VIA MEDICA

REVIEW PAPER / OBSTETRICS

Ginekologia Polska
2022, vol. 93, no. 7, 591–600

ISSN 0017–0011, e-ISSN 2543–6767

DOI 10.5603/GP.a2022.0061

Coffee consumption during pregnancy — what the gynecologist should know? Review of the literature and clinical studies

Stanislaw Surma, Andrzej Witek

Department of Gynecology, Obstetrics and Gynecological Oncology, University Clinical Hospital, Medical University of Silesia, Katowice, Poland

ABSTRACT

Coffee is one of the most consumed beverages in the world. The impact of coffee consumption on human health has been the subject of many clinical studies and meta-analyses. Taking into account the results of these studies, it can be concluded that coffee has a number of health benefits in terms of the population, including the reduction of the risk of death from any cause. From a clinical point of view, the safety of coffee consumption in a specific subpopulation of pregnant women is important. A large percentage of women continue to consume this drink during pregnancy, while a significant proportion of them exceed the permissible daily dose of caffeine (≤ 200 mg). During pregnancy, the metabolism of caffeine slows down significantly, which prolongs its action and penetrates into the body of the fetus. These biochemical observations have become the driving force behind numerous clinical studies assessing the impact of coffee consumption during pregnancy on its course, complications and the health of the newborn. This review article summarizes the current knowledge of these important issues.

Key words: coffee; caffeine; pregnancy

Ginekologia Polska 2022; 93, 7: 591–600

COFFEE — AN OVERVIEW OF THE MOST IMPORTANT INFORMATION

Coffee, next to water, is the second most consumed drink in the world [1]. According to the National Coffee Association USA, about 2.25 billion cups of coffee are consumed worldwide every day. The data of the International Coffee Organization indicate that the inhabitants of the Netherlands consume the most coffee — on average around 8.3 kg/*per capita*/year (data from 2020). In Poland, coffee consumption *per capita* is about 3 kg/year, which is on average 1–2 cups of coffee/day. In the last 10 years, coffee consumption in Poland has increased significantly, by over 80% [2].

In the world, from a commercial point of view, the most important are Arabica coffee (*Coffea arabica*), Robusta coffee (*Coffea canephora*) and Liberian coffee (*Coffea liberica*) [3]. The largest amounts of coffee are produced in Brazil [1]. It is estimated that there are over 1000 chemical compounds in coffee, and the most common ones are phenols (chlorogenic acid and diterpenes: kahweol and cafestol) and alkaloids (caffeine and trigonelline). Less abundant compounds found in coffee include: mannose, galactose polysaccharide chains, melanoidins, flavonoids, catechins, anthocyanins, ferulic acid, caffeic acid, p-coumaric acid, and tocopherols [4].

The composition of coffee depends on many factors, including the type of coffee (*e.g.*, *Coffea Arabica*, *Coffea Canephora*, *Coffea Liberica*), the production method (wet, dry, semi-dry/semi-wet, bio-processing) and the method of preparation (*e.g.*, traditionally brewed coffee, espresso) [1, 5]. Factors before harvest (*e.g.*, sunlight) and after harvest (*e.g.*, the way of processing coffee beans) account for approx. 40% and 60% of the organoleptic, physical and chemical properties of coffee, respectively [1, 5]. Interestingly, due to a different capacity of the "coffee cup", the caffeine content varies depending on the geographic region. In Northern Europe and Great Britain, a cup of coffee contains 140 mg of caffeine, in Southern Europe 50 mg, and in the United States 85 mg [6]. Caffeine is also found in drinks such as

Corresponding author:
Stanisław Surma
Department of Gynecology, Obstetrics and Gynecological Oncology, University Clinical Hospital, Medical University of Silesia, 14 Medykow St, 40–752 Katowice, Poland
e-mail: surma.stanislaw96@gmail.com

Received: 22.05.2022 Accepted: 27.05.2022 Early publication date: 15.06.2022

decaffeinated coffee (small amounts, approx. 0.02 mg/mL), cola, green tea, black tea, and energy drinks [7].

Coffee is a very popular drink all over the world. Consuming coffee, especially brewed with a paper filter and without the addition of sugar or milk, in a regular and moderate manner (2–3 cups/day) has a beneficial effect on human health in the general population. It was shown that consumption of coffee according to such a pattern was characterized by antihypertensive properties and had a positive effect on the activity of the nervous, digestive, cardiovascular and kidney systems [3, 8–11]. In a recent study by Simon et al. [12], including 468,629 subjects, drinking 0.5–3 cups of coffee/day was associated with a lower risk of death from any cause [HR (hazard ratio) = 0.88; 95% CI (confidence interval): 0,83–0.92; $p < 0.001$] and death from cardiovascular causes (HR = 0.83; 95% CI: 0.74–0.94; $p = 0.006$), and stroke (HR = 0.79; 95% CI: 0.63–0.99 $p = 0.037$) during 11 years of follow-up. A number of other studies have also shown that coffee consumption reduces the risk of death from any cause [13].

Thus, consumption of coffee is associated with a number of health benefits in the population dimension, which makes it a very popular drink. However, special attention should be paid to the safety and impact of coffee consumption on a very specific population group, that is pregnant women. This issue is the subject of current discussions and numerous clinical studies. The most significant and recent information on this issue is summarized in the further part of the article.

