Original Research Article

Effects of Caffeine Restriction on Fetal, Neonatal and Pregnancy Outcomes

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Abstract

Background: Caffeine is a stimulant found in tea, coffee, cola, chocolate and some over-the-counter medicines. Clearance of caffeine from the mother's blood slows down during pregnancy. Some authors of observational studies have concluded that caffeine intake is harmful to the fetus, causing growth restriction, reduced birth weight, preterm birth or still birth. The newborn could also have withdrawal symptoms if the mother has a high intake of caffeine (more than eight cups of coffee per day). Drinking three cups of coffee a day in early pregnancy had no effect on birth weight, preterm births or growth restriction. *Aim of the study:* The aim of this study was to assess the effects of restricting caffeine by mothers on fetal, neonatal and pregnancy outcomes. *Subjects and methods: Research Design:* A quasi experimental design was used in conducting this study. *Sample:* A purposive sample composed of 200 pregnant women. The study sample was divided randomly into 2 groups (the control and study group). *Tools:* Two tools were used for data collection which named; interviewing questionnaire and fetal, neonatal and pregnancy outcomes tool. *Main Results:* the current study revealed a relation between caffeine intake and gestational anemia, occurrence of cesarean deliveries, abnormal placental weight, neonatal low birth weight, neonatal apnea and neonatal caffeine withdrawal syndrome. *Conclusion:* Research hypotheses 1 is rejected while 2 and 3 are accepted. *Recommendations:* Preconception counseling for women about correcting the unhealthy habits including caffeine consumption. Women with previous neonatal complications must consider eliminating caffeine.
Keywords: Caffeine, Restriction, Fetal, Neonatal, Pregnancy.

INTRODUCTION

Caffeine is the most commonly used psychoactive substance in the world. It is found in a range of beverages and food, mainly in tea, coffee, cola, chocolate bars and some medications. There has been a concern that maternal consumption of caffeine in pregnancy may be associated with adverse pregnancy outcomes. However, studies investigating antenatal caffeine intake and pregnancy outcomes have had mixed results. Some authors have concluded that caffeine intake is harmful, causing stillbirth and fetal death [1], some that it has no effect [2], and others claim that it is beneficial in reducing the risk of gestational diabetes mellitus (GDM) [3].

Caffeine, a trimethylxanthine alkaloid, is readily available in coffee (containing from 85 to 110 mg/cup), tea (about 50 mg/cup), cola beverages (30 to 45 mg/serving), cocoa (about 5 mg/cup), chocolate (25 mg/small bar), as well as preservatives, analgesics and other pharmaceutical preparations [4]. Caffeine's

primary metabolite, paraxanthine, can pass the placental barrier, exposing the fetus to maternally ingested caffeine. Adenosine is an endogenous modulator of neuronal excitability in mammals' central nervous systems. Paraxanthine antagonises adenosine receptors (A1) in materno-fetal brain and heart inhibit glutamate release in peripheral tissues, which may have a dose-dependent and cumulative adverse effect on the metabolic activity of both mother and fetus [5-7].

Animal studies have shown that chronic caffeine exposure during pregnancy promotes a decrease in adenosine A1 receptors in both maternal and fetal whole brain, which in turn increases stimulatory activities, making the brain and other tissues vulnerable to the harmful effect of caffeine because there is no blood-brain barrier or placental barrier to caffeine [8]. Moreover, clearance of caffeine from the mother's blood slows down during pregnancy and its half life is tripled during the second and third

trimester [9], while the fetus is lacking a sufficient amount of the enzyme needed to metabolize it [10].

Maternal consumption of caffeine may possibly affect the pregnancy at any time throughout intrauterine life. Animal studies suggest that caffeine is teratogenic when administered in large amounts (more than eight cups per day), resulting in congenital anomalies, namely oral cleft and cardiovascular malformation [11-13]. However, so far, current epidemiological evidence is unable to detect appreciable teratogenic effect of caffeine exposure in the human fetus [14]. Excessive maternal caffeine consumption (more than eight cups per day)may result in increased levels of catecholamine in both the mother and fetus which may lead to utero-placental vasoconstriction [15], increased fetal heart rate and arrhythmias (irregularity of heart rate) [16] and, as a consequence, lack of fetal oxygenation. A recent study suggests caffeine impaired insulin sensitivity in women with GDM [17].

