The interaction between maternal smoking, illicit drug use and alcohol consumption associated with neonatal outcomes

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ABSTRACT

Background The adverse effects of smoking on neonatal outcomes, such as small-for-gestational-age (SGA), has been extensively studied however, the consequences of smoking combined with alcohol and/or drug use is less clear.

Methods This retrospective observational study analyzed clinical and sociodemographic details of 40156 women who delivered a singleton baby between the years 2011 and 2015.

Results Compared with women who had never smoked, smokers who did not engage in alcohol or drug use had an odds ratio (OR) of delivering a baby who was SGA of 3.2 (95% CI: 3.1–3.5). Smokers who used illicit drugs in isolation or in combination with alcohol during pregnancy had higher ORs for SGA (1.4, 95% CI: 1.1–1.7, $P = 0.006$ and 1.8, 95% CI: 1.2–2.7, $P = 0.007$) compared to women who smoked but did not engage in alcohol or drug use in pregnancy. These women also delivered babies with lower mean birthweights (125 g, $P < 0.001$ and 181.4 g, $P = 0.003$) and head circumferences (0.4 cm, $P < 0.001$ and 0.3 cm, $P = 0.048$). Women who smoked and used alcohol, but not illicit drugs were not associated adverse outcomes above that of smoking in isolation.

Conclusion Illicit drug use combined with maternal smoking during pregnancy increases the risk of adverse neonatal outcomes above that of smoking in isolation.

Keywords alcohol, illicit drugs, pregnancy, smoking

Introduction

Smoking is arguably the most important modifiable risk factor in pregnancy. Smoking is consistently linked to adverse outcomes that have profound effects in both the short and long term for mother and child. Common outcomes associated with maternal smoking include low birth weight (LBW), preterm birth, foetal growth restriction (FGR) and small-for-gestational-age (SGA).[1–3]

Even in the absence of prematurity, babies born to women who smoke often do not reach their full growth potential in terms of head circumference (HC) or birth weight (BW).[3,4] These babies are defined as being growth restricted which may present at birth as SGA. SGA is linked to an increased risk of mortality, respiratory complications, hypothermia and sepsis as well an increased length of hospital stay.[5–7] Furthermore, growth restricted babies may be at an elevated risk of chronic diseases such as hypertension, coronary heart disease, stroke and diabetes in later life.[8]

Although some risk factors for FGR are not amenable to change, smoking is modifiable.[9,10] Other modifiable maternal lifestyle behaviors linked to FGR include alcohol consumption during pregnancy and illicit drug abuse, particularly

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cocaine use.[11–13] The association between alcohol and FGR, however, is less well defined. There is also limited information as to how these modifiable risk factors interact in restricting foetal growth in terms of BW, HC and SGA.

We aimed to examine the effect of maternal cigarette smoking combined with illicit drug use and alcohol consumption on mean BW, HC, GA and SGA risk.

Methods

This retrospective, observational cohort study used data routinely computerized at the woman's first antenatal visit (~12 weeks gestation) using the Hospital's clinical electronic recording system, Euroking K2. The clinical records were updated after delivery with pregnancy and neonatal outcome data. Data were analyzed for women with a singleton pregnancy who delivered a baby weighing >500 g over the 5 years 2011–15.

The Hospital is one of the largest maternity units in Europe and accepts women without differentiation from all socioeconomic groups across the urban rural divide, whether they are privately or publicly funded.[14] All women are offered sonographic dating of their pregnancy.

Smoking behavior was categorized into the following: 'never smoked' (never smoked in their lifetime), 'ex-smoker' (smoked at some point in their lifetime but not smoking at the time of the first antenatal appointment) or 'smoker' (reported currently smoking any number of cigarettes daily at first antenatal appointment).