CONSUMING COFFEE DURING PREGNANCY: RECOMMENDATIONS AND REALITY

The European Food Safety Authority (EFSA) concludes that maternal consumption of up to 200 mg of caffeine per day "is of no concern for fetal safety", and the UK National Health Service (NHS) recommends that women in pregnancy "limit" the daily intake to 200 mg [14, 15]. This amount of caffein is contained in approx. two cups of coffee. Recent studies show that a significant proportion of pregnant women consume more caffeine than allowed by EFSA and the NHS. A study by Lehtonen et al. [16] of 2840 Finnish women in the third trimester of pregnancy showed that 31% of them consumed 200–299 mg of caffeine/day and 10% over 300 mg of caffeine/day. The most common source of caffeine was coffee (81%). The highest amounts of caffeine were consumed by elderly, multiparous, overweight or obese women and smokers. Moreover, the amount of caffeine consumed by the mother correlated with the amount of this compound in the hair of the newborns ($p < 0.001$). Thus, in this study, over 40% of women in the third trimester of pregnancy consumed more or much more of the daily allowable dose of caffeine. A study by Lama et al. [17] assessed caffeine consumption among 724 pregnant French women. Coffee consumption was declared by 47.1% of women. Average daily caffeine consumption has been shown to decrease slightly from the first to third trimester of pregnancy: 587 caffeine users with 59.2 ± 61.5 mg/day caffeine intake in the first trimester compared with 577 users (54.3 ± 55.4 mg/day) in the third trimester, respectively. In a study by Mannucci et al. [18], which included 5,405 pregnant Italians, it was shown that 42.3% of them reported consuming coffee during pregnancy (70% consumed one cup/day, 23% two cups/day, and 6% at least three cups/day). Differences in the amount of caffeine consumed between Finnish and French and Italian women are most likely due to the general pattern of coffee consumption in these countries. A study by Peacock et al. [19] involving 1,232 Australian women assessed adherence to recommendation for caffeine consumption during pregnancy. With regard to the first trimester of pregnancy, the prevalence of coffee consumption depended on awareness of this condition. Among women who were not aware of being pregnant, 89% consumed caffeine in the amount of 107 mg/day (60–147 mg), while among those aware of pregnancy, this percentage was lower and amounted to 68% in the amount of 60 mg/day (40–107 mg). The percentage of women in the second and third trimesters of pregnancy who consumed caffeine was 79% (80 mg/day; 40–107 mg) and 80% (80 mg/day; 40–107 mg), respectively. It is worth noting that the percentage of women who consumed ≥ 200 mg/day of caffeine was 22% (first trimester, unaware pregnancy), 7% (first trimester, conscious pregnancy), 11% (second trimester) and 13% (third trimester). A very high frequency of caffeine consumption by pregnant women was also shown in a study by Alamneh et al. conducted among women in Ethiopia. The consumption of caffeine out of 352 women was declared by 98.2% of them, while the average daily consumption of this substance was 170.5 mg. The consumption of ≥ 300 mg of caffeine/day was declared by 17.6% of the surveyed women. Caffeine was most often consumed by the richest pregnant women and those in the first trimester of pregnancy [20]. In the United States, approximately 70% of women still consume caffeine during pregnancy [21, 22]. It was even reported that some women consumed more than 300–500 mg of caffeine per day during pregnancy [23].

To sum up, the available literature shows that pregnant women frequently consume caffeine during pregnancy (mainly in coffee), while a significant percentage of it exceeds the acceptable daily consumption. This is important due to the negative effect of *in utero* exposure to caffeine that has been described in numerous clinical studies. A recent review of the literature by James indicated that the available data support the conclusion that caffeine consumption during pregnancy is associated with a higher risk of: miscarriage, stillbirth, low birth weight and/or low pregnancy weight, premature birth and/or premature pregnancy, childhood

acute leukemia as well as overweight/obesity later in the life of the child. It has been found that there is no safe dose of caffeine to consume during pregnancy [24].

CAFFEINE METABOLISM DURING PREGNANCY

The metabolism of caffeine and its influence on the function of individual organs and systems depends on many factors. It has been shown that the effect of caffeine on the course of pregnancy and fetal development is highly variable between different women [25]. This variability results mainly from: 1) the ability to metabolize caffeine, which is determined by the activity of CYP1A2 (mono-oxygenase and xanthine oxidase enzymes); 2) interaction of caffeine with cells, mainly related to the sensitivity of ADORA1 and ADORA2A adenosine receptors; and 3) the presence of various factors of fetal or maternal origin modulating the effect of caffein [25].

Cytochrome P450 A1 activity and caffeine metabolism

The rate of caffeine metabolism depends primarily on the activity of CYP1A2, because this enzyme is responsible for 95% of the metabolism of this compound that takes place in the liver [26]. It has been shown that in the case of exposure to the same doses of caffeine, women with higher activity of the enzyme CYP1A2 (rapid caffeine metabolism) were characterized by an increased risk of pregnancy disorders compared to women with lower activity of this enzyme [25]. In women who metabolize caffeine quickly (CYP1A2 AA polymorphism) after coffee consumption, a higher concentration of paraxanthine (the main metabolite of caffeine) was found compared to women who metabolize caffeine more slowly (CYP1A2 AC/CC polymorphisms) [27].

Another very important issue is the influence of pregnancy on the activity of CYP1A2. During pregnancy, the half-life of caffeine is significantly extended up to 18 hours, especially in the third trimester. Several weeks after childbirth, the caffeine metabolism rate normalizes to the baseline state. The prolongation of the half-life of caffeine in the body is related to the decreasing activity of CYP1A2 during pregnancy (Fig. 1) [28].

It has been found that the activity of CYP1A2 decreases in the first to third trimester of pregnancy [28]. In a study by Liang et al. [29], the metabolomic profile of 784 weekly blood samples from 30 pregnant women was analyzed. Five metabolites have been shown to belong to the same pathway of caffeine metabolism. All five metabolites were continuously elevated during pregnancy and caffeine reached levels three times higher at the end of pregnancy than at the beginning. The authors of the study indicate that this increase could have been caused by slower metabolism of caffeine in pregnant women, and not by an increase in coffee consumption. The study by Abduljalil et al. [30] summarized the changes in caffeine metabolism occurring during pregnancy (Tab. 1).

It should also be emphasized that apart from polymorphisms and pregnancy itself, the activity of CYP1A2 is also influenced by other factors, such as smoking and larger amounts of coffee consumed, which increase the activity of this enzyme [9, 25]. Moreover, genetic and environmental

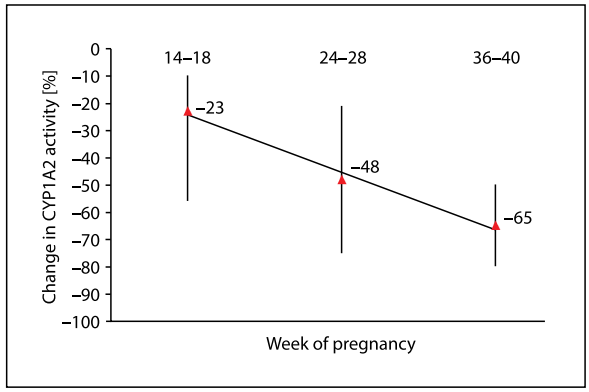

Figure 1. Changes in CYP1A2 activity during pregnancy in humans. Prepared on the basis of [28]

Table 1. Summary of changes in caffeine metabolism during pregnancy

Parameter	Change during pregnancy	Reference
CYP1A2 activity (compared to the level in non-pregnant women)	Progressive reduction throughout pregnancy	[30]
CYP1A2 abundance (µmol CYP1A2/whole liver)	Progressive reduction throughout pregnancy	[30]
Caffeine concentration (mg/L)	Longer lasting increase in blood levels compared with non-pregnant women	[31]
Caffeine half-life (h)	Progressive extension throughout pregnancy	[32, 33]
Caffeine clearance (l/h/kg)	Progressive reduction throughout pregnancy	[33]
Elimination of caffeine from the body (1/h)	Progressive reduction throughout pregnancy	[33]

factors explain only 30–40% of the individual variability in CYP1A2 activity, suggesting the complexity of CYP1A2 regulation, which may involve epigenetic mechanisms [25].