Thus, it is theoretically plausible that these effects could adversely affect the pregnancy and increase the risk of miscarriage [18], low birth weight [19, 20] stillbirth [21] and sudden infant death syndrome [22]. The Rondo study suggested that the proportion of mothers who delivered growth restricted babies increased as the average consumption of coffee increased [23]. Moreover, neonatal withdrawal symptoms have been observed as a result of high levels of maternal caffeine intake [24]. However, other investigators have failed to find any association between caffeine intake and poor pregnancy outcomes.

Wen [25] showed that pregnant women who were taking coffee before pregnancy had fewer incidents of spontaneous miscarriage. His population-based prospective study was carried out on a group of 575 women who delivered singleton live births and 75 women who had spontaneous miscarriages. Clausson [26] in his prospective population-based cohort study of 953 women showed that there was no association between caffeine consumption and birth weight, gestational age and birth weight ratio. Another large prospective study of 2291 mothers also showed that caffeine consumption in the first and third trimesters was not associated with intrauterine growth restriction, low birth weight or preterm delivery [19].

Beneficial effects of caffeine intake during pregnancy are reported in some other studies. Moderate prepregnancy coffee consumption may have a protective association with GDM [3]. It has been found that the consumption of coffee increases ventilatory frequency in the general population [27]. A study on rats suggests that caffeine present in drinking fluid of lactating dams (mothers) may prevent ponto-medullary respiratory disturbances [28]. Moreover, the beneficial effect of caffeine has been shown in neonatal rodents.

Caffeine as an adenosine antagonist may prevent brain injures due to lack of oxygen.

Therefore, it is postulated that caffeine administration during early postnatal development may prevent brain injury, which is the most common cause of cerebral palsy and cognitive impairment in premature infants [29].

Conflicting results found in the literature make it difficult for health professionals to advise pregnant women about avoiding caffeine during pregnancy. The significance of this study, therefore, is to investigate the impact of avoidance of maternal consumption of caffeine on pregnancy outcome.

Aim of the Study
The aim of this study was to assess the effects of caffeine restriction by mothers on fetal, neonatal and pregnancy outcomes.

Research Hypotheses
- Mothers of the study group will have positive fetal outcomes compared to those of the control group.
- Mothers of the study group will have positive neonatal outcomes compared to those of the control group.
- Mothers of the study group will have positive pregnancy outcomes compared to those of the control group.

Subject and Methods
Research Design
A quasi experimental design was used in conducting this study [30].

Inclusion criteria of the sample
All recruited subjects were:
- Primigravida
- At their first trimester at the beginning of the study
- Without any pregnancy complications
- Caffeine consumers before pregnancy

Study Setting
This study was conducted at MCH centers and 2 private clinics at Shebin El- Koom; Menoufiya Governorate.

Sample of the Study
A purposive sample was used; the sample recruited in this study consisted of 200 pregnant women. The study sample was divided randomly into 2 groups (the control and study group). The study group: participants who were instructed to prevent caffeine intake during their gestational period. Control group: participants who keep their regular daily caffeine intake.

Data Collection Tools

Throughout the course of the present study; data were collected using two tools which were developed by the researchers and revised by a jury of qualified experts, then tested for validity and reliability. Tools were: interviewing questionnaire and fetal, neonatal and pregnancy outcomes tool.

- *Interviewing questionnaire*: it consisted of closed ended questions about age, history of chronic diseases, menstrual history (e.g, age of menarche, menstrual regularity,…..), data about present pregnancy (e.g, LMP, EDD, fetal condition, …..).

