Received: 26 April 2022 | Revised: 28 July 2022 | Accepted: 29 July 2022

DOI: 10.1111/aogs.14439

ORIGINAL RESEARCH ARTICLE

Intrauterine cannabis exposure and fetal and maternal blood flow: a case–control study

Maia Brik[1] | Miguel Sandonis[2,3] | Judit Gil[1] | Alina Hernandez-Fleury[1] | Gemma Parramón-Puig[2] | Nerea Maiz[1] | Anna Suy[1] | Elena Carreras[1]

[1]Obstetrics Department, Maternal-Fetal Medicine Unit, Hospital Universitari Vall d'Hebron, Barcelona, Spain

[2]Psychiatry Department, Hospital Universitari Vall d'Hebron, Barcelona, Spain

[3]Department of Psychiatry and Forensic Medicine, Universitat Autònoma de Barcelona, Barcelona, Catalonia, Spain

Correspondence
Maia Brik, Maternal and Fetal Medicine Research Group, Hospital Universitari Vall d'Hebron, Passeig de la Vall d´Hebron 119 08035, Barcelona, Spain.
Email: maia.brik@vallhebron.cat

Abstract

Introduction: Cannabis consumption during pregnancy increases the risk of pregnancy and neonatal complications. Since the underlying mechanism is unknown, the purpose of this study is to evaluate the changes in maternal and fetal blood flow in pregnancies exposed to cannabis, Δ9-tetrahydrocannabinol (THC).

Material and methods: A case–control study between 2013 and 2020, included women with continued cannabis exposure during the pregnancies, defined by qualitative detection of THC in urine (Cannabis Group), and low-risk pregnancy women divided into tobacco smokers (Tobacco Group), and non-tobacco smokers (Control Group). We evaluated the association between cannabis consumption and maternal and fetal blood flow parameters measured by Doppler ultrasound: uterine artery at 11–14, 20–22 and 33–35 weeks, umbilical artery and middle cerebral artery at 33–35 weeks. Cerebral-placental ratio was calculated.

Results: Overall, 275 participants were included, 60 in the Cannabis Group, 17 in the Tobacco Group and 198 in the Control Group. At 33–35 weeks, differences were found in the umbilical artery pulsatility index (PI) (1.05 ± 0.23, 1.06 ± 0.19, 0.93 ± 0.15, $P < 0.01$), middle cerebral artery PI (1.75 ± 0.35, 1.90 ± 0.45, 1.88 ± 0.34, $P < 0.05$), cerebral-placental ratio (1.69 ± 0.40, 1.85 ± 0.53, 2.07 ± 0.47, $P < 0.05$) and mean uterine artery PI (0.89 ± 0.26, 0.73 ± 0.19, 0.74 ± 0.20, $P < 0.01$), respectively. On logistic regression analysis, adjusted for maternal age, maternal body mass index, maternal weight and white ethnicity, both cannabis and tobacco were predictors for increased umbilical artery PI, but only cannabis was a predictor for a decreased cerebral-placental ratio and an increased uterine artery PI at 33–35 weeks.

Conclusions: Data from a large cohort of continuous cannabis exposure pregnancies show that cannabis is associated with maternal and fetal blood flow changes. However, it is not possible to disentangle the association of the tobacco and cannabis.

KEYWORDS

cannabis, Doppler, drugs, fetal blood flow, pregnancy, uterine artery, Δ9-tetrahydrocannabinol

Abbreviations: CPR, cerebral-placental ratio; MCA, middle cerebral artery; PI, pulsatility index; THC, Δ9-tetrahydrocannabinol; Umb Art, umbilical artery; Ut Art, uterine artery.

1 | INTRODUCTION

Cannabis is the most commonly used illicit drug among general and pregnant populations. The prevalence of consumption during pregnancy is around 4.5%.[1] Cannabis consumption during pregnancy increases the risk of maternal, fetal and neonatal complications such as fetal growth restriction or preterm birth and is, later in life, associated with poor neurodevelopmental outcomes in the infants.[2–4] Nevertheless, the mechanisms underlying these effects are still unknown.