As mentioned, a reduction in the rate of caffeine metabolism leads to a prolonged period of this compound's presence in the mother's body. Caffeine, due to its high lipophilicity, quickly crosses the placental barrier, and since the cytochrome P450 system remains undeveloped until infancy, this compound accumulates in the tissues of the fetus (the placenta is also unable to metabolize caffeine), which is additionally confirmed by the presence of caffeine in its hair (a clear correlation especially in the third trimester of pregnancy) and a high percentage of unchanged caffeine removed (80% in the fetus vs 3–4% in an adult) [33].

Taking into account the significant changes in caffeine metabolism described above, an important question is the safety of coffee consumption in this period for the mother and child. Clinically important are the effects of coffee consumption on fertility, course of pregnancy and the health of the newborn in the short and long term.

POTENTIAL CONSEQUENCES OF MOTHER'S COFFEE CONSUMPTION ON THE COURSE OF PREGNANCY — DATA FROM CLINICAL STUDIES

Fertility

The effects of coffee consumption on fertility have been the subject of numerous clinical studies. It is an important clinical topic as the incidence of fertility disorders in 2017 was 1571.35/100000 women (95% CI: 1115.30–2111.94) and it is increasing year by year [34]. In a meta-analysis of 2 cohort studies by Lyngsø et al. [35], caffeine consumption was not shown to significantly affect time to pregnancy. A more recent meta-analysis of four studies by Bu et al. [36] showed that the consumption of caffeine at a dose of ≤ 100 mg/day, ≥ 200 mg/day, and ≥ 400 mg/day was not significantly associated with the risk of infertility (OR = 0.95; 95% CI: 0.78–1.16, OR = 1.14; 95% CI: 0.69–1.86 and OR = 1.86; 95% CI: 0.28–12.22). Interestingly, a study by Lyngsø et al. [37], involving 1708 Danes undergoing fertility treatment, assessed the effect of coffee consumption on the success of this therapy. It was shown that consumption of coffee by women treated with *in vitro* fertilization and intracytoplasmic sperm injection did not significantly affect the risk of pregnancy and having a live child. However, it was found that consumption of 1–5 cups of coffee/day by women undergoing intrauterine insemination increased the likelihood of becoming pregnant (RR = 1.49; 95% CI: 1.05–2.11) and having a live child (RR = 1.53; 95% CI: 1.06–2.21). No negative influence of coffee consumption on the risk of infertility was also demonstrated by Soylu et al. [38] in a prospective cohort study involving 7,574 Danish women. These investigators concluded, based on a 20-year follow-up, that coffee consumption did not influence the risk of primary infertility (HR = 1.00; 95% CI: 0.97–1.03). In a meta-analysis conducted by Lyngsø et al. no association was found between coffee/caffeine consumption and outcomes of fertility treatment (based on 2 studies). No clear association was found between exposure to coffee/caffeine and natural fertility as measured by fecundability odds ratio (based on 3 studies) [35].

In conclusion, the results of clinical studies and their meta-analyses do not indicate that consumption of coffee increases the risk of infertility.

Pregnancy loss

Bleeding within the first 20 weeks of gestation is one of the most common pregnancy complications (15–20% of ongoing pregnancies) and is an unfavorable prognostic factor, increasing the risk of miscarriage [39, 40]. A cross-sectional analysis by Choi et al. [40], including 3510 Korean women, showed that women up to 35 years of age, consuming ≥ 2 cups of coffee/day, had a significant bleeding risk (adjusted OR = 1.358; 95% CI: 1.050–1.757). Consumption of ≤ 1 cup of coffee/day was not significantly associated with the risk of bleeding (regardless of the age of the pregnant woman).

Spontaneous abortion (SAB), defined as loss of pregnancy naturally before twenty-four weeks of gestation, is a not uncommon clinical problem. In the study by Zhao et al. [41], covering 102,259 pregnant women, it was shown that 14.3% of them experienced SAB. In a prospective cohort study by Gaskins et al. [42], including 15590 pregnant women, it was shown that compared to women who had not consumed coffee before pregnancy, women consuming ≥ 4 cups of coffee/day had 20% (RR = 1.20; 95% CI: 1.06–1.36) higher risk of SAB. Consumption of < 1–3 cups of coffee/day did not significantly affect the risk of SAB. Similar results were obtained by Hahn et al. [43] in a prospective cohort study of 5,132 Danish women planning pregnancy. It has been shown that in the pre-pregnancy period, coffee consumption ≥ 3 cups/day and consumption of up to 2 cups/day in early pregnancy were not significantly associated with SAB risk. A mendelian randomization study by Yuan et al. [44], which included 259,142 women from the UK and Finland, assessed the relationship between coffee consumption and the risk of pregnancy loss taking into account genetic predisposition. It was shown that coffee consumption was not significantly associated with the risk of pregnancy loss (OR = 0.96; 95% CI: 0.87–1.06). In a meta-analysis of 27 studies by Lyngsø et al. [35], compared with no caffeine consumption, the relative risk of SAB was 1.08 (95% CI: 1.03–1.13) for 100 mg caffeine/day, 1.37 (95% CI: 1.19–1.57) for 300 mg caffeine/day and 2.32 (95% CI:

1.62–3.31) for 600 mg caffeine/day. Similar results were obtained in a meta-analysis of 26 studies by Li et al. [45]. The authors showed that caffeine consumption was associated with an increased risk of pregnancy loss (OR = 1.32; 95% 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. The effect of coffee consumption on the risk of pregnancy loss was also assessed by Chen et al. [46] in a meta-analysis of 14 prospective clinical studies. It has been shown that women who consumed ≥ 350 mg/day of caffeine had a significant risk of pregnancy loss (350–699 mg/day, RR = 1.40; 95% CI: 1.16–1.68; ≥ 700 mg/day, RR = 1.72; 95% CI: 1.40–2.13). It was found that for every 100 mg/day increment of caffeine consumption, the risk of SAB was increased by 8% (RR = 1.08; 95% CI: 1.04–1.13) and stillbirth by 9% (RR = 1.09; 95% CI: 1.02–1.16). In a meta-analysis of 2 studies by Ng et al. [47] it was shown that the risk of recurrent pregnancy loss in the group of women with higher caffeine consumption (> 99 mg/day) compared to the group with lower caffeine consumption (< 99 mg/day) was higher, but not statistically significant (OR = 1.35; 95% CI: 0.83–2.19).

The potential mechanisms by which coffee consumption may increase the risk of pregnancy loss are not fully understood. It is indicated that caffeine may reduce blood flow through the placenta, and disrupt the hormonal profile during pregnancy. Caffeine and estradiol are both metabolized by the hepatic enzyme CYP1A2 so a possible pathway for caffeine to interfere with estradiol levels. Moreover, besides caffeine, coffee contains numerous other bioactive substances including lignans and isoflavonoids, both belonging to the phytoestrogen family with great affinity for the estrogen receptor. It should also be mentioned that caffeine may cause chromosomal anomalies (structure of caffeine is similar to that of adenine and guanine, so it might be incorporated into the DNA macromolecule during mitosis) [35, 45].