- *Fetal, neonatal and pregnancy outcomes tool*: it consists of three parts including data about: part 1 *fetal outcomes* like: birth weight (g): low birth weight (a fetus that weighs less than 2500 g), regardless of gestational age (assessed at time of birth), very low birth weight which is less than 1500 g, and extremely low birth weight, which is less than 1000 g. Small-for-gestational age (those whose birth weight lies below the 10th percentile for that gestational age, assessed at time of birth). First trimester fetal loss or miscarriage. Stillbirth (delivery of a dead fetus at 28 weeks' gestation or more). Fetal hypoxia. Preterm birth (i.e. the birth of a baby before 37 weeks). Post-term birth (i.e. the birth of a baby after 40 weeks). Part 2 *Neonatal outcomes* like: neonatal caffeine withdrawal syndrome, neonatal apnoea, tachycardia and arrhythmias, sudden infant death syndrome (a syndrome marked by the symptoms of sudden and unexplained death of an apparently healthy infant). Part 3 *Pregnancy outcomes* like: mode of delivery, pregnancy complication including: anemia, hyperemesis gravidarum, gestational diabetes, preterm labor, premature rupture of membrane, pregnancy induced hypertension, intrauterine growth restriction, intrauterine fetal death.

Validity of the Data Collection Tools

The validity of the tools was ascertained by a group of subject area experts who reviewed the tools for content and internal validity. They were also asked to judge the items for completeness and clarity. Suggestions were incorporated into the tools.

Reliability of the Data Collection Tools

Test – retest reliability was applied by the researcher for testing the internal consistency of the tool. It was done through the administration of the same tools to the same participants under similar conditions on two or more occasions. Scores from repeated testing were compared.

Ethical Consideration

Approaches to ensure ethics were considered in the study regarding confidentiality and the informed consent. Confidentiality was achieved by the use of locked sheets with the names of women replaced by numbers. All women were informed that the information they provided during the study would be kept confidential and used only for statistical purpose and after finishing the study, the findings would be presented as a group data with no personal women's information remained.

Pilot Study

Piloting was conducted to test the applicability of the tools, the feasibility of the study and to estimate the time needed for data collection. It was conducted on 10% of the total sample (20 women). On the basis of the pilot study results; the researcher rephrased some questions and sentences then set the final fieldwork schedule.

Data Analysis

Upon completion of data collection, each answer sheet was revised, coded and scored. The researcher coded the data into a coding sheet so that data could be prepared for computer use. Data was statistically analyzed using statistical package for social science (SPSS. IBM, USA, 2012) version 20 on IBM compatible computer. Test of significance was used and level of significance was at p< 0.05 [36].

The following statistical techniques were used: frequencies and percentage, Chi square, Spearman's rho coefficient and correlation analysis.

Frequencies and percentage distribution

Was done to sociodemographic data of participants.

The Chi-square test (χ^2) was used for comparing frequencies or proportions. The test is also referred to as a test of a measure of fit or "goodness of fit" between data.

$$(\chi^2) = \frac{(O-E)^2}{E}$$

Where:

O= observed frequency
E= Expected frequency

T- Test to compare mean scores it was used to test the difference between two means.

Significance of Results

For all the statistical tests done, the threshold of significance is fixed at the 5% level (P value), as follows:

Non – significant difference if   P > 0.05

Significant difference if   P < 0.05

Highly significant difference if   P < 0.001

Procedure and Maneuver of Intervention
The current study was carried out in two consecutive phases, namely preparatory and implementation or data collection phases.

The Preparatory Phase
An extensive review related to the study area was done including electronic dissertations, available books, articles and periodicals. A review of literature to formulate knowledge base relevant to the study area was also done. An official permission was granted from the centers and clinics authorities.

The Implementation or data collection phase
The researchers applied this phase in the following steps:

The 1st step: After determining the sample of the study, the researchers introduced themselves to the pregnant women and provided verbal explanation of the study, answered all related questions, and provided a study packet to each woman. The study packet included a written overview of the study including main sources of caffeine and information detailing how to contact with the researchers for questions or additional information. Women's telephone number and e-mails (if available) were taken to facilitate communication and follow up.