Exogenous cannabis such as Δ9-tetrahydrocannabinol (THC) and its metabolites freely pass the placental barrier and act over the two cannabinoid-receptors identified: CB1-receptor, highly expressed in the brain, but also in the peripheral tissues, and CB2-receptor, predominantly expressed in immune and hematopoietic cells, but also in the heart and endothelial cells of various origins.[5] Endogenous cannabinoid system plays an important role in cardiovascular regulation, and exogenous cannabinoid such as THC, acting via endogenous cannabinoid receptor, shows a cardiovascular effect similar to the endogenous cannabinoid. They reduce the tone of the blood vessel with a decrease in blood pressure and increased vascular flow.[6]

THC is consumed mixed with tobacco most of the time, and it is difficult to determine the isolated effect of cannabis in the placental and fetal vascular system. It has been reported that nicotine exposure during pregnancy impairs the uterine vascular function, leading to an increased vascular resistance and a decrease in uterine blood flow.[7] Few studies have focused on the cannabis vascular adaptations during pregnancy. It has been suggested that cannabis use during pregnancy is indeed associated with adaptations in fetal placental and cardiac blood flow, but not with cerebral blood flow.[8] However, the maternal and fetal hemodynamic changes related to cannabis exposure during the pregnancy need to be investigated further. Therefore, this study aims to analyze the changes in maternal and fetal blood flow through the pregnancy, in pregnancies exposed to cannabis, for a better understanding of the physiopathology of the cannabis effect.

Key message

Cannabis consumption during pregnancy is associated with maternal and fetal blood flow changes. However, it is not possible to disentangle the association of tobacco and cannabis.

2 | MATERIAL AND METHODS

A case–control study over an 8-year period, from January 2013 to December 2020, was performed. Women consuming cannabis during pregnancy, and having a follow-up and birth at Hospital Universitari de Vall d'Hebron (Barcelona), were included in the study.

2.1 | Continued cannabis use group

Women with cannabis use disorder were included if they had a positive urine test for THC in the first trimester, and in the third trimester or peripartum. Qualitative detection of THC in human urine, using enzyme immunoassay to analyze its main inactive metabolite 11-nor-carboxi-delta9-THC (THC-COOH), was performed, after self-report of cannabis consumption. Participants in this group were checked routinely to assess the cannabis consumption by urine analysis in all three trimesters of pregnancy using enzyme immunoassay.

The local antenatal care protocol includes a routinely check on drug abuse. If women confirm drug abuse during the routine medical anamnesis, they are referred to a hospital-based perinatal mental health specialized unit, where, after consent, a urine analysis for the detection of drugs is performed.

2.2 | Control group

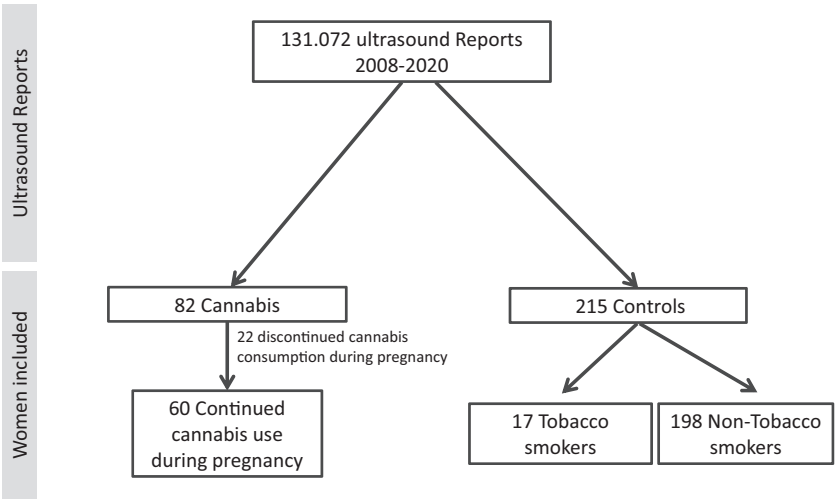
Participants in the control group were selected from the ultrasound database (Viewpoint) and only included women with low-risk pregnancies. Women with prenatal risk factors, fetal growth restriction, diagnosis of hypertension, diabetes, multiple pregnancies and congenital abnormalities were excluded. The rationale for excluding these women was that the objective of the study was to analyze the effect of cannabis on the vascular system, and therefore a priori women with high risk of complications may have an altered vascular system. This group was divided into tobacco smokers during pregnancy group and control group, according to tobacco smoking after the first trimester of pregnancy. Women consuming other drugs (cocaine, opioids, alcohol, etc.) tested by urine analysis and or self-reported, were excluded in order to isolate the effect of cannabis in all the study groups.