Thus, the results of clinical studies and meta-analysis indicate that caffeine consumption may increase the risk of pregnancy loss.

METABOLIC DISORDERS

The most common metabolic complications of pregnancy include diabetes mellitus (10.9% in Europe; 95% CI: 10.0–11.8) and hypertension (approx. 4.4%) [48, 49].

In a prospective multicenter cohort study by Hinkle et al. [50], involving 2,583 women, the impact of the consumption of caffeinated beverages on the cardiometabolic profile of pregnant women was assessed. Daily total caffeine consumption was estimated over the period: 10 to 13 weeks of gestation and 16 to 22 weeks of gestation. It has been shown that consumption of caffeinated beverages in the first trimester of pregnancy did not affect the risk of gestational diabetes and gestational hypertension, while in the second trimester it reduced the risk of gestational diabetes (only 1–100 mg caffeine/day; RR = 0.53; 95% CI: 0.35–0.80, up to 200 mg/day — no effect), and did not affect the risk of gestational hypertension. Similar results were obtained in a prospective cohort study of 85533 Japanese women, Kawanishi et al. [51]. These authors showed that the consumption of 2–3 cups of coffee/day was associated with a lower risk of hypertension-related pregnancy disorders (OR = 0.79; 95% CI: 0.62–0.99). It is also worth taking note of the results of the study by Bakker et al. [52], which assessed the influence of coffee consumption on the risk of pre-eclampsia among 7890 pregnant women. It was shown that as compared to women with caffeine intake of < 2 cups/day, those using 2–4 cups/day had a lower risk of pre-eclampsia (OR = 0.63; 95% CI: 0.40–0.96). It is worth mentioning that coffee may reduce the risk of pre-eclampsia by reducing the concentration of lipoprotein (a) in plasma [53].

Thus, studies results do not indicate that coffee consumption increases the risk of metabolic disorders during pregnancy.

PRETERM BIRTH

The incidence of preterm labor is not a rare clinical problem. According to the World Health Organization, the global prevalence of preterm birth is around 5–18%. The prevalence of preterm births is a measure of the level of gynecological and obstetric care in a given country.

In a case-control study by Sindiani et al. [54], involving 1110 pregnant women, the relationship between coffee consumption and the risk of preterm birth was assessed. It was shown that after taking into account numerous risk factors, coffee consumption did not affect the risk of preterm labor (OR = 0.72; 95% CI: 0.40–1.29). In a cohort study by Vitti et al. [55], involving 7,607 Brazilian women, no association was found between high caffeine consumption and risk of preterm birth (RR = 1.03; 95% CI: 0.65–1.63). The results of these studies are confirmed by an earlier meta-analysis by Maslova et al. [56], including 15 cohort and 7 case-control studies. This meta-analysis shows no significant association between caffeine intake during pregnancy and the risk of preterm birth.

Thus, the results of the available literature indicate that coffee consumption is unlikely to influence the risk of preterm birth.

NEWBORN HEALTH

The impact of maternal coffee consumption on the health of the newborn is a very important issue. As al-

ready mentioned, the fetus does not have the ability to metabolize caffeine, and therefore it accumulates in the body. Measuring the caffeine content in a newborn's hair is a good method to assess fetal cumulative caffeine exposure [16]. So far, many studies have been conducted to assess the effects of coffee consumption during pregnancy on the health of the newborn.

Low birth weight and childhood obesity

In a cross-sectional study by Mannucci et al. [57], involving 5,405 pregnant Italian women, the effect of coffee consumption during pregnancy on the birth weight of the newborn was assessed. It was shown that newborns of women who consumed ≥ 3 cups of coffee/day during pregnancy were characterized by significantly lower birth weight (OR = 1.566; 95% CI: 1.081–2.267, p = 0.018). A retrospective study by Oh et al. [58] of 1657 pregnant Korean women also found that consumption of ≥ 2 cups of coffee/day during pregnancy was associated with an increased risk of low birth weight (OR = 1.92; 95% CI: 1.22–3.03). Less pessimistic observations came from a study by Lamy et al. [59], involving 724 pregnant French women. It was shown that the influence of caffeine consumption on anthropometric parameters of the newborn, adjusted for other factors, was statistically insignificant. Similar results were obtained by Wierzejska et al. [60] in a study involving 100 pregnant Polish women. No relationships were found between caffeine intake and neonatal weight, length, or head and chest circumference (p > 0.05). The authors of the study indicate, however, that the amount of caffeine consumed by the studied women was low (only 2% consumed > 200 mg of caffeine/day). Nevertheless, the literature predominates data showing that coffee consumption during pregnancy increases the risk of low birth weight. An interesting multicenter cohort study by Gleason et al. [61], involving 2055 pregnant women, has shown that women who consumed about 50 mg of caffeine/day (~ 1/2 cup of coffee) gave birth to lower birth weight newborn with smaller arms, smaller thighs and a smaller anterior flank skin fold. Moreover, these observations did not differ depending on the genotype of fast or slow caffeine metabolism. The adverse effect of maternal coffee consumption on the child's birth weight is also confirmed by a cross-sectional study by Ferreira et al. [62], involving 260 pregnant Brazilian women. It was found that women who consumed, inter alia, coffee during pregnancy more often gave birth to children with low birth weight (PR = 1.27; 95% CI: 1.11–1.45). In the meta-analysis of 8 cohort and 4 case-control studies conducted by Rhee et al. [63], the impact of coffee consumption on birth weight was summarized. It was shown that the risk of low birth weight, comparing the highest versus lowest level of caffeine intake during pregnancy, was 1.38 (95% CI: 1.10-1.73). Every additional 100 mg of caffeine intake (1 cup of coffee) per day during pregnancy was associated with a 3.0% increase in odds ratio for low birth weight. These observations were confirmed in a more recent meta-analysis of 15 cohort studies by Jin and Qiao, which showed that the risk of low birth weight was 1.33 (95% CI: 1.12–1.57) for mothers with the highest compared with the lowest level of caffeine intake during pregnancy. In the dose-response meta-analysis, this risk was found to be 1.07 (95% CI: 1.02–1.11) for each 100 mg/day increase of caffeine intake [64]. Adverse results were also obtained in the meta-analysis of seven studies by Soltani et al. [65]. Was showed a significant positive association between maternal caffeine intake and the risk of low birth weight (RR = 1.70; 95% CI: 1.19–2.43). Moreover, each additional 100 mg per day of maternal caffeine intake was shown to be significantly associated with an increased risk of low birth weight (RR = 1.12; 95% CI: 1.03–1.22). The results consistent with these observations were also obtained in the meta-analysis of 13 prospective studies by Chen et al. [66].

It should also be mentioned here that the previously cited meta-analysis by Jin and Qiao also found that the risk of childhood overweight and obesity was 1.39 (95% CI: 1.15–1.69) for mothers with the highest compared with the lowest level of caffeine intake during pregnancy. In the dose-response analysis, this risk was 1.31 (95% CI: 1.11–1.55) for each 100 mg/day increase of caffeine intake [64].

