Clinical and Experimental Health Sciences

Review / *Derleme*

An Overview of The Relationship Between Fertility and Caffeine Intake

Fertilite ve Kafein Alımı Arasındaki İlişkinin Değerlendirilmesi

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Cite this article as: Macit MS, Akdevelioğlu Y. An Overview of The Relationship Between Fertility and Caffeine Intake. Clin Exp Health Sci 2018; 8: 138-45.

Abstract

Caffeine is a psychoactive component with a chemical composition of 1,3,7-trimethylxanthine. Coffee, tea, energy drink, and chocolate are the main sources of caffeine. There are several positive health effects of caffeine on diabetes, Parkinson's disease, and cardiovascular disease. However, the relationship between caffeine consumption and reproductive health is controversial. The aim of the present study was to determine the effects of caffeine consumption on fertility. A literature search was conducted using the electronic databases PubMed, Web of Science, Cochrane, and LILACS with the search terms "fertility," "infertility," "fecundability," "reproductive," "caffeine," "coffee," "tea," and "caffeinated." An additional manual search was also performed for missing articles. At the end of the search, a total of 13 studies were included in the present study. Six studies reported negative and two studies reported positive effects of caffeine on fertility by several mechanisms such as affecting sex hormones and reducing clearance during the luteal phase. However, no association was found between caffeine and fertility or fecundability in five studies. According to study results that revealed negative effects of caffeine, it may be recommended to males and females who are planning to conceive to decrease caffeine intake, especially from coffee. It may also be recommended to consume other types of healthy beverages and foods without caffeine.

Keywords: Caffeine, coffee, fertility, fecundability, pregnancy

Öz

Kafein 1,3,7-trimetilksantin kimyasal yapısında, biyoaktif bir bileşendir. Kahve, çay, enerji içecekleri ve çikolata kafeinin ana kaynaklarıdır. Kafein diyabet, Parkinson, kardiyovasküler hastalıklar gibi sağlık sorunları üzerine olumlu etkileri vardır. Ancak kafeinin üreme sağlığına etkisi tartışmalıdır. Bu derlemede kafein tüketiminin fertilite üzerine etkilerinin değerlendirilmesi amaçlanmıştır. Pubmed, Web of Science, Cochrane, ve Lilacs elektronik veri tabanlarında "fertilite", "infertilite", "üreme", "kafein", "kahve", "çay", "kafeinli" terimleri ile tarama yapılmıştır. gözden kaçırılan çalışmaların olması ihtimaline karşı ek olarak genel bir tarama yapılmıştır. tarama sonucu toplam 12 çalışma bu derlemeye dahil edilmiştir. Çalışmalardan 5'i kafeinin fertilite üzerine olumsuz, 2'si olumlu etkileri olduğunu rapor etmektedir. Olumsuz sonuçlar sunan çalışmalar genellikle kafeinin seks hormonlarına etkisi ve lüteal fazı kısaltıcı etkilerine yoğunlaşmıştır. Ancak 5 çalışma kafein alımı ve fertilite arasında herhangi bir ilişki bulmamıştır. Çalışma sonuçları doğrultusunda gebelik planlayan çiftlere kafein alımını azaltmaları tavsiye edilebilir. Ayrıca bireyler kafeinsiz içecekleri tüketimleri konusunda teşvik edilmelidir.

Anahtar Kelimeler: Kafein, kahve, fertilite, doğurganlık, gebelik

INTRODUCTION

Caffeine is one of the most common psychoactive components. Its chemical composition is 1,3,7-trimethylxanthine, which is found in more than 60 plants and also produced in the industry (1). After entering the body, caffeine is easily distributed in the body and exists in the saliva, breast milk, embryo, and neonate owing to its ability to pass all membranes including the placental barrier (2,3). Caffeine is a component present in a large range of food such as coffees, teas, chocolates, cocoa products, and soft and energy drinks. However, coffee is its main source (4). Table 1 shows the amount of caffeine in these main sources.

Caffeine is associated with several positive health effects for cardiovascular diseases, diabetes, and Parkinson's disease (7). It is an adenosine receptor antagonist and may also have several effects on reproductive health (8). Adenosine has effects on sperm capacity via tyrosine phosphorylation with N^6-cyclopentyladenosine (9). For the first time, the Food and Drug Administration advised pregnant women to decrease caffeine intake (10). It was also recommended that pregnant women should not exceed 200 mg/day caffeine intake.