All women included in the study were followed up at the hospital antenatal clinics, and delivered at Vall d'Hebron Hospital. Antenatal care of women included three scans during pregnancy: in the first trimester (performed at 11 to 13+6 weeks), second trimester (performed at 20–22 weeks) and third trimester (performed at 33–35 weeks). The local routine antenatal care in most of the cases includes the third trimester scan performed in the primary health care centers; as it was not possible to obtain ultrasound data for these women for the study purposes, they therefore were excluded.

For the cannabis group, any scan performed within these periods of pregnancy was included, whereas in the other groups all three scans were performed during the pregnancy in the hospital. Fetal Doppler assessments were performed using a Voluson S10 (GE Healthcare; Zipf, Austria) ultrasound machine with convex transducer (RAB6-RS) at every scheduled antenatal appointment. Pulsed-wave Doppler ultrasound was used for the maternal and fetal vascular variables.

The following demographic variables were recorded: maternal age, maternal weight before pregnancy, body mass index, ethnicity

FIGURE 1 Flow diagram.



(caucasian vs non-caucasian), cigarette smoking during pregnancy (yes or no), parity (parous or multiparous, according to previous delivery at ≥24 weeks' gestation), and gestational age in weeks and days from the last menstrual period calculated according to the first trimester ultrasound. Birthweight at delivery was recorded in grams.

Main outcomes were feto-placental blood flow during pregnancy. Uterine artery (Ut Art) pulsatility index (PI) was assessed at the 11–14, 20–22 and 33–35-week scans. Mean Ut Art PI was calculated (Right Ut Art PI + Left Ut Art PI/2). At the 33–35-week scan, the umbilical artery (Umb Art) PI and middle cerebral artery (MCA) PI were measured. Cerebral-placental ratio (CPR) was calculated (MCA PI/ Umb Art PI). Estimated fetal growth was assessed at the 33–35-week scan using Hadlock IV formula including femur length, head, abdominal circumference and biparietal diameter. The outcomes Ut Art PI, MCA PI, Umb Art and CPR were normalized according to gestational age by multiples of the median.[9,10] The proportion of fetuses with Umb Art and Ut Art PI values >95th centile, and of MCA PI and CPR <5th centile in each group was calculated.[9,10]

2.3 | Bias

Women abusing other drugs were excluded for analysis purposes, since they were potential confounders. It was not possible to differentiate the effect of cannabis from that of tobacco in the cannabis group, since most women consuming cannabis mixed it with tobacco. However, as there is a group of only tobacco-smokers, it was possible to approximate the isolated cannabis effect.

2.4 | Statistical analyses

Mothers were categorized in three groups: (1) continued cannabis use ($n = 60$), (2) tobacco smokers during pregnancy ($n = 17$), and (3) controls ($n = 198$).

A descriptive analysis was performed using median (interquartile range) for continuous variables, and frequency and percentage for categorical variables. A Chi-square analysis for proportions and analysis of variance (ANOVA) for continuous data were used to determine differences between the study groups. Scheffé's method was used for multiple comparisons. When a difference was detected, a multivariate regression analysis was performed to determine whether cannabis and tobacco use were independently associated with these blood flow parameters. We adjusted for maternal age, maternal body mass index, maternal weight and white ethnicity.

Analysis of repeated measures with a mixed-effects linear model (fixed effects and random effects) was performed for Ut Art PI. The fixed effect component included up to second-order polynomial terms of gestational age, group (control, tobacco or cannabis) and first-order interaction between gestational age and each group. The random effect component includes the intercept as well as linear effects of gestational age.

SPSS 23.0 and "R" packages were used for calculations. $P < 0.005$ was considered statistically significant.

2.5 | Ethics statement

The study was approved by the Local Research Ethics Committee (Ethics Committee of Vall d'Hebron Institute of Research; reference number PR[AMI]204/2021) on May 5, 2021. Patient consent was waived.

3 | RESULTS

3.1 | Participants

A total of 131 072 scan reports were analyzed for the selection of the cannabis, tobacco and control cases. A total of 275 participants were included in the study, 60 in the continued cannabis use group, 17 in the tobacco smokers group and 198 in the control group. The flow diagram is shown in Figure 1.

3.2 | Descriptive data

A one-way analysis of variance was conducted to evaluate the null hypothesis that there were no differences among the three study groups in maternal characteristics including maternal age, body mass index, maternal weight, white ethnicity and parity (Table 1). Women in the cannabis group were younger than women in the control group (28.5 ± 5.21 vs 30.7 ± 4.2 years, $P = 0.001$).