Current alcohol consumption was categorized into 'no' (no alcohol) or 'weekly alcohol' (consumed an undefined level of alcohol each week). For the purpose of the study 'binge' was defined as having consumed >5 units of alcohol at one sitting and categorized into 'never' (reported never binging on alcohol) or 'yes' (reported binging on alcohol in at least once). Illicit drug use was categorized into 'none' (reported no illicit drugs use) or 'illicit drugs' (reported using any type of illicit drugs, including cannabis). Variables described as 'previous' refers to any behaviors engaged in prior to pregnancy. Variables described as 'current' refers to any behaviors engaged in at least once during pregnancy and/or were ongoing at the first antenatal visit.

For the purpose of this study, illicit drugs were defined as the non-medical use of a variety of drugs that are prohibited by international law. Women were given written information and brief advice as part of routine antenatal care on lifestyle behaviors, but no intervention programs were provided.[15] Maternal occupation was defined according to the occupational classifications used in the national census. Women who had delivered more than once over the 5 years had all pregnancies included.

Available delivery data computerized immediately following birth included onset of labor, mode of delivery, high dependency unit and neonatal intensive care unit (HDU/NICU) admissions, as well as GA, HC and birth weight which were routinely measured by a midwife. Women with a multiple pregnancy were excluded from analysis to reduce the number of confounding variables.[16] Body mass index (BMI) was calculated based on the accurate measurement of maternal weight and height at the first antenatal visit.

The data were pseudonymized on an Excel (Microsoft Corp., Redmond, WA, USA) spreadsheet. Data were then exported to the statistical software program SPSS version 20.0.0 for analysis (IBM Corp., Armonk, NY, USA). Normality of continuous data were assessed using descriptive statistics for kurtosis and skewness, visual inspection of distribution histograms and the Kolmogorov–Smirnoff statistics. Relevant continuous data were collapsed into categories. Missing data were coded in SPSS and presented in footnotes of tables.

Descriptive statistics were used to describe the sociodemographic characteristics and birth outcomes of the study cohort by smoking category. Normally distributed continuous data were reported as mean and standard deviation. Categorical data were reported as proportions. Inferential χ^2 tests for independence were used to analyze differences in the categorical study population characteristics.

Analysis of variance (ANOVA) was used to examine the mean difference between BW, GAs and HCs of infants born to women in each of the smoking categories combined with weekly alcohol, binges and drug use. In this analysis no women binged on alcohol alone. All women that reported binging on alcohol also reported consuming weekly alcohol therefore, there was no stand-alone 'binge' group available for analysis. The reference category for which all other groups were compared consisted of women who reported never smoking, consuming alcohol or using drugs during pregnancy at their first antenatal appointment (n = 20 834). Results were reported in the table and expressed as means and standard deviations and P-values denote statistical difference from the reference group. Additional ANOVA analyses compared all groups to women who smoked but did not consume alcohol or use illicit drugs in pregnancy. The results of these analyses were reported in the narrative of the results section.

SGA was defined as a BW <10th centile. Centiles were customized for maternal and neonatal factors using the Global Bulk Centile Calculator version 8.0.1.[17] In terms of maternal factors, measured maternal height, weight and

ethnicity were included. Neonatal factors included GA at delivery and infant gender. Any woman with missing data of any of these variables was excluded to avoid the use for 'global averages' being substituted.

Descriptive statistics were used to examine the rates (%) of SGA by categories of smoking, weekly alcohol and drug use both independently and combined. Univariate analyses were then used to investigate the association between SGA and various categories of smoking, alcohol consumption and drugs use in isolation and combination. Results were reported as odds ratios (OR), 95% CI and associated *P*-values. Ethical approval was received by the Hospital's Research Ethics Committee (4-2013).

Results

The total number of deliveries during the 5 years was 42 509. Women with multiple births ($n = 1782$) and who reported smoking e-cigarettes ($n = 21$) were excluded. Women who had missing data required for the Global Bulk Centile Calculator were also excluded ($n = 550$). After exclusions, 40 156 (94.5%) births were available for analysis.