Caffeine is presented as one of the nutrients that have effects on dysmenorrhea and premenstrual syndrome (11). In addition, it is reported to decrease fertility (12). The relationship between caffeine and fertility was first reported by Wilcox et al. in a prospective study. According to their study results, per cycle probability of conceiving was decreased by 50% due to drinking one cup of coffee. However, study results are controversial owing to its designs, methodological failings, and call of bias. Caffeine intake, below the recommend-

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Received/Geliş Tarihi: 21.08.2017 **Accepted/Kabul Tarihi:** 12.11.2017 **DOI:** 10.5152/clinexphealthsci.2017.663

Table 1. Amount of caffeine in some foods and beverages.

Foods and beverages	Caffeine content (mg)
Filter coffee (200 mL)	90
Espresso (60 mL)	80
Black tea (220 mL)	50
Green tea (220 mL)	24
Coke (335 mL)	40
Plain chocolate (50 g)	50
Milk chocolate (50 g)	10
Standard energy drink (250 mL)	80

United States Department of Agriculture, Agricultural Research Service, USDA Food Composition Databases. Available from: https://ndb.nal.usda.gov/ndb/search/list (5).
European Food Safety Authority. Available from: http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/efsaexplainscaffeine150527.pdf (6).

ed levels (<200–300 mg/day), appears to have no serious effects on reproductive life. It is still advisable to avoid excessive caffeine intake for women and men who plan to conceive. The recommended amount for conception is 100–200 mg/day, which is defined as mild consumption and equivalent to fewer than two cups of coffee per day (12).

This relationship has been explained by several mechanisms in studies:

- There is an inverse correlation between caffeine and estradiol in pregnant woman.
- There is a positive correlation between caffeine and sex hormone-binding globulin.
- Caffeine may decrease prolactin levels and may inhibit ovulation.
- Caffeine may affect the transportation of conceptus (4,13–16).

It was stated that the effects of coffee may be due to different components rather than caffeine (4). However, it is difficult to distinguish the effects of coffee and caffeine due to high correlation in their intake (17).

Pregnancy is a natural process and affected by several factors. It is important to eliminate the possible risk factors for a healthy conception and pregnancy. In terms of nutrition, caffeine is one of the nutrients that is thought to influence reproductive health. However, study results are not clear owing to different study types and designs. This review aimed to sum up these study results and to assess the relationship between caffeine intake and fertility, fecundability, and conception time.

METHODS

A literature search was conducted using the electronic databases PubMed, Web of Science, Cochrane, and LILACS. The search terms "fertility," "infertility," "fecundability," "reproductive," "caffeine," "coffee," "tea," and "caffeinated" were used. The search was performed through appropriate methods and keywords by using "AND" and "OR." An additional manual search was also performed for missing articles, and one article was added to the study. Three studies were excluded in this review owing to no access to full text and abstract (18–20). Outcomes were determined by birth, fertility, fecundability, fecundability rate (FR), and spontaneous abortion. With this regard, this review is restricted to human studies of caffeine and its associated factors and excluded fetal death, congenital malformations, and gestational age/preterm birth. We have only included spontaneous abortion outcome that appears after conception.

Articles were viewed according to the following inclusion and exclusion criteria.

Inclusion criteria:

- written in English
- human studies
- clinical trial or randomized controlled design or presenting cross-sectional or prospective data.

Exclusion criteria:

- case studies, reviews, and meta-analyses
- animal studies.

Figure 1 shows the selection methodology and number of articles. A total of 318 articles from PubMed, 274 articles from Web of Science, 33 articles from Cochrane, and 25 articles from LILACS were found. Articles were screened with a review process according to:

- title and abstract
- full-text examination.

According to the selection criteria, eight studies with prospective design, two studies with retrospective design, and three studies with follow-up were included in this review. Heterogeneity of study designs and study characteristics does not allow to conduct any statistical analyses.

CLINICAL AND RESEARCH CONSEQUENCES

Studies have revealed controversial results for the relationship between caffeine intake and reproductive health. The present review aimed to review studies evaluating outcomes, fertility, and live births. According to the literature search, 13 studies were included in this review. Table 2 shows the study results.

