The deleterious effects of cannabis during pregnancy on neonatal outcomes

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The known: Cannabis is the illicit drug most widely used by women of reproductive age in Australia, but the effects of its use during pregnancy on neonatal outcomes are unclear.

The new: In our international cohort study, continued use of cannabis at 15 weeks of pregnancy was associated with significantly lower birthweight, head circumference, birth length, and gestational age at birth, as well as with more frequent severe neonatal morbidity or death.

The implications: We provide evidence for the negative impact of cannabis use by pregnant women on important neonatal outcomes, and that this impact is independent of tobacco use.

Abstract

Objectives: To evaluate whether cannabis use during pregnancy is associated with adverse neonatal outcomes that are independent of cigarette smoking.

Design: Prospective cohort study.

Setting: Adelaide (Australia), Auckland (New Zealand), Cork (Ireland), and Leeds, London and Manchester (United Kingdom).

Participants: 5610 pregnant nulliparous women with low risk pregnancies recruited for the Screening for Pregnancy Endpoints (SCOPE) study, November 2004 – February 2011. At 14–16 weeks of pregnancy, women were grouped by self-reported cannabis use.

Main outcome measures: Infant birthweight, head circumference, birth length, gestational age, and severe neonatal morbidity or mortality.

Results: 314 women (5.6%) reported using cannabis in the 3 months before or during their pregnancy; 97 (31%) stopped using it before and 157 (50%) during the first 15 weeks of pregnancy, while 60 (19%) were still using cannabis at 15 weeks. Compared with babies of mother who had never used cannabis, infants of those who still used it at 15 weeks had lower mean values for birthweight (adjusted mean difference [aMD], –127 g; 95% CI, –238 to –17 g), head circumference (aMD, –0.5 cm; 95% CI, –0.8 to –0.1 cm), birth length (aMD, –0.8 cm; 95% CI, –1.4 to –0.2 cm), and gestational age at birth (aMD, –8.1 days; 95% CI, –12.1 to –4.0 days). The differences for all outcomes except gestational age were greater for women who used cannabis more than once a week than for those who used it less frequently.

Conclusions: Continuing to use cannabis during pregnancy is an independent risk factor for poorer neonatal outcomes.

Cannabis is the most frequently used illicit drug in Australia, probably because of its increasing social and medical acceptance, as well as the recent legalisation of cannabis use in many parts of the world.[1]

According to the 2016 National Drug Strategy Household Survey, more than 10% of women of reproductive age had used cannabis during the preceding 12 months.[2] The findings of studies evaluating neonatal outcomes associated with cannabis use by women during pregnancy have been mixed.[3,4] A recent meta-analysis found a significant association between prenatal cannabis exposure and reduced birthweight, as well as increased risk for infants of admission to intensive care.[4] Many studies, however, did not take concurrent cigarette smoking or other illicit substance use into account, and some did not report the time or frequency of cannabis exposure. The largest and most recent study of self-reported cannabis use during pregnancy found increased risks of pre-term birth (adjusted risk ratio [aRR], 1.41, 95% confidence interval [CI], 1.36–1.47), small-for-gestational age (aRR, 1.41, 95% CI, 1.36–1.45), and neonatal intensive care unit admission (aRR, 1.40; 95% CI, 1.36–1.44).[5] Once again, however, the number of cigarettes smoked each day and the time and duration of cannabis use were not assessed.

High quality information about the effect of cannabis use during pregnancy on important neonatal outcomes linked to immediate and long term health and wellbeing is needed for informing clinical practice and improving the education of women and health care providers about the potential risks. The aim of our study was therefore to assess associations between duration and frequency of cannabis use during pregnancy on infant birthweight, head circumference, birth length, gestational age, and neonatal morbidity and mortality.