The 2nd step: The researchers met each woman in her next antenatal visit and the interviewing questionnaire was used for collecting data. The study group was informed about caffeine sources and instructed to restrict the intake along the gestational period.

The 3rd step: Weekly and by telephone, researchers followed-up each group to ensure caffeine restriction (by the control group) and regular caffeine consumption (by the control group).

The 4th step: At the 3rd trimester and near term; the researchers completed part I and part 3 from the 2nd data collection tool (fetal outcome and pregnancy outcomes).

The 5th step: At delivery; the researchers completed part 3 from the 2nd data collection tool (neonatal outcomes) then followed-up the infant condition for one month by telephone for detecting sudden infant death syndrome and neonatal caffeine withdrawal syndrome.

RESULTS

Table-1: Sociodemographic Characteristics of the Sample

Variable	Study group (n =100)		Control group (n =100)		Test	P-value
	No	%	No	%		
Age					t	> 0.05
Mean ± SD	25.09±1.56		25.01±2.50		0.1	
Level of education					χ^2	
Illiterate	-	-	-	-	0.2	> 0.05
Basic	2	2	-	-		
Secondary	45	45	41	41		
University	53	53	59	59		
Residence					χ^2	> 0.05
Urban	15	15	10	10	1.1	
Rural	85	85	90	90		
Accommodation					χ^2	> 0.05
With husband family	13	13	9	9	5.0	
Alone	87	87	91	91		
Monthly income					χ^2	> 0.05
Enough	17	17	15	15	0.1	
Not-enough	83	83	85	85		

Table-1 displays the sociodemographic characteristics of the studied sample. It shows that the majority of the sample in both groups was rural residents, and was living alone (away from their husbands' family). There was no statistically significant difference between groups regarding any one of the sociodemographic characteristics.

Table-2: Distribution of the Sample regarding their History of Current Pregnancy

Variable	Study group (n =100)		Control group (n =100)		χ² Test	P-value
	No	%	No	%		
Gestational age at the start of the study					0.0	> 0.05
1st	100	100	100	100		
2nd	0	0	0	0		
3rd	0	0	0	0		
Pregnancy complications at the start of the study					0.0	> 0.05
Yes	0	0	0	0		
No	100	100	100	100		
Follow-up					2.7	> 0.05
MCH	95		91			
Private Clinic	5		9			

Table-2 presents the history of current pregnancy; the table reflects the inclusion criteria of the sample. It is noticed that all women were at their first trimester of pregnancy and were free from any complications; they were also following-up their pregnancy at the MCH center.

Table-3: Distribution of the control group regarding sources and the average daily caffeine intake

Variable	Control group (n =100)	Unit	Caffeine per unit, Mg
Sources of caffeine			
Coffee			
Brewed 0 1-2 3-4	100%	237 mL (1 cup, 8 oz)	135
Instant 0 1-2 3-4	20% 59% 21%	237 mL (1 cup, 8 oz)	76-106
Tea			
Instant 0 1-2 3-4	7% 33% 60%	237 mL (1 cup, 8 oz)	30
Green 0 1-2 3-4	100%	237 mL (1 cup, 8 oz)	15
Soft drinks			
Cola 0 1-2 3-4	16% 83% 1%	355 mL (1 can, 12 oz)	36-46
Diet cola 0 1-2 3-4	100%	355 mL (1 can, 12 oz)	39-50
Cacao products			
Candy (milk chocolate) 0 1-2 3-4	71% 29% 0%	28 g (1 oz)	7
Hot cocoa mix 0 1-2 3-4	100%	237 mL (1 envelope, 8 oz)	5

Amount of caffeine per unit is calculated according to: Food and nutrition. Caffeine in foods. Ottawa, ON: Health Canada; 2012.

