriage (aHR 2.33, 95% CI, 1.48 to 3.67). There was no association among women with a history of previous miscarriage (aHR 0.81, 95% CI, 0.34 to 1.94). (Appendix A, Table 2).

A positive correlation between caffeine intake during pregnancy and late miscarriages and stillbirths was demonstrated in this study. The results of this study show that increasing amounts of caffeine are associated with increased risks of fetal death especially at intakes of 200 mg or more per day. At these levels, the risk of miscarriage is two times higher compared to women with no caffeine intake. Based on these

conclusions, the authors recommend limiting or stopping caffeine intake during pregnancy.

Caffeine and Miscarriage Risk, Written by Savitz et al., (2008)

This study was performed in Galveston, Texas; Memphis, Tennessee; and Raleigh, North Carolina and published in January 2008. Information on possible participants was obtained through public and private prenatal care providers. Pregnant females at less than 12 weeks' gestation and 18 years of age or older were eligible to participate. Women between the ages of 18 and 45 who had been trying to conceive for over 6 months were identified and enrolled if they became pregnant. This resulted in 2,407 pregnant female subjects.

The women were contacted by telephone prior to 16 weeks' gestation. They were interviewed regarding their daily caffeine intake and any changes in their consumption over the perinatal period. Information about alcohol, drugs, and cigarette usage, water exposure, medical history, and reproductive history were also gathered at this time. The women were asked about caffeinated, brewed and instant, coffee; caffeinated, iced and hot, tea; and caffeinated soda consumption per day. They assigned cups of coffee and hot tea as being small (4-10 oz), medium (12-14 oz), or large (16-24 oz). A cup of iced tea was defined as being small (4-10 oz), medium (12-20 oz), or large (22-34 oz). Soda was categorized as being small (8-12 oz), medium (14-22 oz), or large (24-34 oz). The caffeine content was determined using the midpoint of the cup size. Changes in

consumption, including the amount and timing of any changes were also obtained. 92% of women reported a change in their normal caffeine intake during pregnancy.

The women were followed from the day of enrollment up to 20 weeks' gestation. Pregnancy outcomes, which consisted of pregnancy survival, miscarriage, or loss to follow-up, were identified during the follow-up interview and were confirmed by medical records or by vital records. A miscarriage was defined as loss of a clinically recognized pregnancy at or before 20 weeks' gestation. Among the 2,407 females in the study, 258 (10.7%) miscarriages were reported. Caffeine and coffee consumption were divided into 3 groups: none, less than median, greater than median. This study also compared those with caffeine intake in and above the 75th percentile to those who consumed none.

Potential confounders were taken into consideration when results were calculated and included maternal age, race/ethnicity, education, marital status, income, smoking, alcohol use, body mass index, age at menarche, employment status, diabetes, miscarriage history, induced abortion history, vitamin use, and nausea and vomiting in early pregnancy. After adjustments were made for nausea and vomiting, no differences in the results were shown.

At the time of the interview, caffeine intake was divided into 0 mg/day, 0-144.3 mg/day, greater than 144.3 mg/day, and greater than 273.2 mg/day. The odds ratio and 95% confidence intervals are as follows; 1.0; 0.9 (95% CI 0.6-1.4); 1.1 (95% CI 0.7-1.7); 1.1 (95% CI 0.6-1.8) for the previously stated amounts of caffeine intake. (Appendix A, Table 3).

Based on the results of this study, the authors conclude that caffeine consumption is not related to miscarriage rates.

Coffee and Fetal Death: A Cohort Study with Prospective Data, Written by Bech
et al. (2005)

The intention of this study was to evaluate the relationship between coffee consumption during pregnancy and the risk of miscarriage. This prospective cohort study was performed in Denmark within the Danish National Birth Cohort from March 1996 to November 2002 and published in June of 2005. Women were recruited to the Danish National Birth Cohort by their general practitioner. Pregnant females were informed of this study at their first antenatal visit which fell between week 6 to 10 of gestation and approximately 60% of all eligible women choose to participate. The inclusion criteria consisted of; being accessible by telephone, being able to speak Danish, and the intention to continue their pregnancy until term, resulting in 88,570 total participants.