Methods

Study population

The primary aim of the Screening for Pregnancy Endpoints (SCOPE) study, a multicentre prospective cohort study, is to develop screening tests for predicting pre-eclampsia, spontaneous pre-term birth, and small for gestational age babies.[6] A total of 5628 nulliparous women without common risk factors for pregnancy complications were recruited between November 2004 and February 2011 in Adelaide (Australia), Auckland (New Zealand), Cork (Ireland), and Leeds, London and Manchester (United Kingdom).[7] Research midwives collected information on demographic and lifestyle characteristics and medical history from participants at 14–16 weeks of pregnancy. Women were excluded from our analysis if their pregnancy ended earlier than 20 weeks (Supporting Information, figure).

Cannabis use by participants

The research nurse asked women about the duration and frequency of cannabis use from 3 months before until 15 weeks into their pregnancy. Women were allocated to four categories: never used cannabis, used cannabis but quit before pregnancy, used cannabis but quit during early pregnancy (by 15 weeks), and continued to use cannabis at 15 weeks of pregnancy. Women were also classified according to whether they used cannabis up to once or more than once a week, consistent with previous

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studies.[8,9] We did not quantify the amount or strength of cannabis consumed.

Other variables assessed

Self-reported smoking status was classified as never smoked, quit before pregnancy, quit during early pregnancy (by 15 weeks), and continued use at 15 weeks; for women still smoking, the number of cigarettes smoked was recorded. Women who used illicit substances other than cannabis during pregnancy were included in a single group (the individual numbers were too small for separate analyses). Alcohol consumption was classified as never used, quit before pregnancy, quit during early pregnancy (by 15 weeks) and continued use at 15 weeks; binge alcohol consumption (at least 6 units of alcohol per drinking episode) during pregnancy was also recorded. Ethnic background was self-reported as European origin or other. Socio-economic status of participants was assessed with the socio-economic index (SEI). Developed in New Zealand, the SEI is an optimally weighted combination of income and education variables, corrected for age; ranging from 10 to 90 points, a higher score indicates higher socio-economic status.[10] At the 15-week interview, participants also completed a lifestyle questionnaire that included the short form of the State–Trait Anxiety Inventory[11] and the Edinburgh postnatal depression scale.[12]

Neonatal outcomes

Anthropometric measurements (infant birthweight, head circumference, birth length) were recorded by research midwives within 72 hours of birth. Information about severe neonatal morbidity or death (as a composite outcome) were collected by research midwives from case notes after infants had been discharged from hospital. Serious morbidity was defined by the original SCOPE consortium for infants born pre-term (earlier than 37 weeks' gestation) as grade III or IV intraventricular haemorrhage, chronic lung disease (receiving oxygen at home, or at 36 weeks' gestation if the baby was born before 32 weeks' gestation), necrotising enterocolitis, retinopathy of prematurity (stage 3 or 4), sepsis (confirmed in blood or cerebrospinal fluid), or cystic periventricular leukomalacia; for infants born at term, serious morbidity included grade II or III hypoxic ischaemic encephalopathy, ventilation for more than 24 hours, admission to a neonatal unit for more than 4 days, an Apgar score at 5 minutes of less than 4, cord arterial pH below 7.0 or base excess of less than –15 mEq/L, and neonatal seizures.

Statistical analysis

We used causal diagrams (directed acyclic graphs) to guide our selection of covariates for analyses.[13] Frequencies and descriptive statistics were expressed as numbers and proportions or as means with standard deviations (SDs). Medians with interquartile ranges (IQRs) were reported when continuous variables were not normally distributed.

Possible confounding maternal characteristics identified a priori included age, body mass index (BMI), SEI, ethnic background, cigarette smoking, study centre, alcohol use, binge alcohol consumption, illicit drug use, and symptoms of anxiety or depression at 15 weeks. Anthropometric outcomes were further adjusted for infant sex; birthweight, head circumference, and birth length were also adjusted for gestational age at birth (using fractional polynomials for gestational age).

Associations between duration and frequency of cannabis use during pregnancy and gestational age at birth, birthweight, head circumference, and birth length were evaluated by multivariable mixed effects linear regression. The association between duration of cannabis use during pregnancy and severe neonatal morbidity or death was evaluated by logistic regression. We used mixed effects models, with country as a random effect and other covariates as fixed effects. We evaluated the robustness of our findings to uncontrolled confounding by calculating E-values[14] for the associations between cannabis use and outcomes.