3.3 | Outcome data

Table 2 shows the result of the fetal and maternal Doppler measurements in the study groups. One-way ANOVA was performed and differences were found in the MCA PI and CPR at 33–35 weeks, showing lower results in the cannabis group than in the control group (1.75 ± 0.35 vs 1.88 ± 0.34, $P < 0.05$; 1.69 ± 0.40 vs 2.07 ± 0.47, $P < 0.05$, respectively). Umb Art Doppler PI at 33–35 weeks showed higher results in both the cannabis group and tobacco group compared with the control group (1.05 ± 0.23, 1.06 ± 0.19, 0.93 ± 0.15, $P < 0.01$, respectively).

At the 11–14 and 20–22-week scans, no differences were found in the Mean Ut Art PI among all three study groups, but at 33–35 weeks, the cannabis group women showed higher levels compared with the control group women (0.89 ± 0.26 vs 0.74 ± 0.20, $P < 0.01$, respectively). The tobacco group showed lower levels compared with the control group (0.73 ± 0.19 vs 0.74 ± 0.20; $P < 0.01$). In addition, the tobacco smokers group showed lower Mean Ut Art PI compared with the cannabis group (0.73 ± 0.19 vs 0.89 ± 0.26, $P < 0.01$; Figure 2).

3.4 | Main results

A multivariate regression analysis was performed to determine whether cannabis and tobacco use were independently associated with the blood flow parameters that showed differences among groups in the previous ANOVA.

We adjusted for maternal age, maternal body mass index, maternal weight and white ethnicity since they can increase the risk for fetal growth restriction with affected maternal and fetal Doppler parameters. This analysis showed that the both cannabis and tobacco were predictors for Umb Art PI, but only cannabis was a predictor for CPR (coef. −0.476, 95% confidence interval [CI] −0.225 to −0.097, $P < 0.001$), and Mean Ut Art PI (coef. 0.092, 95% CI 0.013–0.131, $P = 0.017$) in the 33–35-week scan (Table 3).

A longitudinal analysis of Ut ArtPI was performed and a quadratic decrease in Ut Art PI with gestational age was found. Although in cannabis and tobacco consumers, Ut Art PI did not differ significantly from the control group, there was a significant interaction between gestational age and cannabis, with higher Ut Art PI towards the third trimester in the cannabis group than in the control group (Figure 2, Table 4).

4 | DISCUSSION

The aim of this study was to analyze the changes in maternal and fetal blood flow through the pregnancy, in pregnancies exposed to cannabis. The main findings of this study are, first, that cannabis exposure during pregnancy is associated with a vascular effect on the fetal and maternal blood flow that is evident from the third trimester. Secondly, the effect of a continued cannabis exposure during pregnancy resulted in a higher Ut Art pulsatility index, which is independent of the tobacco effect. Thirdly, cannabis is associated with an increase of the Umb Art pulsatility, and a decrease in the MCA pulsatility.

The main strengths of the present study are the sample size, the classification of women in the cannabis group according to biological sample (measured in the first and third trimesters—peripartum) and the exclusion of other drug consumption. This study represents the first study that includes at least 60 women consuming cannabis during pregnancy to study maternal and fetal vascular adaptations.

TABLE 1 Maternal demographics according to the study group ($n = 275$)

	Continued cannabis ($n = 60$)	Tobacco smokers ($n = 17$)	Control ($n = 198$)	P
Maternal age, years[a]	28.5 ± 5.21 (27.7–29.3)	31.2 ± 3.4 (30.2 ± 32.1)	30.7 ± 4.2 (30.3 ± 31.1)	0.001
Body mass index (BMI)[a]	23.2 ± 6.4 (22.2–24.2)	22.8 ± 2.1 (22.2–23.4)	23.2 ± 2.6 (23.03–23.4)	0.760
Nulliparous[b]	22/39.3 (26.0–52.4)	8/47.1 (20.6–73.5)	94/55 (47.4–62.5)	0.118
Ethnicity[b]				
Caucasian	53/88.4 (88–97)	17/100 –	167/84.3 (79–89)	0.332
Maternal tobacco use at first trimester (%)	–	17/100	–	0.001

[a]Mean ± standard deviation (IQR).

[b]Number/frequency (95% confidence interval).