Six studies revealed negative effects of caffeine intake on reproductive health, two of them reported positive effects, and five studies found no association. According to studies that were included in this review, Wilcox et al., Jensen et al., Bolumar et al., Klonoff-Cohen et al., Wesselink et al., and Gaskins et al. reported negative effects of caffeine, coffee, or tea intake on reproductive health parameters (2,4,8,21–23). Hatch et al. and Florack et al. reported a positive relationship (24,25). However, Hakim et al., Taylor et al., Chavarno et al., Curtis et al., and Caan et al. found no association (26–30).

First, studies that found a negative association of caffeine determined the FRs as an outcome. Wilcox et al. conducted the first study that reported a negative association between caffeine and fecundability. They found 50% lower FRs in the group who consumed high amounts of caffeine (21). Jensen et al. found that more than 700 mg/day caffeine

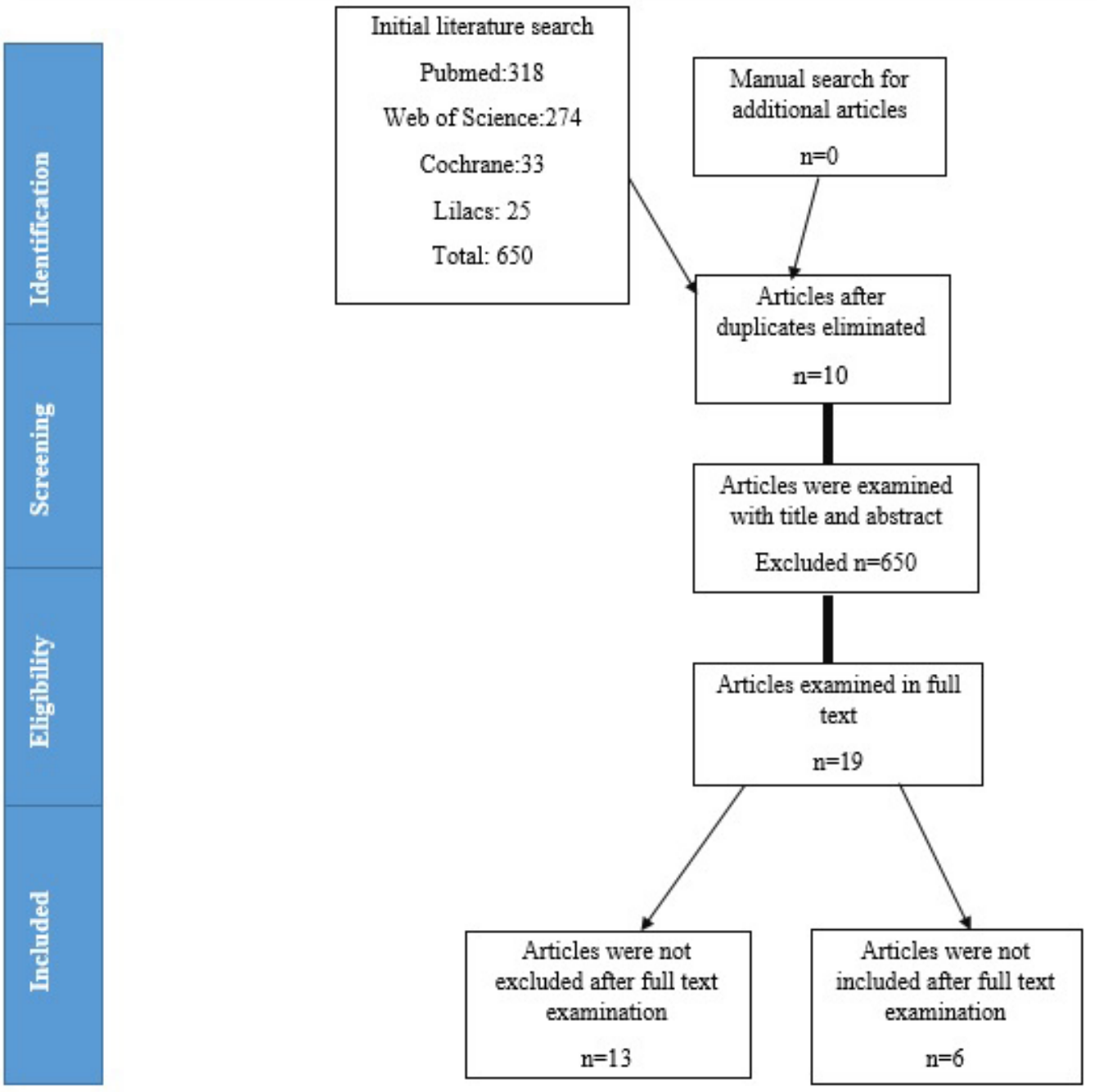

Figure 1. Selection methodologhy of articles

intake is associated with reduced fecundability among non-smokers (men, OR: 0.47, 95% CI: 0.26–0.82 and female, OR: 0.63, 95% CI: 0.25–1.60) (2). They reported the effect of caffeine with reduced clearance during the luteal phase and accumulation in implantation. Among smokers, fecundability was decreased when caffeine intake was more than 300 mg/day among non-smokers (OR: 0.74, 95% CI: 0.59–0.92) (20). It was stated that smokers may consume more caffeinated beverages, and smoking also enhances the metabolism of caffeine via the induction of hepatic cytochrome P-450 enzymes and increases N-demethylation (27). Caffeine is the first-choice substrate for CYP1A2 and is often used for phenotyping of human cytochrome P450 (31,32). Smoking also increases the metabolism of xanthine oxidase activity and caffeine (4). Bolumar et al. also reported that a 501 mg/day caffeine intake is associated with subfecundity (OR: 1.03–2.04, 95% CI: 1.45). Contradictory to these results, the association was stronger in smokers. They explained this difference in previous studies that heavy coffee drinkers smoke more (4).

Gaskins et al. examined the Nurses' Health Study II (1991–2009) cohort and reported the effects of caffeine consumption (23). When caffeine intake was categorized, there was a positive linear trend across categories of pre-pregnancy caffeine intake and risk of spontaneous abortion such that women consuming >400 mg/day had 1.11 (95% CI: 0.98–1.25) times the risk of spontaneous abortion compared

Table 2. Overview of studies.

Studies	Year	Sample	Study design	Method	Country	Outcome	Adjustment	Inclusion	Exclusion	Results
Hakim et al. (26)	1998	124 females (23–41 years)	Prospective observational	Steroid hormones and human chorionic gonadotropin assessment (urine), caffeine intake (food frequency for the last 1 month), caffeine content for coffee: 100 mg, tea: 40 mg, cola: 50 mg Caffeine intake classification: 0–25 mg, 26–100 mg, 101–300 mg, ≥301 mg	America	Probability of conception per 100 menstrual cycles	Smoking, alcohol, age, intercourse frequency	Women with reproductive	Using oral contraceptive and intrauterine device	Caffeine (mg/day) n Birth/no. of menstruation 0–25 30 39/196 (19.9) 26–100 32 26/184 (14.1) 101–300 53 28/258 (10.9) ≥300 9 6/40 (15.0)