As the SEI has not been validated outside New Zealand, in sensitivity analyses we adjusted outcomes for alternative individual measures of socio-economic status, including income (< $75 000, ≥ $75 000), education (no tertiary, tertiary education), and employment status (employed, unemployed, other: including homemaker or parent, student, disabled).

$P < 0.05$ (two-tailed) was defined as statistically significant. All analyses were undertaken in Stata IC 14.

Ethics approval

Ethics approval was obtained from the Northern X Regional Ethics Committee in New Zealand (reference, AKX/02/00/364), the Central Northern Adelaide Health Service Ethics of Human Research Committee in Australia (reference, REC 1712/5/2008), the South-East Multi-Centre Research Ethics Committee, St Thomas Hospital Research Ethics Committee, and Central Manchester Research Ethics Committee in the United Kingdom (reference, 06/MRE01/98), and the Clinical Research Ethics Committee of the Cork Teaching Hospitals in Ireland (reference, ECM5 (10) 05/02/08). The women involved in the study provided written informed consent for the analysis of their data.

Results

After excluding 18 women whose pregnancies ended at less than 20 weeks' gestation, 5610 women were included in our analysis (Supporting Information, figure), of whom 314 (5.6%) reported using cannabis before or during pregnancy; 97 (31%) had stopped using it before pregnancy, 157 (50%) had stopped by 15 weeks, and 60 (19%) continued to use cannabis at 15 weeks of pregnancy. The mean age and socio-economic status of women who continued to use cannabis were lower, and their mean anxiety and depressive symptom scores higher than for other participants; the proportions who consumed alcohol, used other illicit drugs, or were smoking at 15 weeks of pregnancy were also higher (Box 1).

Neonatal outcomes: effect of cannabis use

Compared with the babies of women who had never used cannabis, the infants of women who continued to use cannabis at 15 weeks had lower mean values for birthweight (adjusted mean difference [aMD], –127 g; 95% CI, –238 to –17 g), head circumference (aMD, –0.5 cm; 95% CI, –0.8 to –0.1 cm), birth length (aMD, –0.8 cm; 95% CI, –1.4 to –0.2 cm), and gestational age (aMD, –8.1 days; 95% CI, –12.1 to –4.0 days). Neonatal outcomes for babies of women who quit before or during early pregnancy were not significantly different from those for infants of women who had never used cannabis (Box 2). The difference in birthweight associated with continued use of cannabis was similar to that for babies of mothers who smoked up to nine cigarettes per day (*v* never smoked during pregnancy: aMD, –104 g; 95% CI, –162 to –46 g) or more (aMD, –166 g, 95% CI, –219 to –112 g) at 15 weeks.