Table 1 shows the characteristics of the study population analyzed by self-reported smoking behavior. Overall, 52.6% of women reported they had never smoked, 34.8% reported they were ex-smokers and 12.6% were current smokers. The number of women who reported they did not smoke, consume alcohol or use illicit drugs during pregnancy was 20 834 (51.9%).

Notably, the characteristics of the ex-smokers were similar to never smokers in terms of age, parity and BMI (Table 1). Compared to never-smokers, ex-smokers were more likely to have previously consumed alcohol both weekly and in binges and to have used illicit drugs before pregnancy (all $P < 0.001$).

The current smokers, in contrast, were more likely than never smokers to be younger, multiparous, obese and to have an unplanned pregnancy (all $P < 0.001$). They were also more likely to report consuming alcohol weekly and in binges as well as illicit drug usage at time of their first antenatal appointment (all $P < 0.001$).

Smokers were the most likely of all other groups to have poorer pregnancy outcomes, particularly in terms of lower BW and HC as well as shorter duration of gestation (all $P < 0.001$) (Table 2).

Table 3 shows the mean BWs, HCs and GAs of women who engaged in various combinations of smoking, weekly alcohol and illicit drug use. The reference group for all analysis was the 20 834 women who reported never smoking and did not consume alcohol or use illicit drugs during pregnancy. The most common combination of adverse behaviors was smoking and illicit drug use ($n = 344$, 0.9%).

Compared to current smokers who did not engage in any other adverse behavior both current smokers who consumed alcohol and, current smokers who consumed alcohol and used illicit drugs had higher rates of smoking >11 cigarettes per day (14.7 versus 24.9% and 31.2%). However, women who smoked in isolation did not differ from women who smoked and used illicit drugs in terms of smoking >11 cigarettes per day (15.7 versus 14.7%, $P = 0.301$).

Smokers who did not engage in any other adverse behavior ($n = 4454$) had the lowest BW, HC and shortest gestational compared to never- and ex-smokers (all $P < 0.001$). BW, HC and GA did not differ from the reference group when never or ex-smoking was combined with weekly alcohol, illicit drugs or concurrent alcohol and illicit drug use during pregnancy.

In addition to differing from the overall reference group of 'no other adverse behavior', current smokers who used illicit drugs in isolation or combination with weekly alcohol had lower BWs (125 g, $P < 0.001$ and 181.4 g, $P = 0.003$) and HCs (0.4 cm, $P < 0.001$ and 0.3 cm, $P = 0.048$) than current smokers who did not engage in the other adverse behaviors. Women who smoked and consumed weekly alcohol did not differ from current smokers who did not engage in other adverse behaviors in any outcomes measured (all $P > 0.05$).

Table 4 shows the effect combined adverse behaviors have on SGA. No difference in the risk of SGA existed between current smokers who reported weekly alcohol consumption and current smokers who reported no other adverse behaviors. In contrast, current smokers who used illicit drugs in isolation or combination with weekly alcohol were more likely to have an SGA affected birth than current smokers who engaged in no other adverse behavior, indicating an amplification affect (1.4 95% CI: 1.1–1.7, $P = 0.006$ and 1.8 95% CI: 1.2–2.7, $P = 0.007$, respectively). Furthermore, the consumption of weekly alcohol did not increase the risk of SGA further than combined smoking and illicit drug use ($P > 0.05$).

Never- and ex-smokers who consumed alcohol, used illicit drugs, or used both in combination had no increase in OR for SGA with the exception of women who never smoked but consumed weekly alcohol and used illicit drugs concurrently ($P = 0.045$).