TABLE 2 Feto-placental blood flow characteristics according to study group

	Continued cannabis ($n = 60$)	Tobacco smokers ($n = 17$)	Control ($n = 198$)
Umbilical artery			
33–35 weeks' assessment	33.93 ± 1.25	33.76 ± 0.90	34.24 ± 1.04
Umbilical artery PI	1.05 ± 0.23*	1.06 ± 0.19	0.93 ± 0.15
Umbilical artery MoMs	1.138 ± 0.25*	1.142 ± 0.20*	1.014 ± 0.16
Umbilical artery PI >95th centile	16/63 (25.4%)*	2/17(11.8%)	4/193(2.0%)
Scans included	63	17	193
Middle cerebral artery			
33–35 weeks' assessment	33.93 ± 1.25	33.76 ± 0.90	34.24 ± 1.04
Middle cerebral artery PI	1.75 ± 0.35**	1.90 ± 0.45	1.88 ± 0.34
Middle cerebral artery PI MoMs	0.957 ± 0.19**	1.023 ± 0.23	1.030 ± 0.18
Middle cerebral artery PI <5th centile	8/57 (14%)**	3/17 (17.6%)**	10/182 (5.5%)
Scans included	57	17	182
Cerebral placental ratio			
33–35 weeks' assessment			
Cerebral placental ratio	1.69 ± 0.40*	1.85 ± 0.53	2.07 ± 0.47
Cerebral placental ratio MoM	0.855 ± 0.20*	0.929 ± 0.26	1.042 ± 0.24
Cerebral placental ratio <5th centile	9/53 (16.9%)**	2/17 (11.8%)	6/174 (3.4%)
Scans included	53	17	174
Uterine arteries			
11–14 weeks' assessment	11.93 ± 0.75	11.94 ± 0.42	12.16 ± 0.74
Right uterine artery PI	1.72 ± 0.54	1.54 ± 0.49	1.75 ± 0.66
Left uterine artery PI	1.83 ± 0.57	1.63 ± 0.48	1.80 ± 0.59
Mean uterine arteries PI	1.77 ± 0.48	1.59 ± 0.41	1.77 ± 0.53
Mean uterine arteries PI MoMs	1.046 ± 0.27	0.942 ± 0.24	1.069 ± 0.32
Mean uterine artery PI >95th centile	1/43 (2.3%)	0 (0%)	20/186 (10.7%)
Scans included Missing data	42	17	186
20–24 weeks' assessment	20.95 ± 1.69*	20.29 ± 0.68	20.17 ± 0.61
Right uterine artery PI	0.98 ± 0.38	0.87 ± 0.24	0.98 ± 0.34
Left uterine artery PI	0.97 ± 0.36	1.02 ± 0.42	0.98 ± 0.32
Mean uterine arteries PI	0.98 ± 0.31	0.95 ± 0.28	0.98 ± 0.27
Mean uterine arteries PI MoMs	0.930 ± 0.31	0.876 ± 0.25	0.906 ± 0.25
Mean uterine artery PI >95th centile	2/53 (3.7%)**	0 (0%)	5/196 (2.6%)
Scans included	53	17	196
33–35 weeks' assessment	33.93 ± 1.25	33.76 ± 0.90	34.24 ± 1.04
Right uterine artery PI	0.91 ± 0.43*	0.67 ± 0.24	0.74 ± 0.26
Left uterine artery PI	0.86 ± 0.29*	0.79 ± 0.21	0.75 ± 0.25
Mean uterine artery PI	0.89 ± 0.26*	0.73 ± 0.19*	0.74 ± 0.20
Mean uterine artery PI MoMs	1.270 ± 0.37*	1.042 ± 0.26*	1.070 ± 0.29
Mean uterine artery PI >95th centile	12/53 (22.6%)	1/15 (6.6%)	14/161 (8.7%)
Scans included	52	15	161
EFW at 33–35 weeks	2107 ± 360*	2222 ± 294	2407 ± 300
Gender, percentage of boys	31 (49.2%)	8 (47.5%)	97 (49.5%)
Gestational age at birth	37.3 ± 1.4*	38.5 ± 1.5	38.9 ± 1.3
Birthweight	2556 ± 533*	3035 ± 569	3288 ± 438

Note: *$P < 0.01$, **$P < 0.05$, compared with the control group.

Abbreviations: EFW, estimated fetal weight; MoM, multiples of the median; PI, pulsatility index.