1 Characteristics of 5610 SCOPE study participants, 2004–2011, by cannabis use of mothers before and during pregnancy

	Cannabis use			
	Never used	Quit before pregnancy	Quit early in pregnancy	Continued use at 15 weeks
Number of participants	5296	97	157	60
Age (years), mean (SD)	28.9 (5.4)	26.8 (5.9)	24.6 (5.8)	21.7 (4.9)
Body mass index (kg/m^2), mean (SD)	25.3 (4.9)	24.9 (4.5)	25.5 (5.0)	24.0 (5.5)
Socio-economic index, mean score (SD)	42.3 (16.5)	38.1 (15.9)	32.4 (13.6)	26.6 (9.0)
Location				
Australia	1025 (19%)	13 (13%)	78 (50%)	42 (70%)
Ireland	1704 (32%)	26 (27%)	36 (23%)	5 (8%)
New Zealand	1934 (36%)	46 (47%)	33 (21%)	11 (18%)
United Kingdom	633 (12%)	12 (12%)	10 (6%)	2 (3%)
Ethnic background (European)	4768 (90%)	87 (90%)	142 (90%)	52 (87%)
Psychological scales				
Anxiety (STAI), mean score (SD)	33.6 (11.4)	33.0 (11.6)	35.7 (12.7)	39.4 (15.1)
Depression (EPDS), mean score (SD)	6.6 (4.7)	8.8 (5.5)	8.1 (5.5)	9.6 (6.2)
Alcohol use during pregnancy				
Never used during pregnancy	2088 (39%)	27 (28%)	38 (24%)	27 (45%)
Quit during early pregnancy	2687 (51%)	51 (53%)	102 (65%)	20 (33%)
Continued use at 15 weeks	521 (10%)	19 (20%)	17 (11%)	13 (22%)
Cigarette smoking pregnancy				
Never smoked during pregnancy	4158 (79%)	48 (50%)	42 (27%)	5 (8%)
Quit smoking during early pregnancy	667 (13%)	27 (28%)	49 (31%)	10 (13%)
1–9 cigarettes/day at 15 weeks	209 (4%)	10 (10%)	28 (18%)	21 (35%)
10 or more cigarettes/day at 15 weeks	255 (5%)	12 (12%)	38 (24%)	24 (40%)
Substance misuse during pregnancy before 15 weeks				
Binge alcohol consumption*	1196 (23%)	28 (29%)	56 (36%)	10 (17%)
Illicit drug use†	36 (1%)	3 (3%)	12 (8%)	5 (8%)
Used cannabis more than once weekly				
Before pregnancy	NA	9 (10%)	83 (53%)	49 (82%)
During pregnancy (before 15 weeks)	NA	NA	65 (42%)	43 (72%)

EPDS = Edinburgh Postnatal Depression Scale; NA = not applicable; SCOPE = Screening for Pregnancy Endpoints study; SD = standard deviation; STAI = State–Trait Anxiety Inventory. * At least 6 units of alcohol per drinking episode. † Including cocaine, substance P, amphetamines, opiates. ◆

E-values for the association between continued cannabis use and adverse perinatal outcomes ranged between 1.74 for birthweight and 2.58 for gestational age. This means that the risk ratio, after adjusting for measured covariates, for an unmeasured confounder associated with both cannabis use and the outcome would need to be 1.74 in the case of birthweight (corresponding to a reduction of about 350 g) or 2.58 in the case of gestational age (corresponding to a reduction of about 14 days) to reduce the aMDs associated with cannabis use to zero (Supporting Information, table 1).

Neonatal outcomes: effect of level of cannabis use during early pregnancy

Compared with the babies of women who used cannabis up to once a week during early pregnancy, the infants of women who used cannabis more than once a week had lower mean values for birthweight (aMD, –197 g; 95% CI, –334 to –60 g), head circumference (aMD, –0.9 cm; 95% CI, –1.3 to –0.5 cm), and birth length (aMD, –1.0 cm; –1.7 to –0.4 cm) (Box 3). The odds ratio for severe infant morbidity or death increased with persistence of cannabis use during pregnancy (for trend in adjusted odds ratio: $P = 0.041$) (Box 4).

Sensitivity analyses

Adjusting for individual markers of socio-economic status (education status, employment status, income level) instead of SEI score did not substantially alter our findings (Supporting Information, table 2–4).

Discussion

We report robust evidence that continued cannabis use during pregnancy is associated, independent of continued cigarette

2 Birthweight, head circumference, birth length, and gestational age of infants, by cannabis use of mothers before and during pregnancy

	Cannabis use						
	Never used (reference)	Quit before pregnancy		Quit early in pregnancy		Continued use at 15 weeks	
Outcome	Mean (SD)	Mean (SD)	Adjusted mean difference (95% CI)	Mean (SD)	Adjusted mean difference (95% CI)	Mean (SD)	Adjusted mean difference (95% CI)
Number of infants	5296	97		157		60	
Birthweight (g)*	3410 (580)	3405 (569)	14 (–70 to 99)	3339 (687)	38 (–30 to 106)	2930 (797)	–127 (–238 to –17)
Head circumference (cm)*	34.7 (1.7)	34.9 (2.1)	0.3 (–0.1 to 0.5)	34.4 (2.3)	0.0 (–0.2 to 0.3)	33.2 (2.5)	–0.5 (–0.8 to –0.1)
Birth length (cm)*	50.3 (3.1)	50.7 (3.0)	0.1 (–0.4 to 0.5)	49.4 (3.7)	0.0 (–0.3 to 0.4)	47.0 (4.5)	–0.8 (–1.4 to –0.2)
Gestational age (days)†	278 (13)	278 (16)	–0.1 (–3.0 to 3.2)	276 (18)	–1.9 (–4.4 to 0.6)	270 (22)	–8.1 (–12.1 to –4.0)