Jensen et al. (2)	1998	430 couples (20–35 years)	Follow-up (3 years)	Follow-up for 6 menstruation cycles or until conception Intercourse frequency, reproductive health, vaginal bleeding Semen sample Caffeine intake: daily or weekly Caffeine content 1 cup of coffee: 100 mg, 1 cup of tea: 50 mg, 1 cup of chocolate beverage: 25 mg, 0.25 L cola: 100 mg, 50 g chocolate bar: 12.5 mg Caffeine classification: 0–299 mg, 300–699 mg, >700 mg	Denmark	Each cycle (pregnant or not pregnant)	BMI and alcohol intake, diseases of the female reproductive organs, semen quality, and duration of the menstrual cycle	Not having a child before, not using birth control methods		Among non-smokers, intake of more than 700 mg/day Caffeine was associated with an FR of 0.63 (95% CI: 0.25–1.60) among females and 0.47 (95% CI: 0.26–0.82) males
Bolumar et al. (4)	1997	3187 females (25–44 years)	Retrospective	Conception time, caffeinated beverage consumption Caffeine content: Tea: 40 mg, cola: 50 mg, coffee: 130 mg for Denmark, 115 mg for South Europe, 115 mg for Germany (according to coffee type, size of cup, and brewing method) Caffeine classification: 0–100, 101–300, 301– 500, and ≥501 mg Conception time: 0–3.4, 3.5–9.4, 9.5–15.4 and >15.5	Denmark, Germany, Italy, Poland, Spain	Conception time	Age (20, 21–25, 26–30, 31 years), smoking for the last 12 months			≥501 mg caffeine intake is associated with subfecundity (OR: 1.03–2.04, 95% CI: 1.45)
Curtis et al. (29)	1997	2607 (planned pregnancies <44 years)	Retrospective cohort	Daily coffee, tea, and cola consumption Caffeine content for coffee: 100 mg, tea: 40 mg, cola: 50 mg	Canada	–	–	Planned pregnancies	Using oral contraceptive, trying to become pregnant more than 1 year	There was no relationship between caffeine intake and fertility (<100 mg and >100 mg). Coffee intake in women and tea intake in men were associated with FR (0.92, 95% CI: 0.84–1.00 and 0.85, 95% CI: 0.69–1.05, respectively)
Caan et al. (30)	1998	187 females	Follow-up	Food frequency (last 1 month)	America	–	Age, BMI, frequency of intercourse, smoking, and alcoholic beverages	Women planning for pregnancy		There was no relationship between caffeine intake and fertility. However, an increase in tea intake caused a decreased in getting pregnant (OR: 7.25, 95% CI: 3.06–17.17)
Klonoff-Cohen et al. (22)	2002	221 couples (M = 22–55 years, F = 26–49 years)	Prospective	Daily coffee (100 mg), tea (50 mg), and cola (50 mg) consumption Caffeine intake: 0–2 mg, 2–50 mg, 50–200 mg, >200 mg	America	Oocyte retrieval, fertilization, multiple pregnancies abortus, live birth	Smoking, alcohol, age, ethnicity, number of embryo transfer, education, parity, treatment type	Couples with in vitro fertilization or gamete intrafallopian transfer therapy		There was no association between outcomes and caffeine intake during the study. However, lifetime caffeine intake was a risk factor (2–50 mg and >50 mg) (OR: 3.1–3.9). In men, 100 mg increase in caffeine consumption increased the risk for multiple pregnancies