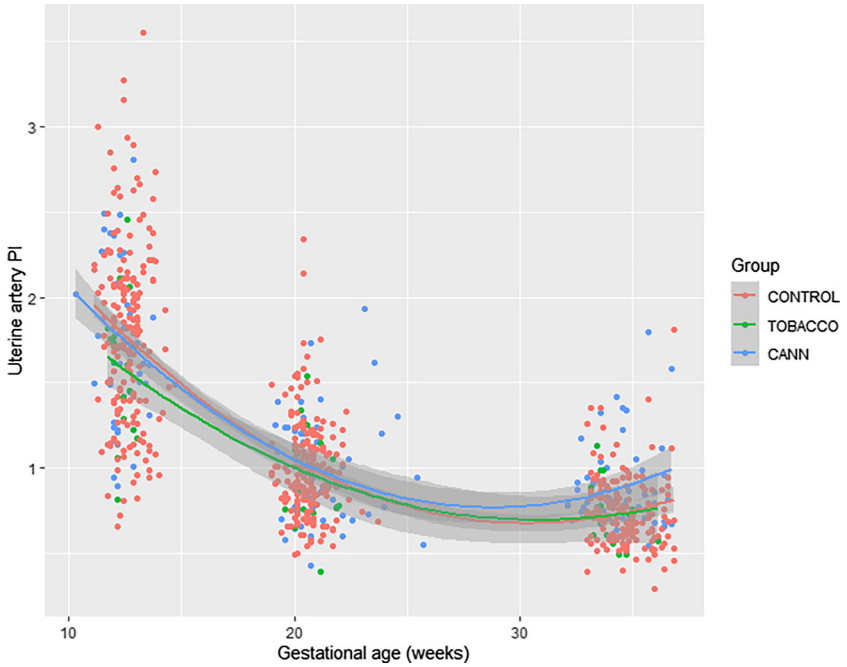


FIGURE 2 Longitudinal changes of the mean uterine artery pulsatility index (PI) during pregnancy according to study group.

TABLE 3 Multivariable logistic regression analysis of maternal-fetal Doppler

	Umbilical artery PI MoM 33–35 weeks			CPR MoM 33–35 weeks		
	Coefficient	95% CI	*P*	Coefficient	95% CI	*P*
Cannabis	0.273	0.072–0.187	0.000	−0.476	−0.225 to −0.097	0.000
Tobacco	0.152	0.028–0.220	0.011	−0.116	−0.232 to 0.008	0.067
Maternal weight	−0.033	−0.004 to 0.003	0.741	−0.552	−0.006 to 0.004	0.582
BMI	0.013	−0.009 to 0.011	0.898	−0.139	−0.015 to 0.013	0.890
Maternal age	−0.067	−0.008 to 0.002	0.278	0.064	−0.003 to 0.010	0.329
White	0.061	−0.033 to 0.103	0.313	−0.060	−0.130 to 0.047	0.355
	MCA MoM 33–35 weeks			Mean uterine artery PI MoM 33–35 weeks		
	Coefficient	95% CI	*P*	Coefficient	95% CI	*P*
Cannabis	−0.129	−1.117 to 0.002	0.058	0.092	0.013 to −0.131	0.017
Tobacco	−0.013	−0.102 to 0.084	0.843	−0.045	−0.148 to 0.036	0.231
Maternal weight	−0.099	−0.006 to 0.002	0.276	−0.068	−0.007 to 0.002	0.354
BMI	0.041	−0.008 to 0.002	0.661	0.086	−0.005 to 0.021	0.245
Maternal age	−0.001	−0.005 to 0.005	0.987	−0.066	−0.009 to 0.001	0.085
Caucasian	−0.004	−0.070 to 0.066	0.954	−0.031	−0.099 to 0.041	0.412

Abbreviations: BMI, body mass index; CPR, cerebral-placental ratio; MCA, middle cerebral artery; MoM, multiples of the median; PI, pulsatility index.

The main limitations are overestimation due to misclassification, since women in the control group were not checked for cannabis consumption in biological sample like the ones in the cannabis group, and the retrospective study design. To improve the quality of cannabis use data, a 2-step approach starting with self-report, and whether positive urine analysis should be used.[11] On the other hand, in the cannabis group, some factors about cannabis such as frequency of consumption or levels of Δ9-tetrahydrocannabinol in cannabis products were not recorded; only women consuming during the whole pregnancy, and not just during the first trimester, were included.

Furthermore, the fact that the women included in the cannabis group were younger could represent a bias. However, maternal age is not a factor that affects Doppler measurements, and this was shown in the multivariate regression analysis.