Information on various exposures during pregnancy was collected through computer-assisted telephone interviews which took place at approximately 16 weeks' gestation. The exposure of interest was coffee. Participants were asked about the number of cups of coffee that they consumed in a day. In the analysis, coffee intake was measured in numbers of cups consumed per day; 0, ½–3, 4–7, and more than 8 cups/day. 100 mg of caffeine was assigned per cup of coffee and 50 mg for a cup of tea. They were also asked about cups of tea consumed daily and amount of soda consumed in a week's time, none, less than 1 liter, or more than 1 liter per week. Information on potential confounders, such as previous fetal death, parity, smoking, alcohol intake, height, pre-

pregnancy body weight, and socio-occupational status, was also collected in the first interview.

The main outcome in the study was fetal death, defined as either spontaneous abortion (gestational age <196 days) or stillbirth (gestational age greater than or equal to 196 days). Birth outcomes were identified in the Civil Registration System and the Danish Medical Birth Registry. The follow-up period was divided into three gestational age intervals <140 days, 140–195 days, and greater than or equal to 196 days to study whether coffee increased the risk of fetal death during a specific time period. A total of 49,042 (55.4 %) women reported no coffee consumption during pregnancy; 27,803 women (31.4 %) drank ½–3 cups/day, 8,619 women (9.7%) drank 4–7 cups/day, and 3,018 women (3.4 %) drank more than 8 cups/ day. Among the 88,482 pregnancies, 1,102 fetal deaths were reported. According to the results, there was an elevated risk of fetal death based on coffee consumption with the risk increasing based on the number of cups of coffee consumed. Compared with females who did not consume coffee, the adjusted hazard ratios for fetal death associated with coffee consumption of 1/2–3 cups, 4–7 cups, and greater than or equal to 8 cups of coffee per day were 1.03 (95% CI: 0.89-1.19), 1.33 (95% CI: 1.08-1.63), and 1.59 (95% CI: 1.19- 2.13), respectively. Those who consumed eight or more cups of coffee per day had twice the risk of miscarriage or stillbirth compared to women who did not drink coffee. After adjustment for potential confounders, the risk was still present and remained high (HR = 1.59, 95% CI: 1.19-2.13). (Appendix B, Table 4).

The results of this study show a positive dose-response effect on coffee intake during pregnancy with higher rates of miscarriage. Compared to women with no coffee

consumption, consumption of more than 8 cups per day is associated with an increase in fetal death of over 1.5 %. Therefore based on these results, the authors of this study recommend limiting coffee intake to 3 or less than cups per day while pregnant.

Maternal Caffeine Consumption and Fetal Death: A Case-control Study in
Uruguay, Written by Matijasevich et al. (2006)

The purpose of this study was to investigate the link between caffeine consumption during pregnancy and fetal mortality. This was the only case-controlled study in this systematic review. This population-based study was conducted between August 1, 2002 and December 31, 2003, and took place in Montevideo, Uruguay. A total of 1,174 pregnant females were involved in this study, 792 in the control group and 382 in the case group. The controls were women who had a live, vigorous and term adequate-for-gestational-age newborn. Cases were women with a confirmed diagnosis of spontaneous fetal death of at least 20 weeks' gestational age. Multiple gestations and fetuses or newborns with congenital malformations were excluded from this study.

The main sources of caffeine in South America are from coffee and mate drinking, and so caffeine intake was estimated from these two sources. Mate drinking is a common South American drink prepared from steeping dried leaves of yerba mate in hot water. For coffee and mate drinking, daily intake was obtained for each trimester using a questionnaire. The questionnaire also collected information on the following variables, some of which are potential confounders: maternal anthropometric measures, marital status, family income, crowding, level of education of the mother and her partner,

mother's age, smoking during pregnancy, prenatal care attendance, obstetric history and morbidity during pregnancy. Information about birth weight, sex and causes of death were obtained from maternal and newborn hospital records.

Interviews were conducted during the first twenty-four hours after birth by trained medical students. Information was collected on the usual method of preparation, the size of the serving, and the reported strength of the beverage. Daily caffeine intake was calculated by trimester and throughout the entire pregnancy. Women who did not consume caffeine during pregnancy made up the control group. Women who consumed 0- 300 mg of caffeine per day made up the case group with consumption of 300 mg of caffeine or more making up the highest category.

This study was made up of 1,174 pregnant females with 792 (67.4%) live births and 382 (32.6%) fetal deaths. Based on the results, caffeine intake during pregnancy was significantly associated with fetal mortality ($P > 0.001$), and a dose-response effect of an increased risk of fetal death with higher caffeine intakes during pregnancy was observed. After controlling for possible confounders, the mean caffeine intake of 300 mg/day or more showed a significantly increased risk of fetal death OR 2.33 95% CI 1.23; 4.41 compared with no caffeine consumption during pregnancy. (Appendix B, Table 5).