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Studies	Year	Sample	Study design	Method	Country	Outcome	Adjustment	Inclusion	Exclusion	Results
Hatch et al. (24)	2012	3628 (18–40 years)	Prospective cohort	Caffeine intake was assessed at baseline and every 8 weeks (coffee, soda, tea, green tea)	Denmark	Fecundability	Age, BMI, alcohol, smoking, relationship frequency, tea, coffee	Women with a regular relationship, not using oral contraception, planning pregnancy (less than 12 months)	–	Increase FR in women who consumed more than >300 mg compared with <100 mg (FR = 1.04, 95% CI: 0.90–1.21). There was an inverse association with soda intake (0.89, 0.80–0.98; 0.85, 0.71–1.02; 0.84, 0.57–1.25; 0.48 0.21–1.13)
Florack et al. (25)	1994	259 females (18–39 years)	Prospective study	Smoking habits, alcohol consumption, and caffeine intake (e.g., coffee, tea, and cola consumption) were evaluated	Holland	Fecundability		Non-medical hospital workers	–	Participants with a moderate caffeine intake (400–700 mg/day) showed a higher fecundability than those with a lower intake level (adjusted OR: 2.1, 95% CI: 1.2–3.7). Heavy caffeine intake (>700 mg/day) among partners was negatively related to fecundability when compared with the lowest intake level (adjusted OR: 0.6, 95% CI: 0.3–0.97)
Wilcox et al. (21)	1988	104 females	Follow-up	Caffeine intake: coffee: 100 mg, instant coffee: 65 mg, tea: 50 mg, soft drinks: 40 mg	USA	Fecundability	Age, frequency of intercourse, age at menarche, prenatal exposure to mother's smoking	Healthy females who were planning to become pregnant	–	Lower FR in the group who consumed high amounts of caffeine
Gaskins et al. (23)	2016	15,590 females (20–44 years)	Prospective cohort	Dietary intake: a 131-item Food Frequency Questionnaire Caffeinated coffee: 137 mg caffeine/cup, tea: 47 mg caffeine/cup, caffeinated sodas: 46 mg caffeine/bottle or can, and chocolate: 7 mg caffeine/serving	USA (Nurses' Health Study II)	Spontaneous abortion	Pre-pregnancy caffeine intake	Female nurses	–	There is a positive association between caffeine intake and spontaneous abortion that women consuming >400 mg/day had 1.11 (95% CI: 0.98–1.25) times the risk compared with women consuming <50 mg/day (p<0.05)
Chavarro et al. (28)	2009	18,555 females (24–42 years)	Prospective, cohort (Nurses' Health Study II), follow-up (8 years)	Food frequency (2 times), ovulatory disorder, infertility reported	America	Fertility	Age, total energy intake	Women without infertility history	Women with diabetes	438 ovulatory disorder infertilities were assessed after follow-up. There was no relationship with caffeine intake
Taylor et al. (27)	2011	319 females (20–41 years)	Prospective	Daily caffeine intake 1 cup of coffee: 150 mg, 1 cup of tea: 55 mg, 1 cup of cola: 45 mg Caffeine classification: <150 mg, 150–300 mg, >300 mg	America	Fecundability	Age, BMI, intercourse without, planning pregnancy, alcohol, smoking	Participants with N-acetyltransferase 2 polymorphisms (161 slow, 158 fast acetylators)	Hormonal contraceptive, intrauterine device, infertility (not having a conception more than 1 year), hysterectomy, polycystic ovary, tube ligation, vasectomy	There was no relationship between caffeine and FR