Since the cannabis active ingredient Δ-9-tetrahydrocannabinol (THC) readily crosses the placenta, and studies have demonstrated expression of cannabinoid receptors in fetal brain and placenta,[12,13] there is concern about adverse fetal outcomes. Maternal cannabis use has been associated with fetal growth restriction, preterm birth and fetal neurodevelopmental consequences.[2,14]

TABLE 4 Fixed effects in the prediction of mean uterine artery pulsatility index

Fixed part	Estimate	SE	*P*
Intercept	3.870	0.098	<0.001
Gestational age (weeks)	−0.210	0.008	<0.001
Gestational age (weeks)^2	0.003	0.000	<0.001
Tobacco	−0.219	0.170	0.196
Cannabis	−0.197	0.116	0.091
Interaction between GA and tobacco	0.007	0.006	0.186
Interaction between GA and cannabis	0.009	0.004	0.015

The long-term effects of cannabis consumption in pregnancy, during the childhood, can be due to environmental factors, since maternal cannabis use can be associated with other multiple unfavorable characteristics.[15] In addition, there could also be a physiological effect, such as the regulation of the cardiovascular system, on the mother and the fetus. This study shows that cannabis has an effect that can be evident during the third trimester on the maternal and fetal vascular systems.

Few studies have analyzed changes on the blood flow measured by Doppler ultrasound in regard to cannabis consumption during pregnancy.[8,16] Prenatal continued cannabis exposure was associated with changes in the hemodynamic programming of the vascular system of the fetus in late pregnancy, mainly due to tobacco exposure, but intrauterine cannabis exposure did demonstrate a specific effect on the uterine blood flow.[8] This study, including only nine women with continued cannabis use, showed an increase of the Ut Art PI in the third trimester. Another study reported an increase in the Umb Art systolic to diastolic ratios in the second and third trimesters, reflecting an impaired fetal growth and increased placental vascular resistance.[16] These results agree with our study results and may indicate an increased placental resistance during pregnancy leading to placental insufficiency, which is one of the causes of fetal growth restriction. This may be an important aspect of the pathophysiology, which explains the association between daily cannabis use and fetal growth restriction.[17] The main differences with our study are that we included Ut Art Doppler in the first and second trimesters, but results were similar among the study groups, leading to the conclusion that the vascular effect of cannabis on the uterine arteries is evident from the third trimester of pregnancy but not early in the pregnancy. In addition, as opposed to the El Marroun[8] study, our study resulted in a decrease in the MCA pulsatility and CPR in the cannabis group. The rationale for this discrepancy could be the lower sample size in the continuous cannabis exposure group of that study, and the fact that they included cannabis case based on self-report rather than on biological samples, as used in our study.

Animal studies have shown that cannabis receptors are expressed in placental tissues in early pregnancy.[18] It has been reported in animal studies that Δ9-THC-exposed pregnancies exhibited a phenotype characterized by increased labyrinth area, reduced Epcam expression (marker of labyrinth trophoblast progenitors), altered maternal blood space, decreased fetal capillary area and an increased recruitment of pericytes with greater collagen deposition.[19] We hypothesized that exposure to cannabinoids during pregnancy could lead to inappropriate activation of the cannabis pathways in the placenta, which can be associated with placental insufficiency later in pregnancy, producing fetal growth restriction with a Doppler pattern of increased uterine and umbilical artery pulsatility, and decreasing the MCA pulsatility, meaning a redistribution of the blood flow.

Cannabis use is often combined with tobacco, which makes disentangling the specific effect of cannabis difficult. The association of the continued cannabis exposure with the vascular effect on the fetal and maternal blood flow could be explained by the co-occurrence of tobacco use during the pregnancy. Nevertheless, we found a statistically significant specific association between maternal cannabis use and the increase of the mean Ut Art PI, which remained present after taking into account maternal tobacco use, which has already been reported.[8]

The results of the present study highlight the fact that the cannabis vascular effect during pregnancy is evident in the third trimester, which may explain the poor outcomes associated with the use of cannabis during pregnancy. However, a better understanding of the physiopathology of the cannabis exposure during pregnancy is still needed.

5 | CONCLUSION

The current study suggests that cannabis exposure during pregnancy is associated with maternal and fetal blood flow changes. However, it was not possible to disentangle the association of tobacco and cannabis in these changes.

ACKNOWLEDGMENTS

We want to thank Dr M.T. Higueras for her support in the data collection for this project and her expertise in ultrasound research projects.

AUTHORS' CONTRIBUTION

MB: Protocol and project development, data analysis, manuscript writing and editing. MS: protocol and project development, data analysis. JG: data collection or management, data analysis. AH: data collection or management, data analysis. GP: protocol and project development, manuscript writing and editing. NM: protocol and project development, data analysis, manuscript writing and editing. AS: protocol and project development, data analysis, manuscript writing

and editing. EC: protocol and project development, manuscript writing and editing.