The women in the case group consumed more caffeine than the women in the control group. Only a small proportion of the mothers (8.1% of the cases and 9.5% of the controls) did not consume caffeine during pregnancy. After controlling for all potential confounders, caffeine intake remained significantly associated with fetal death ($P \text{ trend} > 0.001$).

The results of this study demonstrate that consuming more than 300 mg of caffeine per day is associated with an almost 2.5 time increase in fetal death compared to women with no caffeine consumption. Based on the results of this study, the authors feel that caffeine is a preventable risk factor and therefore should be limited or avoided during pregnancy.

DISCUSSION

Based on the combined results from the five previously conducted studies, which looked at the relationship between caffeine intake during pregnancy and its proposed associations to an increased risk of miscarriage and stillbirth rates, there is still much uncertainty. Four of the studies that were included in this systematic review, all demonstrate a positive dose-response related effect on caffeine and negative pregnancy outcomes. There was only one study that did not show a relationship between caffeine and miscarriages or stillbirths.

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group was first established in 2000 in order to develop a systematic approach for grading the quality of evidence found in studies and the strength of their recommendations while minimizing confusion and bias. The GRADE working group recognizes four levels or types of recommendations based on the quality of the study; very low, low, moderate, and high. The interpretation of each recommendation is as follows:

High = further research is very unlikely to change our confidence in the estimate of effect; moderate = further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low = further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; very low = any estimate of effect is very uncertain (Guyatt et al., 2008, 926).

A discussion about each study, its limitations, strengths, and final results will follow.

The first article, “Caffeine Intake During Pregnancy, Late Miscarriage and Stillbirth,” was a well performed cohort study that identified a positive correlation between caffeine intake during pregnancy and late miscarriages and stillbirths (Greenwood et al., 2010). The authors of this study strived to improve their methodology by using a highly detailed caffeine assessment tool to identify all dietary sources of caffeine including beverages, food, and medications; gaining information prospectively rather than retrospectively; and adequately adjusting and correcting for potential confounders, most importantly alcohol and tobacco use. Daily caffeine intake was divided into 4 categories; less than 100 mg, 100-199 mg, 200-299 mg, and greater than 300 mg. These 4 categories cover a wide range of intake amounts that make it possible to better assess a correlation between intake and fetal death. Despite all of this, there are several biases that may have had an impact on the results of the study. These biases include; imprecise estimation of caffeine intake as well as alcohol consumption and tobacco use, or inadequate control for important confounding factors. Retrospective data was collected for intake that occurred at four weeks prior to pregnancy and at weeks one to four which adds to miscalculations of caffeine consumption. This study also did not address women with different CYP1A2 genes, which affect the rate of caffeine metabolism.

Due to the small study size and few numbers of miscarriages and stillbirths, the confidence intervals are wide for the estimated effects. Therefore, even though the results are statistically significant it is hard to determine the exact magnitude of association between caffeine intake and miscarriages or stillbirths. Due to ethical and moral reasons, a randomized controlled trial would not be feasible therefore much

information has been gained with this study (Greenwood et al., 2010). This cohort study was well designed and executed. All sources of caffeine were addressed and all potential confounders were assessed and adjusted for. The magnitude of effect, the positive dose-response that was seen, and the overall quality of the study make this a high quality study.

The second article, “Maternal Caffeine Consumption During Pregnancy and the Risk of Miscarriage: A Prospective Cohort Study,” also identified a positive correlation between caffeine intake during pregnancy and late miscarriages and stillbirths (Weng et al., 2008). The limitations that were present in this study were numerous. The study size was small with only 1,063 women participating, again making confidence intervals quite large. The participants were asked only about caffeine consumption based on beverages; coffee, tea, caffeinated soda, and hot chocolate. No information was gathered on foods and medications that contain caffeine which results in an under reporting of the actual amount of caffeine consumed. This study used conversion factors to calculate the amount of caffeine given the source and amount provided by the participant. But miscalculations of caffeine intake are probable as different brands and different brewing methods produce differing amounts of caffeine. Women were then divided into three groups based on daily caffeine consumption and yet there was some overlap between the groups; 0mg, 0-200mg, and 200+ mg. This allows for miscalculations as some women may have been included in multiple groups. There was some retrospective information collected as women reported caffeine intake from the time of their last menstrual period. There is some concern about potential recall bias as 59% of the total miscarriages had already occurred at the time of initial contact due to early recruitment. These women

were interviewed soon after their miscarriage, with a median delay of 19 days, and so a bias about their consumption could be present as these women had just gone through a great emotional event. The purpose of this study was to examine the effects of caffeine intake on miscarriages, which was defined as a fetal death that occurred at or before 20 weeks' gestation. No outcomes after 20 weeks were assessed in this study and so additional fetal deaths may and probably did occur after the study period that would have lead to additional incidents.