The exact pathophysiological mechanisms underlying the above observations are not fully understood. It is indicated that caffeine has been shown to inhibit phosphodiesterase and increase concentration of cyclic adenosine monophosphate in cells which in turn may interfere with fetal cell growth and development. Moreover, caffeine consumption during pregnancy is associated with reduced placental blood flow and hypoxia (A1AR receptor antagonism) that result from the blockage of adenosine receptors, as well as from increased epinephrine concentrations in the mother and in the fetus [65]. *In-utero* caffeine exposure has been linked to abnormal fetal growth through impacting normal development of the fetal hippocampus and the hypothalamic — pituitary — adrenal axis, which may lead to abnormal neuroendocrine changes. Children with low birth weight have a tendency to accumulate intra-abdominal fat mass [64]. Caffeine, a neural stimulant, can alter fetal brain development and impact normal neural transmission, which is important to normal brain function and metabolic processes [64].

Thus, the results of the studies and their meta-analyzes indicate a clinically significant influence of coffee consumption on the risk of low birth weight and childhood obesity.

Table 2. Summary of the safety of coffee consumption for the health of mother and child

Conditions	Consumption of coffee in an amount containing ≤ 200 mg of caffeine per day	
Risk of:	**Probably safe**	**Probably unsafe**
Infertility	X	
Bleeding		X
Pregnancy loss		X
Gestational diabetes	X	
Gestational hypertension	X	
Preeclampsia	X	
Preterm birth	X	
Low birth weight		X
Childhood obesity		X
Childhood acute leukemia		X

Childhood acute leukemia

We cannot fail to mention the reports indicating the influence of coffee consumption during pregnancy on the risk of childhood acute leukemia. A meta-analysis of 12 case-control studies by Thomopoulos et al. [67] found that high maternal coffee consumption was positively associated with acute lymphoblastic leukemia (OR = 1.43, 95% CI: 1.22-1.68) and acute myeloid leukemia (OR = 2.52; 95% CI: 1.59-3.57). Similar observations were made in the meta-analysis of 7 studies by Cheng et al. [68]. These authors found that compared with non/lowest drinkers, the combined odds ratio regarding the relationship of maternal coffee consumption during pregnancy and childhood acute leukemia was 1.22 (95% CI: 1.04–1.43) for ever drinkers, 1.16 (95% CI: 1.00–1.34) for low to moderate-level drinkers, and 1.72 (95% CI: 1.37–2.16) for high-level drinkers [68]. The Childhood Leukemia International Consortium (CLIC) analysis by Milne et al. [69], including 2,552 cases and 4,876 controls showed that the risk of childhood acute lymphoblastic leukemia for > 2 cups/day vs none was 1.27 (95% CI: 1.09–1.43, p = 0.005) [69]. Another CLIC study by Karalexi et al. [70], including 318 cases and 971 controls, also showed a positive association between increasing coffee intake and the risk of acute myeloid leukemia (> 1 cup per day; OR = 1.40; 95% CI: 1.03–1.92, increment of one cup per day; OR = 1.18; 95% CI: 1.01–1.39) [70]. However, it should be emphasized that not all studies have confirmed a relationship between coffee consumption during pregnancy and the risk of childhood acute leukemia. In a cohort study of 96 children by Madsen et al. [71], maternal coffee intake of 0.5–3 cups/day during pregnancy was not associated with a higher risk of childhood acute leukemia (RR = 0.89; 95% CI: 0.48–1.65), however, an intake of > 3 cups/day resulted in insignificant increase of this risk (RR = 1.37; 95% CI: 0.56–3.32) [71].

As in other cases, the mechanism underlying the effect of coffee consumption during pregnancy on the risk of childhood acute leukemia observed in some studies is unclear. It is indicated that high levels of caffeine may inhibit the activity of topoisomerase II, which is involved in gene transcription, DNA recombination, and replication. Moreover, caffeine has the capacity to inhibit some genes, such as the tumor suppressor gene *p53* and ataxia telangiectasia mutated gene which were associated with childhood acute leukemia [68].

Thus, the results of clinical trials and their meta-analyzes indicate that coffee consumption during pregnancy may increase the risk of childhood acute leukemia.

There are also reports that coffee consumption during pregnancy may increase the risk of autism spectrum disorder in offspring [72].

CONCLUSIONS AND LIMITATIONS

This literature review shows that coffee consumption during pregnancy is not completely safe (Tab. 2).

It should be emphasized that even consumption of the amount of coffee containing an acceptable daily dose of caffeine in some studies has turned out to be unsafe.

Of course, it should be remembered that most of the studies were carried out using self-reporting of the amount of coffee consumed during pregnancy, which means that the obtained results could be influenced by recall/respondent bias [73]. These are observational studies, the results of which do not allow for the determination of a cause-and-effect relationship [9]. Another factor limiting the strength of the evidence obtained is the capacity of the cup of coffee and the strength of the brew. What is a cup of coffee? 150 mL or 240 mL… What is a mug of coffee? 240 mL or 300 mL or maybe 360 mL. Similar concerns apply to the "strength of the brew", as well as to additions (*e.g.*, sugar, non-nutritive sweeteners, milk, cream) [9, 73]. An important limitation is also the fact that the influence of other risk factors, such as

smoking (smoking while pregnant increases the risk of childhood acute leukemia, and coffee drinkers are more likely to smoke) has not been analyzed [73]. Publication bias may also influence the obtained results. Despite many confounding factors, the results of clinical studies and their meta-analyzes presented in this paper should be taken seriously.

The authors of this study indicate that patients should certainly be asked about the amount of coffee and other caffeine-rich products consumed during pregnancy. You should actively look for women who clearly consume more caffeine than the currently accepted limit of 200 mg/day. This group of women should be particularly intensively educated and encouraged to reduce caffeine consumption. All women who decide to consume coffee during pregnancy should be educated about the possible risks associated with it. Taking into account the research results cited by us, a revision of the current recommendations regarding the safety of caffeine consumption during pregnancy should be expected.

Conflict of interest

None.