Table-3 discusses the main intervention of the study. The table shows that the study group was restricting caffeine intake along the study period.

Table-4: Distribution of the Sample regarding their Pregnancy Outcomes

Variable	Study group (n =100)		Control group (n =100)		χ^2 Test	P-value
	No	%	No	%		
Length of gestation					1.2	> 0.05
Full term pregnancy	98	98	97	97		
Preterm delivery	2	2	3	3		
Pregnancy complication (by the end of gestational period)						
Anemia					14.4	< 0.001*
Yes	27	27	54	54		
No	73	73	46	46		
Hyperemesis gravidarum					0.2	> 0.05
Yes	0	0	1	1		
No	100	100	99	99		
Gestational diabetes					0.4	> 0.05
Yes	1	1	3	3		
No	99	99	97	97		
Pregnancy induced hypertension					2.3	> 0.05
Yes	3	3	9	9		
No	97	97	91	91		
Intrauterine growth restriction					0.0	> 0.05
Yes	0	0	0	0		
No	100	100	100	100		
Intrauterine fetal death					0.4	> 0.05
Yes	0	0	1	1		
No	100	100	99	99		
Premature rupture of membrane					3.2	> 0.05
Yes	1	1	5	5		
No	99	99	95	95		
Type of delivery						
Normal labor	25	25	15	15	11.4	< 0.001*
Cesarean section	75	75	85	85	12.1	< 0.001*

(*) Statistically significant at p<0.001

Table-4 shows one of the main study results; which is the pregnancy outcomes. The table displays that there was a highly statistically significant difference between groups regarding occurrence of anemia and rate of cesarean section. From noticing this table; hypothesis 3 is accepted "Mothers of the study group will have positive pregnancy outcomes compared to those of the control group".

Table-5: Distribution of the Sample regarding their Fetal Outcomes

Variable	Study group (n =100)		Control group (n =100)		χ^2 Test	P-value
	No	%	No	%		
1st trimester fetal loss					2.9	> 0.05
Yes	7	7	12	12		
No	93	93	88	88		
Fetal hypoxia					2.2	> 0.05
Yes	2	2	9	9		
No	98	98	91	91		
Pre-term birth					1.8	> 0.05
Yes	2	2	7	7		
No	98	98	93	93		
Post-term birth						> 0.05
Yes	0	0	0	0	0.0	
No	100	100	100	100		
Still birth						> 0.05
Yes	0	0	0	0	0.0	
No	100	100	100	100		

(*) Statistically significant at p<0.001

Table-5 shows another one of the main study results; which is the fetal outcomes. The table displays that there was no statistically significant difference between groups regarding birth weight. Hypothesis 1 is thus rejected "Mothers of the study group will have positive fetal outcomes compared to those of the control group".

Table-6: Distribution of the Sample regarding their Neonatal Outcomes

Variable	Study group (n =100)		Control group (n =100)		χ² Test	P-value
	No	%	No	%		
Placental weight					13.4	< 0.001*
Normal	94	94	80	80		
Less than normal	3	3	18	18		
More than normal	3	3	2	2		
Neonatal Bbirth weight					12.2	< 0.001*
Low	1	1	12	12		
Small for gestational age	1	1	3	3		
Length of fetus						
40 – 50 cm	100	100	100	100		
Neonatal caffeine withdrawal syndrome					17.3	< 0.001*
Yes	0	0	92	92		
No	100	100	8	8		
Neonatal apnea					11.0	< 0.001*
Yes	3	3	12	12		
No	97	97	88	88		
Tachycardia & arrhythmias					0.4	> 0.05
Yes	1	1	2	2		
No	99	99	98	98		
Sudden infant death syndrome					0.0	> 0.05
Yes	0	0	0	0		
No	100	100	100	100		

(*) Statistically significant at p<0.001

Table-6 shows the fetal outcomes of the studied sample as a main result of the study. The table displays that there was a highly statistically significant difference between groups regarding neonatal caffeine withdrawal syndrome and neonatal apnea. Hypothesis 2 is accepted "Mothers of the study group will have positive neonatal outcomes compared to those of the control group".