There were positive aspects to this study that helped to strengthen its final results and recommendations. The early recruitment of women resulted in the in-person interview being conducted soon after the pregnancy was confirmed. This helped to reduce the amount of retrospective information that had to be collected. Not only were the participants asked about current caffeine intake, there were also asked about changes in consumption once their pregnancy had been confirmed. Potential confounders, such as maternal age, race, education, household income, marital status, smoking, alcohol intake, hot tub use, nausea and vomiting, and magnetic field exposure were all included into the statistical analysis. There was no change in the end results when nausea, vomiting, aversion to caffeine, smoking, and changes in consumption rates were adjusted for (Weng et al., 2008). Although there were several limitations, this was a well executed cohort study which demonstrated a positive dose-response after adjustments were made for all potential confounders..

The article, "Caffeine and Miscarriage Risk," was the only study to show no association between caffeine intake and miscarriage risk (Savitz et al., 2008). Caffeine intake and risk of miscarriage were assessed at three separate time periods, and it was

determined that there was no link during any of these time points. This study had the greatest number of limitations that decreased the reliability of the results. This study again looked at miscarriage rates at or before 20 weeks' gestation, again limiting the total number of fetal deaths that may have occurred. Misclassification of coffee and caffeine intake could be present as information about caffeine from chocolate or medications was not obtained. Women were asked about the number of cups of coffee/tea/soda consumed, yet the sizes of cups vary greatly. The amount of caffeine was then determined via conversion tables which also adds to miscalculations. Women were then divided into four groups; 0 mg/day, 0-144.3 mg/day, greater than 144.3 mg/day, and greater than 273.2 mg/day. Again, there is some overlap between two of the groups which may allow for miscalculations. The authors of this study noticed a trend; when comparing levels of caffeine and coffee intake during pregnancy, women who were interviewed after their miscarriage reported elevated levels compared with women who experienced their loss after the interview. The elevated intake could be a result of recall bias or true differences.

The median caffeine intake by the participants was much less when compared to the other studies in this systematic review. Median caffeine intake was measured at 350 mg/day prior to and early in pregnancy, and 200 mg/day at the time of interview. This prevented the study from examining the possible effects at 300+ mg/day. The study population may have been more health conscious than those in previous studies because the authors enrolled volunteers who sought out prenatal care early or were planning a pregnancy.

There were strengths to this study which consisted of identifying and adjusting for potential confounders including; maternal age, race/ethnicity, education, marital status,

income, smoking, alcohol use, body mass index, age of menarche, employment status, diabetes, miscarriage history, induced abortion history, vitamin use, and nausea and vomiting in early pregnancy. Adjustments for nausea and vomiting did not affect the measures of association between coffee or caffeine and miscarriage risk (Savitz et al., 2008). Overall, this was a poorly performed cohort study due to the numerous limitations that were identified as well as a poor study design and methods. Although the study's results demonstrate no association between caffeine intake and negative pregnancy outcomes, the poor quality of the study reduces its level of recommendations.

The article, "Coffee and Fetal Death: A Cohort Study with Prospective Data," was the largest study in this systematic review with 88,482 participants (Bech et al., 2005). This study again produced results which associated caffeine to miscarriages and stillbirths. Consuming over 8 cups of coffee per day was associated with 1.5 times of the risk of fetal death when compared to women with no caffeine consumption.

There were several limitations present in this study. This Danish National Birth Cohort was not intended to be a representative sample but to be a large source of information. Women were asked about daily consumption of coffee, tea, and caffeinated soft drinks. There was no information obtained about foods, medications, and drinks containing chocolate. The authors used conversion factors to best determine the amount of caffeine in a cup of each beverage but differences in caffeine content are seen depending on cup size, brand, and brewing method, all leading to possible miscalculations.