CI = confidence interval; SD = standard deviation. * Adjusted for maternal age, body mass index, socio-economic index score, cigarette smoking, country, alcohol use, binge alcohol consumption, illicit drug use, ethnic background, anxiety and depression scores at 15 weeks' gestation, infant sex, and gestational age at birth and gestational age squared. † Adjusted for same factors except gestational age at birth and gestational age squared. ◆

3 Birthweight, head circumference, birth length, and gestational age of infants, by frequency of cannabis use by mothers during weeks 0–15 of pregnancy

	Frequency of cannabis use during weeks 0–15 of pregnancy		
	No more than once a week (reference)	More than once a week	
Outcome	Mean (SD)	Mean (SD)	Adjusted mean difference (95% CI)
Number of infants	109	108	
Birthweight (g)*	3390 (702)	3060 (745)	–197 (–334 to –60)
Head circumference (cm)*	34.6 (2.3)	33.5 (2.4)	–0.9 (–1.3 to –0.5)
Birth length (cm)*	49.8 (3.5)	47.7 (4.3)	–1.0 (–1.7 to –0.4)
Gestational age (days)†	276 (18)	273 (21)	–5.1 (–11.7 to 1.5)

CI = confidence interval; SD = standard deviation. * Adjusted for maternal age, body mass index, socio-economic index score, cigarette smoking, country, alcohol use, binge alcohol consumption, illicit drug use, ethnic background, anxiety and depression scores at 15 weeks' gestation, infant sex, and gestational age at birth and gestational age squared. † Adjusted for same factors except gestational age at birth and gestational age squared. ◆

4 Cannabis use during pregnancy and severe neonatal morbidity* or death, by cannabis use of mothers before and during pregnancy

	Severe neonatal morbidity or death		Odds ratio (95% CI)	
Cannabis use	No	Yes	Crude	Adjusted†
Never used	5136 (97%)	160 (3%)	1	1
Quit before pregnancy	94 (97%)	3 (3%)	1.02 (0.32–3.27)	1.44 (0.44–4.68)
Quit before 15 weeks	147 (94%)	10 (6%)	2.18 (1.13–4.22)	1.76 (0.86–3.62)
Continued use at 15 weeks	55 (92%)	5 (8%)	2.92 (1.15–7.39)	2.26 (0.83–6.20)
P (trend)			0.002	0.041

* For definition, see Methods. † Adjusted for maternal age, body mass index, socio-economic index score, cigarette smoking, country, alcohol use, binge alcohol consumption, illicit drug use, ethnic background, and anxiety and depression scores at 15 weeks' gestation. ◆

smoking, with significant reductions in infant gestational age at birth, birthweight and length, and head circumference, as well as increased frequency of severe neonatal morbidity. The observed reduction in neonatal birthweight was comparable with that associated with continued tobacco use during pregnancy. The outcomes for infants of women who had stopped using cannabis by 15 weeks of pregnancy did not differ from those of mothers who had never used cannabis. Our findings are of considerable public health importance, particularly given the increasing legal, social, and medical acceptance of cannabis, and they highlight the importance of health care providers counselling women of reproductive aged to stop or reduce cannabis use before becoming pregnant or, at the latest, early in pregnancy.

Our study was an extension of an earlier investigation, with the same cohort of women, of associations between cannabis use during pregnancy and major pregnancy complications.[15] The earlier study identified that continued cannabis use during pregnancy was associated with increased risk of spontaneous pre-term birth, but not with increased risks of small for gestational age babies, pre-eclampsia, gestational hypertension, or gestational diabetes.[15] Our study adds data on key neonatal outcomes, including differences according to frequency of cannabis use during pregnancy.