CONFLICT OF INTEREST

None.

ORCID

Maia Brik https://orcid.org/0000-0002-1840-5087

REFERENCES

1. Hartung DM, Johnston K, Geddes J, Leichtling G, Priest KC, Korthuis PT. Buprenorphine coverage in the medicare part D program for 2007 to 2018. *JAMA*. 2019;321:607-609.
2. Gunn JKL, Rosales CB, Center KE, et al. Prenatal exposure to cannabis and maternal and child health outcomes: a systematic review and meta-analysis. *BMJ Open*. 2016;6:e009986.
3. Singh S, Filion KB, Abenhaim HA, Eisenberg MJ. Prevalence and outcomes of prenatal recreational cannabis use in high-income countries: a scoping review. *BJOG*. 2020;127:8-16.
4. Roncero C, Valriberas-Herrero I, Mezzatesta-Gava M, Villegas JL, Aguilar L, Grau-López L. Cannabis use during pregnancy and its relationship with fetal developmental outcomes and psychiatric disorders. A systematic review. *Reprod Health*. 2020;17:25.
5. Pacher P, Bátkai S, Kunos G. The endocannabinoid system as an emerging target of pharmacotherapy. *Pharmacol Rev*. 2006;58:389-462.
6. Hillard CJ. Endocannabinoids and vascular function. *J Pharmacol Exp Ther*. 2000;294:27-32.
7. Xiao DL, Huang X, Yang S, Zhang L. Direct effects of nicotine on contractility of the uterine artery in pregnancy. *J Pharmacol Exp Ther*. 2007;322:180-185.
8. el Marroun H, Tiemeier H, Steegers EA, et al. A prospective study on intrauterine cannabis exposure and fetal blood flow. *Early Hum Dev*. 2010;86:231-236.
9. Gómez O, Figueras F, Fernández S, et al. Reference ranges for uterine artery mean pulsatility index at 11-41 weeks of gestation. *Ultrasound Obstet Gynecol*. 2008;32:128-132.
10. Ciobanu A, Wright A, Syngelaki A, Wright D, Akolekar R, Nicolaides KH. Fetal Medicine Foundation reference ranges for umbilical artery and middle cerebral artery pulsatility index and cerebroplacental ratio. *Ultrasound Obstet Gynecol*. 2019;53:465-472.
11. el Marroun H, Tiemeier H, Jaddoe VWV, et al. Agreement between maternal cannabis use during pregnancy according to self-report and urinalysis in a population-based cohort: the Generation R Study. *Eur Addict Res*. 2011;17:37-43.
12. Cristino L, Di Marzo V. Fetal cannabinoid receptors and the "disjoint-ed" brain. *EMBO J*. 2014;33:665-667.
13. Kenney SP, Kekuda R, Prasad PD, Leibach FH, Devoe LD, Ganapathy V. Cannabinoid receptors and their role in the regulation of the serotonin transporter in human placenta. *Am J Obstet Gynecol*. 1999;181:491-497.
14. Thompson R, Dejong K, Lo J. Marijuana use in pregnancy: a review. *Obstet Gynecol Surv*. 2019;74:415-428.
15. El Marroun H, Brown QL, Lund IO, et al. An epidemiological, developmental and clinical overview of cannabis use during pregnancy. *Prev Med*. 2018;116:1-5.
16. Brar BK, Patil PS, Jackson DN, Gardner MO, Alexander JM, Doyle NM. Effect of intrauterine marijuana exposure on fetal growth patterns and placental vascular resistance. *J Matern Fetal Neonatal Med*. 2021;34:3330-3334.
17. Burton GJ, Jauniaux E. Pathophysiology of placental-derived fetal growth restriction. *Am J Obstet Gynecol*. 2018;218:S745-S761.
18. Helliwell RJA, Chamley LW, Blake-Palmer K, et al. Characterization of the endocannabinoid system in early human pregnancy. *J Clin Endocrinol Metab*. 2004;89:5168-5174.
19. Natale B v, Gustin KN, Lee K, et al. Δ9-tetrahydrocannabinol exposure during rat pregnancy leads to symmetrical fetal growth restriction and labyrinth-specific vascular defects in the placenta. *Sci Rep*. 2020;10:544.

How to cite this article: Brik M, Sandonis M, Gil J, et al. Intrauterine cannabis exposure and fetal and maternal blood flow: a case–control study. *Acta Obstet Gynecol Scand*. 2022;101:1207-1214. doi: 10.1111/aogs.14439