Coffee drinking is often associated with other lifestyle factors, such as tobacco and alcohol use. This study adjusted for a large number of factors but uncontrolled

confounding factors cannot be ruled out. However, the authors of this study feel that other uncontrolled confounders would need to be strong in order to explain the results. Information on potential confounders, such as previous fetal death, parity, smoking, alcohol intake, height, pre-pregnancy body weight, and socio-occupational status, were obtained and adjustments were made for these factors.

Another limitation identified is the lack of information on early nausea and coffee aversion. Nausea is associated with healthy and viable pregnancies as hormonal changes necessary for pregnancy cause these symptoms. Many women with nausea may reduce their caffeine more than women not experiencing nausea. Some believe that coffee intake remains high in high risk pregnancies, due to the lack of nausea, and therefore caffeine ultimately does not contribute to the fetal demise (Bech et al, (2005). Overall, this was a well performed cohort study based on the quality of this study, the large magnitude, and positive dose-response that was seen.

The final article in this systematic review is titled, “Maternal Caffeine Consumption and Fetal Death: a Case-control Study in Uruguay.” This was the only case-control study in this systematic review. This study again demonstrated a positive correlation between caffeine consumption and the increase risk of fetal death (Matijasevich et al., 2006). This study demonstrates that consuming more than 300 mg of caffeine a day compared with no caffeine is associated with greater than twice the risk of fetal death. This study had numerous limitations which would have decreased the validity of its findings. The rates of fetal death are much higher in Uruguay compared to the United States as access to medical care is less available and medical technology is less advanced. Therefore it is more difficult to associate the fetal deaths to caffeine

consumption alone. In South America, the main sources of caffeine are coffee and mate drinking. Therefore this study used only these two sources to estimate daily caffeine intake. Women were asked about method of preparation, size of the serving, and strength of preparation in order to estimate the amount of caffeine for each beverage. Information on other dietary sources was not obtained and as a result caffeine intake may well be underestimated.

This study divided women into 2 groups, control and case groups. The controls were women who conceived healthy and viable newborns. Women who had a medically confirmed diagnosis of spontaneous fetal death were classified into the case group. No miscarriages were assessed in this study, only information on stillbirths or live births were obtained. When comparing maternal characteristics between the two groups, there were many differences which could have impacted the results of this study. Women in the case group were more likely to be single mothers, to have a lower income and lower educational level, to be younger, tobacco users, experience more nausea and vomiting, and to have a history of adverse pregnancy outcomes when compared to the control group.

Specially trained personnel interviewed the women at approximately 24 hours after the delivery, which may have had an impact on recall in both the control and case groups. The authors feel that the women may have miscalculated their caffeine, alcohol or tobacco use. This was the only study to obtain information retrospectively that also adds to miscalculations.

There were strengths in this case-control study. Potential confounders were assessed and were adjusted for in the statistical analysis of the data. Confounders

included; family income, marital status, and maternal and partner's education, maternal history of abortion and/or fetal death, smoking and caffeine intake during pregnancy, vomiting or nausea during the first trimester of gestation, and attendance in prenatal care classes. After controlling for all potential confounders, high caffeine intake still remained associated with increases in fetal death rates (Matijasevich et al., 2006). Overall, this was a well performed case-control study which demonstrated a positive dose-response association between caffeine intake and fetal death.

The GRADE table for this systematic review compared pregnant females with no caffeine intake to those who consumed caffeine on a daily basis. Ideally, this GRADE table would have looked at specific amounts of caffeine intake per day but each study looked at different levels of caffeine consumption. Therefore this GRADE table compared caffeine intake to no caffeine intake. The purpose of this systematic review was to determine the effects of caffeine consumption on two outcomes; females having a live and healthy newborn versus having a miscarriage. The starting GRADE is low as each study involved was an observational study. The findings of the studies involved differ as four of the studies show an increase in miscarriage rates with increased caffeine consumption. Only one study shows no correlation between caffeine and fetal deaths. Therefore the GRADE cannot be increased for a large magnitude effect or a dose-response and so it remains a low GRADE recommendation. If the one study was not included in this systematic review, the GRADE would have been increased in both of these categories to a moderate level. The GRADE score was increased in only one category, confounders. All five studies indentified, discussed, and factored the potential confounding factors into the statistical analysis. No major changes in the results were

identified after the confounders were adjusted for. This finding demonstrates that the results obtained were based on the relationship between the comparison (caffeine vs. no caffeine) and the outcome (healthy birth vs. miscarriage). The final GRADE is moderate which is defined as the following by the GRADE Working Group:.”

further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate” (Guyatt et al., 2008, 926).