Discussion

Main finding of this study

Our results from this large observational study confirm the strong associations between maternal smoking and lower

Table 1 Characteristics of the study population analyzed by self-reported daily smoking behavior

Study characteristics	*Never smoked (n = 21 136)*	*Ex-smoker (n = 13 981)*	*Maternal smoker (n = 5039)*	*Total population (n = 40 156)*
Age (years) (mean ± SD)	31.8 ± 5.3	31.8 ± 5.3	28.1 ± 5.9	31.3 ± 5.5
BMI (kg/m^2) (mean ± SD)	25.5 ± 5.1	25.6 ± 4.9	25.6 ± 5.4	25.5 ± 5.1
Obese (%)	16.2	16.3	18.8	16.5
Nulliparas (%)	39.6	40.5	34.8	39.3
Planned pregnancy (%)	74.7	72.6	42.3	69.9
Unemployed[a] (%)	27.7	24.2	61.6	30.4
Previous weekly alcohol (%)	55.3	73.5	58.6	62.0
Previous binge(s)[a] (%)	24.4	41.4	41.7	32.5
Current weekly alcohol (%)	1.1	2.2	4.7	1.9
Current binge(s)[a,b] (%)	0.1	0.2	1.6	0.3
Previous illicit drug use (%)	2.0	11.6	25.8	8.3
Current illicit drug use (%)	0.3	2.1	7.3	1.8

BMI, body mass index; obesity categorized as a BMI > 29.9 kg/m^2.
[a]Binge = consuming > 5 units of alcohol in one sitting at least once.
[b]Missing data *n* = 129.
Data are (%) or mean ± SD.

Table 2 Pregnancy outcomes of the study population analyzed by self-reported daily smoking behavior

Study characteristics	*Never smoked (n = 21 136)*	*Ex-smoker (n = 13 981)*	*Maternal smoker (n = 5039)*	*Total population (n = 40 156)*
Induction of labor (%)	32.3	33.6	32.8	32.8
Elective cesarean (%)	14.2	15.2	9.2	13.9
Emergency cesarean (%)	12.5	11.8	10.7	12.0
HDU/NICU admission (%)	6.4	6.1	9.9	6.7
Stillbirth (%)	0.4	0.3	0.6	0.4
Head circumference (mean ± SD)	35.0 ± 1.7	35.1 ± 1.8	34.5 ± 1.7	35.0 ± 1.7
Birth weight (mean ± SD)	3439.6 ± 559.6	3504.2 ± 541.1	3173.8 ± 595.1	3428.8 ± 566.9
Gestation at birth (mean ± SD)	39.5 ± 1.9	39.6 ± 1.8	39.2 ± 2.3	39.5 ± 1.9
Exclusively breastfed on transfer (%)	40.1	40.6	13.9	37.0
Apgar < 7 at 5 min (%)	1.5	1.4	2.2	1.6
Small for gestational age (%)	10.7	10.9	28.7	13.0
Low birth weight (<2500 g) (%)	4.6	3.4	10.6	4.9
Macrosomia (>4500 g) (%)	1.7	2.2	0.6	1.7

HDU, high dependency unit; NICU, neonatal intensive care unit.
Multiple pregnancies excluded.
Data are (%) or mean ± SD.

BW, HC, shorter gestation and risk of SGA. With the exception of GA, we also found that the risk of each of these adverse outcomes in smokers were amplified by the additional use of illicit drugs in isolation and in combination with weekly alcohol compared to smoking alone. We did not find any additional risk of weekly alcohol without illicit drugs use in maternal smokers.

Limitations

A limitation of the study was the absence of the biochemical confirmation of smoking. It is not customary nationally in maternity units to screen women using hematological or urinary toxicology.[18,19] Therefore, we cannot identify underreporting or nondisclosure. It is probable that verification would likely have increased mean BW in the reference group

Table 3 Differences in the birthweights, head circumferences and the gestational ages of babies born to women who engaged in different combinations of health behaviors in pregnancy