DISCUSSION

The current study tried to evaluate the effect of caffeine restriction on pregnancy, fetal and neonatal outcomes. From reviewing literature; there is insufficient evidence to evaluate the effect of caffeine on fetal, neonatal and pregnancy outcomes. The current study showed an association between caffeine intake and pregnancy complications like anemia and outcomes like type of delivery. Some observational studies with cohort study designs and large sample sizes failed to show any association between caffeine intake and poor pregnancy outcomes [19, 26]. Comparative observational studies suggest that caffeine can have a debilitating effect on the natural growth of the fetus, leading to intrauterine growth restriction (IUGR) [23]. The current study findings showed no association between caffeine intake and occurrence of IUGR as one of pregnancy outcomes.

Current findings of fetal outcomes showed no effect of caffeine on the fetus. On contrast Justin C Konje [31] in a large prospective observational study named "Maternal caffeine intake during pregnancy and risk of fetal growth restriction" reported certain fetal complication linked to caffeine intake. He found that average caffeine consumption of >100 mg/day was associated with a reduction in weight of 34-59 g in the first trimester, 24-74 g in the second, and 66-89 g in the third (after adjustment for smoking status and alcohol intake). Similar results were seen by Bracken *et al.*, [32] in a prospective study of 2291 pregnant women in the US, where mean fetal weight was reduced by 28 g for every 100 mg/day of caffeine consumed. In contrast to the current findings; Wisborg [21] who reported that caffeine can result in stillbirth. This difference could be explained by methodological differences in the studies.

The current study showed a decrease in neonatal weight among control group which is linked to caffeine consumption. At the same line a combined analyses of mean birth weigh study results as summarized in a detailed meta-analysis by Iná S. Santos

et al., [33] showed a significant decrease in birth weight of nearly 43g among newborns of the heaviest caffeine-consuming mothers. Comparative observational studies also suggest that caffeine can lead to low birth weight [19].

On contrast, a Danish cohort of 1207 women drinking at least three cups of coffee a day before 20 weeks of pregnancy were randomized to receive either caffeinated or decaffeinated instant coffee: there was no significant difference in birth weight between the two groups after adjustment for parity, gestational age at birth, and smoking [34]**.** However, these women were recruited in the second half of pregnancy, so the effect of first trimester caffeine intake was not assessed, and there was no biochemical confirmation of participants' compliance with caffeinated or decaffeinated coffee consumption.

In addition, Bicalho and Filho [35] reported no association between maternal caffeine consumption and low birth weight after adjusting for confounding variables in a case-control study in Brazil.

The present study assessed placental weight, neonatal caffeine withdrawal syndrome and neonatal apnea as variables of neonatal outcomes and a statistically significant difference between groups was observed. Form reviewing literature; no studies examined caffeine effect on neonatal outcomes had tested those items.

CONCLUSION

In the light of the current study findings, it can be concluded that research hypotheses 1 is rejected while 2 and 3 are accepted:

Research hypothesis 1 Mothers of the study group will have positive fetal outcomes compared to those of the control group. The study findings revealed no difference between groups regarding fetal outcomes items.

Research hypothesis 2 Mothers of the study group will have positive neonatal outcomes compared to those of the control group.

Research hypothesis 3 Mothers of the study group will have positive pregnancy outcomes compared to those of the control group.

RECOMMENDATIONS

In the light of the foregoing study results, the following recommendations are proposed: Preconception counseling for women about correcting the unhealthy habits including caffeine consumption.

Women with previous neonatal complications must consider eliminating caffeine containing beverages from their diet during gestation.

Women who are caffeine consumers can gradually substitute their regular beverages with non-caffeinated ones that taste just like regular beverages.

This area of research needs additional efforts in order to expand the evidence base on the association between caffeine and fetal, neonatal and pregnancy outcomes.

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