After reviewing the five articles in this systematic review, the recommendation to cease caffeine consumption during pregnancy to decrease the risk of miscarriage or still birth is moderate.

A systematic review of the literature was performed in order to determine the effects of caffeine consumption during pregnancy and the risk of miscarriage or stillbirth. The final results of this systematic review still remain inconclusive after five studies were reviewed in their entirety. It is recommended that additional studies be conducted in order to gain supplementary information. Due to ethical and moral concerns, a randomized controlled trial cannot be conducted in this situation. It will be up to future cohort and case-control studies that are well performed and properly conducted to gain the data necessary to finally make a recommendation on this topic.

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APPENDIXES

Appendix A

Table 1. Late miscarriage and stillbirth rates based on caffeine intake over first trimester

Caffeine (mg/day)	Number of fetal deaths	Adjusted Odds Ratio*	(95% Confidence Interval)
<100	6/998	1.0	
100-199	7/656	2.2	(0.7-7.1)
200-299	3/402	1.7	(0.4-7.1)
300 +	9/426	5.1	(1.6-16.4)

*Adjusted odds ratio by maternal age, parity, tobacco intake, alcohol intake.
(Greenwood et al., 2010)

Table 2. Risk of miscarriage occurring at or before 20 weeks' gestation based on caffeine intake

Caffeine (mg/day)	Number of Miscarriages (%)	Number of Non-Miscarriages (%)	Adjusted Hazard Ratio*	(95% Confidence Ratio)
0	33 (12.50)	231 (87.50)	1	
<200	97 (15.30)	538 (84.72)	1.42	(0.93-2.15)
>200	42 (25.45)	122 (74.39)	2.23	(1.34-3.69)

*Adjusted hazard ratio based on maternal age, education, family income, marital status, previous miscarriage, nausea and vomiting since last menstrual period, smoking status, alcohol intake, Jacuzzi use, exposure to magnetic fields.
(Weng et al., 2008)

Table 3. Risk of miscarriage occurring at or before 20 weeks' gestation based on caffeine consumption

Caffeine (mg/day)	Number of Miscarriages	Adjusted Odds Ratio*	(95% Confidence Interval)
0	102	1.0	
1 - < 144.3	71	1.0	(0.7-1.4)
>_144.3	84	1.2	(0.9-1.7)
>273.2	46	1.3	(0.9-1.9)

*Adjusted odds ratio for maternal age, race/ethnicity, maternal education, marital status, alcohol intake, vitamin use, nausea and vomiting.
(Savitz et al., 2008)

Appendix B

Table 4. Fetal death rates based on coffee consumption

Cups of Coffee (cups/day)	Number of Deaths	Adjusted Hazard Ratio*	(95% Confidence Interval)
0	561	1.0	
½-3	307	1.03	(0.89-1.19)
4-7	130	1.33	(1.08-1.63)
8 +	60	1.59	(1.19-2.13)

*Adjusted hazard ratio for maternal age, parity, smoking, prepregnancy body mass index, alcohol intake, sociooccupational status.

(Bech et al., 2005)

Table 5. Fetal death rates based on differing amounts of caffeine consumption

Mean Caffeine (mg/day)	Adjusted Odds Ratio*	(95% Confidence Interval)
0	1.0	
1-59	0.74	(0.42-1.31)
60-149	0.93	(0.51-1.67)
150-299	1.22	(0.69-2.17)
300+	2.33	(1.23-4.41)

*Adjusted odds ratio based on maternal and paternal education, history of abortions and/or fetal death, vomiting and nausea, prenatal care.

(Matijasevich et al., 2006)

Appendix C
Table 6. GRADE Table

Comparison	Outcome	Quantity and type of evidence	Findings	Starting grade	Decrease GRADE					Increase GRADE			Grade of Evidence for Outcome	Overall GRADE of Evidence
					Study Quality	Consistency	Directness	Precision	Publication Bias	Large Magnitude	Dose-Response	Confounders		
Caffeine consumption vs. no caffeine consumption during pregnancy	Live Births	4 cohort, 1 case control	Decreased live births in 4 studies. No relation in 1 study	Low	0	0	0	0	0	0	0	+1	Moderate	Moderate
	Miscarriages	4 cohort, 1 case control	Increased miscarriage rates in 4 studies. No relation in 1 study.	Low	0	0	0	0	0	0	0	+1	Moderate	