	Never smoked	*Ex-smoker*	*Current smoker*
No other adverse behavior			
N	20 834	13 403	4454
Mean birthweight (g)	3439.1 (559.8)	3506.3 (539.4)***	3185.9 (589.4)***
Mean head circumference (cm)	35.0 (1.7)	35.1 (1.8)***	34.6 (1.7)***
Mean gestation (weeks)	39.5 (1.9)	39.6 (1.8)***	39.2 (2.2)***
Weekly alcohol			
N	218	266	145
Mean birthweight (g)	3495.2 (575.0)	3503.7 (593.7)	3182.2 (645.2)***
Mean head circumference (cm)	35.0 (1.3)	35.1(1.4)	34.5 (1.4)
Mean gestation (weeks)	39.4 (2.1)	39.6 (2.2)	39.0 (2.5)
Illicit drugs			
N	64	278	344
Mean birthweight (g)	3422.3 (432.7)	3411.3 (568.6)	3060.9 (599.8)***
Mean head circumference (cm)	35.1 (3.2)	34.8 (1.6)	34.2 (1.6)***
Mean gestation (weeks)	39.8 (1.5)	39.7 (2.0)	39.1 (2.3)*
Weekly alcohol and illicit drugs			
N	20	34	96
Mean birthweight (g)	3563.5 (543.7)	3454.1 (487.1)	3004.5 (699.3)***
Mean head circumference (cm)	35.4 (1.9)	34.9 (1.1)	34.2 (1.5)**
Mean gestation (weeks)	39.7 (1.8)	39.8 (1.2)	38.9 (2.7)

Head circumference missing data—2065. *P*-values indicate differences between women who 'never smoked' and engaged in 'no other adverse behavior' during pregnancy ($n = 20\,834$).*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

Table 4 Differences in the rates and odds ratios of small-for-gestational-age (SGA) based on combinations of maternal behaviors in pregnancy

	Never smoked	*Ex-smoker*	*Current smoker*
No other adverse behavior			
N	20834	13 403	4454
% SGA	10.7	10.8	27.9
OR (95% CI)	Reference	1.0 (0.9–1.8)	3.2 (3.1–3.5)
P-value	Reference	NS	<0.001
Weekly alcohol			
N	218	266	145
% SGA	9.6	13.2	29.7
OR (95% CI)	0.9 (0.6–1.4)	1.3 (0.9–1.8)	3.5 (2.5–5.0)
P-value	NS	NS	<0.001
Illicit drugs			
N	64	278	344
% SGA	9.4	12.6	34.9
OR (95% CI)	0.8 (0.4–2.1)	1.2 (0.8–1.7)	4.5(3.6–5.6)
P-value	NS	NS	<0.001
Weekly alcohol and illicit drugs			
N	20	34	96
% SGA	25.0	11.8	40.6
OR (95% CI)	2.8 (1.0–7.6)	1.1 (0.4–3.2)	5.7 (3.8–8.6)
P-value	0.049	NS	<0.001

but may not have changed mean BW in the groups that contained the reported adverse behaviors. A strength of our study is that information on maternal behavior was prospectively collected at the first antenatal visit, thus minimizing the risk of recall bias. One in eight women nationally delivers in our maternity hospital and the population studied was large and contemporary in an developed country. The information on GA was of high quality because the Hospital routinely dates the pregnancy with ultrasound at the first antenatal visit.

What is already known on this topic

Previous reports have inconsistent effects of alcohol on BW.[20–23] The mechanisms for the interaction between maternal smoking and alcohol consumption during pregnancy are uncertain. Nicotine is metabolized mainly in the liver and heavy alcohol consumption during pregnancy may impair nicotine clearance, disrupting blood flow to the foetus.[24] One study found that although alcohol consumption alone had no effect, smoking >20 cigarettes/day combined with consuming >120 g of alcohol per week resulted in a 7.2% decrease in BW.[24] In contrast, an increase in BW was found with low to moderate alcohol intake, following adjustments for smoking, possibly owing to increased protein synthesis, earlier embryo implantation and/or accelerated growth of the embryo.[21,22,25–27]

Previous reports have suggested that cannabis and illicit drug usage, particularly cocaine, are associated with restrictions in foetal growth.[28–30] However, the associations are far from clear because of the omission of adjustments for confounding variables.[31] In an American multicenter study of 8637 women, for example, cocaine but not cannabis was associated with an increased risk of LBW and IUGR.[32] In another, the rate of LBW babies born to smokers was 5.7% and in women abusing illicit drugs the rate was 5.4%. A combination of smoking and illicit drugs almost doubled the rate of LBW indicating an accumulative effect of these behaviors on BW.[29]