REFERENCES

1. Romualdo GR, Rocha AB, Vinken M, et al. Drinking for protection? Epidemiological and experimental evidence on the beneficial effects of coffee or major coffee compounds against gastrointestinal and liver carcinogenesis. Food Res Int. 2019; 123: 567–589, doi: 10.1016/j.foodres.2019.05.029, indexed in Pubmed: 31285007.
2. Kawa w liczbach - czyli garść statystyk. https://kawa.pl/artykuly/kawa-w-liczbach-czyli-garsc-statystyk/ (14.02.2022).
3. Surma S, Oparil S. Coffee and arterial hypertension. Curr Hypertens Rep. 2021; 23(7): 38, doi: 10.1007/s11906-021-01156-3, indexed in Pubmed: 34370111.
4. Gonzalez de Mejia E, Ramirez-Mares MV. Impact of caffeine and coffee on our health. Trends Endocrinol Metab. 2014; 25(10): 489–492, doi: 10.1016/j.tem.2014.07.003, indexed in Pubmed: 25124982.
5. Wintgens JN. Factors influencing the quality of green coffee. In: Wintgens JN. ed. Coffee: growing, processing, sustainable production. A guidebook for growers, processors, traders and researchers. Factors influencing the quality of green coffee; pp, Weinheim 2009: 797–817.
6. McCusker RR, Goldberger BA, Cone EJ. Caffeine content of specialty coffees. J Anal Toxicol. 2003; 27(7): 520–522, doi: 10.1093/jat/27.7.520, indexed in Pubmed: 14607010.
7. van Dam RM, Hu FB, Willett WC. Coffee, caffeine, and health. N Engl J Med. 2020; 383(4): 369–378, doi: 10.1056/NEJMra1816604, indexed in Pubmed: 32706535.
8. Surma S, Romańczyk M, Fojcik J, et al. Kawa — lekarstwo, używka i narkotyk [article in Polish]. Psychiatria. 2020; 17(4): 237–246, doi: 10.5603/psych.a2020.0031.
9. Surma S, Kokot F. Influence of chronic coffee consumption on the risk of kidney and other organ diseases. Renal Disease and Transplantation Forum. 2022; 15(1): 1–18, doi: 10.5603/RDTF.2021.0015.
10. Surma S, Hyla-Klekot L. Coffee – friend or foe of the kidney? Literature review and clinical studies [article in Polish]. Nephrol Dial Pol. 2021; 25: 70–76.
11. Mazidi M, Dehghan A, Mikhailidis D, et al. The association between coffee and caffeine consumption and renal function: insight from individual-level data, mendelian randomization, and meta-analysis. Arch Med Sci. 2021; 18(4), doi: 10.5114/aoms/144905.
12. Simon J, Fung K, Raisi-Estabragh Z, et al. Light to moderate coffee consumption is associated with lower risk of death: a UK Biobank study. Eur J Prev Cardiol. 2022; 29(6): 982–991, doi: 10.1093/eurjpc/zwac008, indexed in Pubmed: 35048949.
13. Surma S, Banach M. Coffee and caffeine consumption and overall mortality [pre-proof]. Nutrition. 2022: 111747, doi: 10.1016/j.nut.2022.111747.
14. EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies). Scientific Opinion on the safety of caffeine. EFSA Journal. 2015; 13(5): 4102, doi: 10.2903/j.efsa.2015.4102.
15. National Health Service. Foods to avoid in pregnancy. https://www.nhs.uk/common-health-questions/pregnancy/should-i-limit-caffeine-during-pregnancy/ (16.03.2022).
16. Lehtonen A, Uusitalo L, Auriola S, et al. Caffeine content in newborn hair correlates with maternal dietary intake. Eur J Nutr. 2021; 60(1): 193–201, doi: 10.1007/s00394-020-02231-2, indexed in Pubmed: 32246261.
17. Lamy S, Houivet E, Benichou J, et al. Perinatal network of Upper-Normandy. Caffeine use during pregnancy: prevalence of use and newborn consequences in a cohort of French pregnant women. Eur Arch Psychiatry Clin Neurosci. 2021; 271(5): 941–950, doi: 10.1007/s00406-020-01105-2, indexed in Pubmed: 32086556.
18. Mannucci C, Attard E, Calapai F, et al. Coffee intake during pregnancy and neonatal low birth weight: data from a multicenter Italian cross sectional study. J Matern Fetal Neonatal Med. 2020 [Epub ahead of print]: 1–5, doi: 10.1080/14767058.2020.1849120, indexed in Pubmed: 33207986.
19. Peacock A, Hutchinson D, Wilson J, et al. Adherence to the caffeine intake guideline during pregnancy and birth outcomes: a prospective cohort study. Nutrients. 2018; 10(3): 319, doi: 10.3390/nu10030319, indexed in Pubmed: 29518946.
20. Alamneh AA, Endris BS, Gebreyesus SH. Caffeine, alcohol, khat, and tobacco use during pregnancy in Butajira, South Central Ethiopia. PLoS One. 2020; 15(5): e0232712, doi: 10.1371/journal.pone.0232712, indexed in Pubmed: 32384102.
21. Frary CD, Johnson RK, Wang MQ. Food sources and intakes of caffeine in the diets of persons in the United States. J Am Diet Assoc. 2005; 105(1): 110–113, doi: 10.1016/j.jada.2004.10.027, indexed in Pubmed: 15635355.
22. Weng X, Odouli R, Li DK. Maternal caffeine consumption during pregnancy and the risk of miscarriage: a prospective cohort study. Am J Obstet Gynecol. 2008; 198(3): 279.e1–279.e8, doi: 10.1016/j.ajog.2007.10.803, indexed in Pubmed: 18221932.
23. CARE Study Group. Maternal caffeine intake during pregnancy and risk of fetal growth restriction: a large prospective observational study. BMJ. 2008; 337: a2332, doi: 10.1136/bmj.a2332, indexed in Pubmed: 18981029.
24. James JE. Maternal caffeine consumption and pregnancy outcomes: a narrative review with implications for advice to mothers and mothers-to-be. BMJ Evid Based Med. 2021; 26(3): 114–115, doi: 10.1136/bmjebm-2020-111432, indexed in Pubmed: 32843532.
25. Qian J, Chen Qi, Ward SM, et al. Impacts of caffeine during pregnancy. Trends Endocrinol Metab. 2020; 31(3): 218–227, doi: 10.1016/j.tem.2019.11.004, indexed in Pubmed: 31818639.
26. Nehlig A. Interindividual differences in caffeine metabolism and factors driving caffeine consumption. Pharmacol Rev. 2018; 70(2): 384–411, doi: 10.1124/pr.117.014407, indexed in Pubmed: 29514871.
27. Sasaki S, Limpar M, Sata F, et al. Interaction between maternal caffeine intake during pregnancy and CYP1A2 C164A polymorphism affects infant birth size in the Hokkaido study. Pediatr Res. 2017; 82(1): 19–28, doi: 10.1038/pr.2017.70, indexed in Pubmed: 28355205.
28. Tracy TS, Venkataramanan R, Glover DD, et al. National Institute for Child Health and Human Development Network of Maternal-Fetal-Medicine Units. Temporal changes in drug metabolism (CYP1A2, CYP2D6 and CYP3A Activity) during pregnancy. Am J Obstet Gynecol. 2005; 192(2): 633–639, doi: 10.1016/j.ajog.2004.08.030, indexed in Pubmed: 15696014.
29. Liang L, Rasmussen MLH, Piening B, et al. Metabolic dynamics and prediction of gestational age and time to delivery in pregnant women. Cell. 2020; 181(7): 1680–1692.e15, doi: 10.1016/j.cell.2020.05.002, indexed in Pubmed: 32589958.
30. Abduljalil K, Pansari A, Jamei M. Prediction of maternal pharmacokinetics using physiologically based pharmacokinetic models: assessing the impact of the longitudinal changes in the activity of CYP1A2, CYP2D6 and CYP3A4 enzymes during pregnancy. J Pharmacokinet Pharmacodyn. 2020; 47(4): 361–383, doi: 10.1007/s10928-020-09711-2, indexed in Pubmed: 32840724.
31. Brazier JL, Ritter J, Berland M, et al. Pharmacokinetics of caffeine during and after pregnancy. Dev Pharmacol Ther. 1983; 6(5): 315–322, doi: 10.1159/000457332, indexed in Pubmed: 6628163.
32. Knutti R, Rothweiler H, Schlatter C. Effect of pregnancy on the pharmacokinetics of caffeine. Eur J Clin Pharmacol. 1981; 21(2): 121–126, doi: 10.1007/BF00637512, indexed in Pubmed: 7341280.