A recent meta-analysis found that using cannabis during pregnancy was associated with reduced birthweight (pooled mean difference [pMD], –109 g; 95% CI, –180 to –39 g; ten studies), but not reduced gestational age at birth (pMD, –0.20 days; 95% CI, –0.62 to 0.22 days; five studies), birth length (pMD, –0.10 cm; 95% CI, –0.65 to 0.45 cm; six studies), or head circumference (pMD, –0.31 cm; 95% CI, –0.74 to 0.13 cm; six studies).[4] Study heterogeneity (I^2) for the various outcomes ranged, however, between 33% and 97%. Further, pooled risk estimates were not adjusted for cigarette smoking, and growth outcomes were not adjusted for gestational age at birth. As many cannabis users also smoke or drink alcohol, isolating cannabis-specific effects was therefore challenging. Another recent meta-analysis found that cannabis use during pregnancy was associated with increased risks of low birthweight (risk ratio [RR], 1.43; 95% CI, 1.27–1.62; 12 studies) and pre-term delivery (RR, 1.32; 95% CI, 1.14–1.54; 14 studies), but these differences were removed by adjusting for cigarette use and other confounders (low birthweight: adjusted RR, 1.16; 95% CI, 0.98–1.37 [four studies]; pre-term birth: adjusted RR, 1.08; 95% CI, 0.82–1.43 [four studies]).[3] In contrast, we found that cannabis use during pregnancy is an independent risk factor for poorer neonatal outcomes.

A few studies have examined associations between neonatal growth outcomes and the frequency[8,9] or duration (first, second, third trimester)[16,17] of cannabis use, or both.[18,19] Our findings are consistent with those of three studies that found significant reductions in birthweight, head circumference, or birth length with increased frequency[8] or duration of cannabis use during pregnancy;[17,19] the other three studies found no differences.

We found that the frequency of severe neonatal morbidity and death was higher for babies of mothers who continued to use cannabis at 15 weeks, consistent with the results of a recent American study (adjusted odds ratio, 3.11; 95% CI, 1.40–6.91).[20] These findings could reflect the lower gestational age at birth for babies of women who continue using cannabis during pregnancy or be related to altered fetal growth. How cannabis might impair fetal growth is unclear, but the effect may be related to the carbon monoxide generated by smoking cannabis.[21] Alternatively, the effects might be mediated by maternal–placental–fetal neuroendocrine mechanisms, particularly by dysregulation of the diurnal cortisol cycle. A role for the endocannabinoid system in brain homeostasis has been described, and exogenous cannabinoids activate the hypothalamic–pituitary–adrenal axis.[22] Cannabinoid administration dose-dependently increases adrenocorticotropic hormone (ACTH) and cortisol concentrations in blood, but with chronic use tolerance rapidly develops.[23] Further investigation of the neuroendocrine effects on mother and child of cannabis during pregnancy are warranted.

Strengths and limitations

Strengths of our secondary analysis included the prospective and rigorous collection of data on cannabis use during pregnancy (including its duration and frequency) by trained personnel, as well as on smoking, alcohol use, and the use of illicit substances. Limitations include the lack of information about the quantity of cannabis used and about how it was taken. The small numbers of women in the different categories of cannabis use during pregnancy limit the precision of our effect estimates. Further, data on the use and frequency of cannabis use during pregnancy relied on self-reports, and we had no information at all about the second half of pregnancy. Nevertheless, self-report has been found to reliably assess cannabis use during pregnancy in epidemiological studies.[24] Any incomplete ascertainment of cannabis use would have been non-systematic and therefore unrelated to the outcomes we investigated; further, misclassification of some users as non-users would have diminished rather than amplified the reported associations.[25] The E-values for the reported associations indicate that a level of residual confounding sufficient to explain them seems unlikely. Finally, our findings were robust to different approaches to adjusting for socio-economic status.

Conclusion

Our findings provide important information for women and health care providers about the potential harms of cannabis use during pregnancy. Continued and high frequency of cannabis use during pregnancy were each associated with significantly poorer neonatal outcomes. The long term effects on child health and development should be examined in further studies.

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Supporting Information

Additional Supporting Information is included with the online version of this article.