Comparisons of the interactions between modifiable maternal risk factors and BW is challenging because there is no standardization for quantifying, timing and verifying smoking, alcohol and illicit drug use. Also, GA is one of the key determinants of BW and the accuracy of pregnancy dating varies, particularly in socially disadvantaged populations.[33]

What this study adds

Our study is the first, to our knowledge, that investigates the effects of smoking combined with alcohol and drug use on foetal growth in the same cohort of women in a developed country. Furthermore, we used customized centiles that were calculated by adjusting for several confounding variables for SGA such as maternal anthropometry and nationality, thereby limiting their effects on the outcome.

We found the relationships between BW, HC, GA and SGA and maternal alcohol consumption and illicit drug use was complicated and dependent on whether the women smoked or not. Alcohol consumption and drug use were not associated with any change in BW, HC or gestation in never- or ex-smokers. However, never smokers who engaged in alcohol and illicit drug use concurrently had a higher risk of SGA. Women who combined smoking with illicit drug use, in isolation or combination with weekly alcohol had higher rates and ORs for SGA as well as lower mean BWs and HCs than women who smoked alone.

Smoking, alcohol and drug use during pregnancy are consistently linked with lower socioeconomic status.[34,35] Our results showed that smokers had higher levels of unplanned pregnancy and lower levels of employment whilst others have reported an association between maternal smoking and lower income, social class and education levels.[35] Maternal smokers are also less likely to take folic acid and have more nutritional inadequacies than non-smokers which may aggravate FGR.[36] It is possible that nutritional status may deteriorate further in women who smoke and use illicit drugs.[31,37] Thus, the reduction in BW found in our study may be confounded by variables such as lower socioeconomic status and poorer nutritional status in these women.

It is unlikely the amplification effect of concurrent smoking and illicit drug use on foetal growth parameters was a result of a dose-dependent relationship with cigarette use. These women did not differ in terms of the rates smoking >11 cigarettes per day from smokers who did not engage in other adverse behaviors. Furthermore, women who smoked and consumed weekly alcohol had higher rates of smoking >11 cigarettes per day compared to women who smoked alone, however no difference existed in terms of the neonatal outcomes investigated.

The measure of cigarettes per day inaccurately quantifies the dose of carbon monoxide and cotinine exposure during pregnancy due to several factors such as cigarette inhalation intensity and frequency.[38] Over the previous two decades studies have reported that neonatal BW, length and HC correlate better with cotinine concentrations than self-reported number of cigarettes.[39,40]

A study conducted in a non-pregnant population demonstrated that the mean level of cotinine per cigarette was 36% lower in 'heavy smokers' of ≥20 cigarette per day compared to 'light smokers' of <20 cigarettes per day.[41] Although 'light smokers' are considered less dependent smokers, cotinine concentrations indicate that these women are exposed to more chemicals per cigarette due to more intensive inhalation.[38,41]

Tobacco is the most commonly abused substance during pregnancy, and tobacco smoking is, independently, more influential on foetal growth than alcohol or drug use alone.[29] A woman smoking 10 cigarettes per day will receive 100 mg of nicotine daily, which reaches the maternal brain in as little as 7 seconds.[42] The foetus is exposed to no other drug at such a high frequency and thus, it is not surprising that smoking is more strongly associated with aberrant foetal growth than other drugs.

There is evidence that almost half of women who smoke before pregnancy stop smoking in early pregnancy without professional support.[43] However, the number of women who succeed in stopping for the duration of the pregnancy after they present for obstetric care is as low as 1%.[43] Our study shows that smoking is an important modifiable risk factor that merits greater prioritization in the maternity services and that these women may require additional support in addressing not only their nicotine addiction but also other addictive behaviors.

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