Table 2. Overview of studies.

Studies	Year	Sample	Study design	Method	Country	Outcome	Adjustment	Inclusion	Exclusion	Results
Wesselink et al. (8)	2016	2135 females (21–45 years)	Prospective cohort	Daily consumption of beverages (coffee: 135 mg, decaffeinated coffee: 5.6 mg, black tea: 20 mg, green tea: 20 mg, white tea: 15 mg, soda: 23–69 mg, energy drink: 48–280 mg)	America/ Canada	Fecundability	Age, ethnicity, BMI, smoking, alcohol, relationship frequency, stress, sleep, working time, methods to increase pregnancy probability	21–45 years, not using contraception, not having fertility treatment	Women with irregular menstrual cycle	There was no association for women; however, an increase in caffeine intake was related with a decrease in FR (FR ≥300 vs. <100 mg/day = 0.72, 95% CI: 0.54–0.96)

BMI, body mass index.

with women consuming <50 mg/day (p=0.05). Interestingly, when beverages were evaluated separately, both caffeinated and decaffeinated coffee intakes had a positive association with spontaneous abortion (p=0.01 and 0.04, respectively). These results need to be taken into consideration, and further studies should be conducted on non-caffeinated beverages. The possible mechanism associated with pre-pregnancy coffee intake and risk of spontaneous abortion was explained by the effects of coffee on endogenous sex hormone metabolism, pregnanediol-3-glucuronide levels, lower total and free luteal plasma estradiol levels, and higher 2-catechol estrogen metabolites, 2-hydroxyestrone, and 2-hydroxyestradiol (23).

Klonoff-Cohen et al. stated that there is no association between caffeine and fertilization (22). However, lifetime caffeine consumption was a risk factor for no birth. The possible mechanisms were explained with the reduced levels of reproductive hormones such as estradiol. In a recent study, Wesselink et al. found a negative association between caffeine and fecundability in males but not in females (8). According to the results of their study, ≥300 mg/day caffeine consumption was associated with decreased fecundability among males (M = 0.72, 95% CI: 0.54–0.96). It was emphasized that low caffeine intake of cohort may weaken the associations. Hatch et al. also reported that there is a minor negative effect of caffeine on reproductive systems for participants who consumed more than 300 mg/day caffeine (24). They claimed that this association may be stronger in less fertile women.

Hakim et al. found no relationship with daily coffee intake on births (26). However, they found a decrease in the probability of conception that consumed alcohol and claimed that caffeine may worsen the effects of alcohol. Separate analyses were also conducted on participants who did not consume alcohol or cigarette. It was stated that there is also a decrease, though not statistically significant, conception rate in women who consumed more than one cup of coffee (18.0%, adjusted OR: 0.56). Hakim et al. also reported that the association may occur even in low intakes than previous studies suggested for more than three cups of intakes (26). Similar to their study, Curtis et al. found no association between caffeine and fertility (29). However, they reported that fecundability is decreased in females who consumed coffee and in males who consumed tea (0.92, 95% CI: 0.84–1.00 and 0.85, 95% CI: 0.69–1.05, respectively). These results that were explained with the possibility of bias by misclassification of caffeine exposure were consistent with the literature that found reduced FRs.