33. Aldridge A, Bailey J, Neims AH. The disposition of caffeine during and after pregnancy. Semin Perinatol. 1981; 5(4): 310–314, indexed in Pubmed: 7302604.
34. Sun H, Gong TT, Jiang YT, et al. Global, regional, and national prevalence and disability-adjusted life-years for infertility in 195 countries and territories, 1990-2017: results from a global burden of disease study, 2017. Aging (Albany NY). 2019; 11(23): 10952–10991, doi: 10.18632/aging.102497, indexed in Pubmed: 31790362.
35. Lyngsø J, Ramlau-Hansen CH, Bay B, et al. Association between coffee or caffeine consumption and fecundity and fertility: a systematic review and dose-response meta-analysis. Clin Epidemiol. 2017; 9: 699–719, doi: 10.2147/CLEP.S146496, indexed in Pubmed: 29276412.
36. Bu FL, Feng X, Yang XY, et al. Relationship between caffeine intake and infertility: a systematic review of controlled clinical studies. BMC Womens Health. 2020; 20(1): 125, doi: 10.1186/s12905-020-00973-z, indexed in Pubmed: 32546170.
37. Lyngsø J, Kesmodel US, Bay B, et al. Impact of female daily coffee consumption on successful fertility treatment: a Danish cohort study. Fertil Steril. 2019; 112(1): 120–129.e2, doi: 10.1016/j.fertnstert.2019.03.014, indexed in Pubmed: 31043232.
38. Í Soylu L, Jensen A, Juul KE, et al. Coffee, tea and caffeine consumption and risk of primary infertility in women: a Danish cohort study. Acta Obstet Gynecol Scand. 2018; 97(5): 570–576, doi: 10.1111/aogs.13307, indexed in Pubmed: 29364517.
39. Poulose T, Richardson R, Ewings P, et al. Probability of early pregnancy loss in women with vaginal bleeding and a singleton live fetus at ultrasound scan. J Obstet Gynaecol. 2006; 26(8): 782–784, doi: 10.1080/01443610600984412, indexed in Pubmed: 17130030.
40. Choi H, Koo S, Park HY. Maternal coffee intake and the risk of bleeding in early pregnancy: a cross-sectional analysis. BMC Pregnancy Childbirth. 2020; 20(1): 121, doi: 10.1186/s12884-020-2798-1, indexed in Pubmed: 32085746.
41. Zhao Y, Zhao Y, Fan K, et al. Association of history of spontaneous or induced abortion with subsequent risk of gestational diabetes. JAMA Netw Open. 2022; 5(3): e220944, doi: 10.1001/jamanetworkopen.2022.0944, indexed in Pubmed: 35238932.
42. Gaskins AJ, Rich-Edwards JW, Williams PL, et al. Pre-pregnancy caffeine and caffeinated beverage intake and risk of spontaneous abortion. Eur J Nutr. 2018; 57(1): 107–117, doi: 10.1007/s00394-016-1301-2, indexed in Pubmed: 27573467.
43. Hahn KA, Wise LA, Rothman KJ, et al. Caffeine and caffeinated beverage consumption and risk of spontaneous abortion. Hum Reprod. 2015; 30(5): 1246–1255, doi: 10.1093/humrep/dev063, indexed in Pubmed: 25788567.
44. Yuan S, Liu J, Larsson SC. Smoking, alcohol and coffee consumption and pregnancy loss: a Mendelian randomization investigation. Fertil Steril. 2021; 116(4): 1061–1067, doi: 10.1016/j.fertnstert.2021.05.103, indexed in Pubmed: 34187701.
45. Li Ji, Zhao H, Song JM, et al. A meta-analysis of risk of pregnancy loss and caffeine and coffee consumption during pregnancy. Int J Gynaecol Obstet. 2015; 130(2): 116–122, doi: 10.1016/j.ijgo.2015.03.033, indexed in Pubmed: 26026343.
46. Chen LW, Wu Yi, Neelakantan N, et al. Maternal caffeine intake during pregnancy and risk of pregnancy loss: a categorical and dose-response meta-analysis of prospective studies. Public Health Nutr. 2016; 19(7): 1233–1244, doi: 10.1017/S1368980015002463, indexed in Pubmed: 26329421.
47. Ng KYB, Cherian G, Kermack AJ, et al. Systematic review and meta-analysis of female lifestyle factors and risk of recurrent pregnancy loss. Sci Rep. 2021; 11(1): 7081, doi: 10.1038/s41598-021-86445-2, indexed in Pubmed: 33782474.
48. Paulo MS, Abdo NM, Bettencourt-Silva R, et al. Gestational diabetes mellitus in Europe: a systematic review and meta-analysis of prevalence studies. Front Endocrinol (Lausanne). 2021; 12: 691033, doi: 10.3389/fendo.2021.691033, indexed in Pubmed: 34956073.
49. Umesawa M, Kobashi G. Epidemiology of hypertensive disorders in pregnancy: prevalence, risk factors, predictors and prognosis. Hypertens Res. 2017; 40(3): 213–220, doi: 10.1038/hr.2016.126, indexed in Pubmed: 27682655.
50. Umesawa M, Kobashi G. Epidemiology of hypertensive disorders in pregnancy: prevalence, risk factors, predictors and prognosis. Hypertens Res. 2017; 40(3): 213–220, doi: 10.1038/hr.2016.126, indexed in Pubmed: 27682655.
51. Kawanishi Y, Kakigano A, Kimura T, et al. Hypertensive disorders of pregnancy in relation to coffee and tea consumption: the Japan environment and children's study. Nutrients. 2021; 13(2), doi: 10.3390/nu13020343, indexed in Pubmed: 33498916.
52. Bakker R, Steegers EAP, Raat H, et al. Maternal caffeine intake, blood pressure, and the risk of hypertensive complications during pregnancy. The Generation R Study. Am J Hypertens. 2011; 24(4): 421–428, doi: 10.1038/ajh.2010.242, indexed in Pubmed: 21164492.
53. Penson P, Serban MC, Ursoniu S, et al. Lipid and Blood Pressure Meta-analysis Collaboration (LBPMC) Group. Does coffee consumption alter plasma lipoprotein(a) concentrations? A systematic review. Crit Rev Food Sci Nutr. 2018; 58(10): 1706–1714, doi: 10.1080/10408398.2016.1272045, indexed in Pubmed: 28084806.
54. Sindiani AM, Khader Y, Amarin Z. The association between coffee and tea consumption during pregnancy and preterm delivery: case-control study. J Multidiscip Healthc. 2020; 13: 2011–2019, doi: 10.2147/JMDH.S286243, indexed in Pubmed: 33376341.
55. Vitti FP, Grandi C, Cavalli Rd, et al. Association between caffeine consumption in pregnancy and low birth weight and preterm birth in the birth cohort of ribeirão preto. Rev Bras Ginecol Obstet. 2018; 40(12): 749–756, doi: 10.1055/s-0038-1675806, indexed in Pubmed: 30536269.
56. Maslova E, Bhattacharya S, Lin SW, et al. Caffeine consumption during pregnancy and risk of preterm birth: a meta-analysis. Am J Clin Nutr. 2010; 92(5): 1120–1132, doi: 10.3945/ajcn.2010.29789, indexed in Pubmed: 20844077.
57. Mannucci C, Attard E, Calapai F, et al. Coffee intake during pregnancy and neonatal low birth weight: data from a multicenter Italian cross sectional study. J Matern Fetal Neonatal Med. 2020 [Epub ahead of print]: 1–5, doi: 10.1080/14767058.2020.1849120, indexed in Pubmed: 33207986.
58. Oh SS, Park S, You YA, et al. Prenatal exposure to alcohol, tobacco, and coffee: associated congenital complications and adverse birth outcomes. Int J Environ Res Public Health. 2021; 18(6), doi: 10.3390/ijerph18063140, indexed in Pubmed: 33803679.
59. Lamy S, Houivet E, Benichou J, et al. Perinatal network of Upper-Normandy. Caffeine use during pregnancy: prevalence of use and newborn consequences in a cohort of French pregnant women. Eur Arch Psychiatry Clin Neurosci. 2021; 271(5): 941–950, doi: 10.1007/s00406-020-01105-2, indexed in Pubmed: 32086556.
60. Wierzejska R, Jarosz M, Wojda B. Caffeine intake during pregnancy and neonatal anthropometric parameters. Nutrients. 2019; 11(4), doi: 10.3390/nu11040806, indexed in Pubmed: 30970673.
61. Gleason JL, Tekola-Ayele F, Sundaram R, et al. Association between maternal caffeine consumption and metabolism and neonatal anthropometry: a secondary analysis of the NICHD fetal growth studies--singletons. JAMA Netw Open. 2021; 4(3): e213238, doi: 10.1001/jamanetworkopen.2021.3238, indexed in Pubmed: 33764424.
62. Ferreira LB, Lobo CV, do Carmo AS, et al. Dietary patterns during pregnancy and their association with gestational weight gain and anthropometric measurements at birth. Matern Child Health J. 2022; 26(7): 1464–1472, doi: 10.1007/s10995-022-03392-8, indexed in Pubmed: 35195821.
63. Rhee J, Kim R, Kim Y, et al. Maternal caffeine consumption during pregnancy and risk of low birth weight: a dose-response meta-analysis of observational studies. PLoS One. 2015; 10(7): e0132334, doi: 10.1371/journal.pone.0132334, indexed in Pubmed: 26193706.
64. Jin F, Qiao C. Association of maternal caffeine intake during pregnancy with low birth weight, childhood overweight, and obesity: a meta-analysis of cohort studies. Int J Obes (Lond). 2021; 45(2): 279–287, doi: 10.1038/s41366-020-0617-4, indexed in Pubmed: 32518355.
65. Soltani S, Salari-Moghaddam A, Saneei P, et al. Maternal caffeine consumption during pregnancy and risk of low birth weight: a dose-response meta-analysis of cohort studies. Crit Rev Food Sci Nutr. 2021 [Epub ahead of print]: 1–10, doi: 10.1080/10408398.2021.1945532, indexed in Pubmed: 34224282.
66. Chen LW, Wu Yi, Neelakantan N, et al. Maternal caffeine intake during pregnancy and risk of pregnancy loss: a categorical and dose-response meta-analysis of prospective studies. Public Health Nutr. 2016; 19(7): 1233–1244, doi: 10.1017/S1368980015002463, indexed in Pubmed: 26329421.
67. Thomopoulos TP, Ntouvelis E, Diamantaras AA, et al. Maternal and childhood consumption of coffee, tea and cola beverages in association with childhood leukemia: a meta-analysis. Cancer Epidemiol. 2015; 39(6): 1047–1059, doi: 10.1016/j.canep.2015.08.009, indexed in Pubmed: 26329264.
68. Cheng J, Su H, Zhu R, et al. Maternal coffee consumption during pregnancy and risk of childhood acute leukemia: a metaanalysis. Am J Obstet

Gynecol. 2014; 210(2): 151.e1–151.e10, doi: 10.1016/j.ajog.2013.09.026, indexed in Pubmed: 24060443.
69. Milne E, Greenop KR, Petridou E, et al. Maternal consumption of coffee and tea during pregnancy and risk of childhood ALL: a pooled analysis from the childhood Leukemia International Consortium. Cancer Causes Control. 2018; 29(6): 539–550, doi: 10.1007/s10552-018-1024-1, indexed in Pubmed: 29600472.
70. Karalexi MA, Dessypris N, Clavel J, et al. NARECHEM-ST group. Coffee and tea consumption during pregnancy and risk of childhood acute myeloid leukemia: A Childhood Leukemia International Consortium (CLIC) study. Cancer Epidemiol. 2019; 62: 101581, doi: 10.1016/j.canep.2019.101581, indexed in Pubmed: 31416015.
71. Madsen CN, Henriksen TB, Ramlau-Hansen CH, et al. Coffee intake during pregnancy and childhood acute leukemia - A cohort study. Cancer Epidemiol. 2020; 67: 101747, doi: 10.1016/j.canep.2020.101747, indexed in Pubmed: 32526645.
72. Patti MA, Li N, Eliot M, et al. Association between self-reported caffeine intake during pregnancy and social responsiveness scores in childhood: The EARLI and HOME studies. PLoS One. 2021; 16(1): e0245079, doi: 10.1371/journal.pone.0245079, indexed in Pubmed: 33449933.
73. Leviton A. Biases inherent in studies of coffee consumption in early pregnancy and the risks of subsequent events. Nutrients. 2018; 10(9), doi: 10.3390/nu10091152, indexed in Pubmed: 30142937.