Caan et al. also could not find any statistically significant decrease in fertility in terms of caffeine intake (30). Their study was conducted on 187 participants; it was a small sample size compared with the studies with large cohorts (4,27). The aim of their study was to prevent bias in which retrospective studies might involve and assess odds ratios with an 80% power. This power ratio may still be not enough to detect the relationship.

Chavarro et al. conducted a study with a large cohort (Nurses' Health Study II), with 18,555 women with a long follow-up (8 years) (28). After the follow-up period, 438 ovulatory disorder infertilities were reported but no positive association between the intake of caffeine, coffee, tea, or decaffeinated coffee and risk of ovulatory infertility. They emphasized the lack of methodological design of retrospective studies, which Leviton and Cowan discussed in detail in their study (32). Taylor et al. (27) evaluated the effects of caffeine with a similar design but smaller sample size compared with Chavarro et al. (28). Their study conducted on women who had N-acetyltransferase 2 (NAT2) polymorphisms also failed to find an association; however, the relationship was assessed regardless of NAT2 acetylation status.

In this review, caffeine consumption was evaluated in terms of pre-pregnancy. In pregnancy, caffeine intake should also be considered. Buck Louis et al. reported that more than two daily caffeinated drinks are significantly associated with pregnancy loss (preconception [aHR 1/4 1.74, 1.07–2.81], early pregnancy [aHR 1/4 3.05, 1.75–5.34], and periconception [aHR 1/4 2.58, 1.56–4.27]) (33). Their study provides a different perspective on the flow of the present review and supports the idea to decrease caffeine consumption after pregnancy especially in the first trimester in which Gaskins et al. reported higher rates of spontaneous abortion (23).

When we evaluate the studies on caffeine in terms of consumption amounts (mg), the negative effect of caffeine on reproductive health ranges between 300 and 700 mg/day. However, taking into consideration coffee consumption, this amount decreases to 100 mg/day. Even if 200 mg/day caffeine intake is determined as a maximum intake for pregnant women, the effect of coffee at 100 mg/day intake supports the idea to decrease the consumption as much as possible.

CONCLUSION

There are several studies about caffeine consumption and reproductive health. However, different designs make it more difficult to

compare results. Some of the studies focus on caffeine consumption, whereas some of them focus only on coffee consumption owing to its high caffeine content. Focusing on coffee intake alone would probably result in underestimations of total caffeine intake. According to different countries, caffeine intake might differ, and chocolate, black tea, or green tea may become an important source of caffeine. Additionally, coffee consumption is evaluated as "one cup of coffee" or "one serving". Nevertheless, type of coffee beans, brand, roasting degree (soft, medium, and dark roasted), infusion time, and cup size affect coffee content. These covariates should be considered in study designs. In addition, retrospective studies tend to show more relationship between caffeine intake and fertility which may be a result of asseseing caffeine intake with retrospective questionnaire. After analyzing the study designs, it becomes difficult to give a clear recommendation, but if these study results are considered, it may be advisable for couples who are planning to conceive to decrease caffeine intake as much as possible, especially from coffee. There are also other caffeine sources, but coffee is the main source of caffeine in the diet. It may also be recommended to consume other sources of healthy beverages and foods if there is a need. Further studies with a detailed design and accurate measurement of caffeine intake should be conducted to clarify the effects of caffeine including decaffeinated beverages.

Limitations

The selected studies differ in quality of information, study design, and categorization of caffeine exposure. These study limitations affect the present study and make it difficult to present an extensive recommendation. Nevertheless, these limitations reveal the need for an accurate assessment of caffeine intake. Individual assessment of dietary intake may be useful instead of standard questionnaires.

Peer-review: Externally peer-reviewed.

Author contributions: Concept – M.S.M, Y.A.; Design - M.S.M, Y.A.; Supervision - Y.A.; Resource M.S.M.; Materials - M.S.M.; Data Collection and/or Processing - M.S.M.; Analysis and/or Interpretation - M.S.M.; Literature Search - M.S.M.; Writing - M.S.M., Y.A.; Critical Reviews - M.S.M., Y.A.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

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