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PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

Effects of codeine on pregnancy outcome: results from a large population-based cohort study

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Abstract
Background Guidelines on codeine safety during pregnancy rely on small studies with inconsistent results, and associations between codeine use during pregnancy and increased risk of congenital malformations remain unsubstantiated.
Objectives Our objective was to analyze the effect of codeine on pregnancy outcome.
Methods Pregnancy outcomes of 2,666 women who used codeine during pregnancy were compared with 65,316 women who used no opioids during pregnancy. Information on maternal sociodemographic and medical characteristics, potential confounders, and pregnancy outcome was obtained from The Norwegian Mother and Child Cohort Study [den norske Mor & barn-undersøkelsen (MoBa)] data set and the Medical Birth Registry of Norway (MBRN) data set. The data sets were linked via the maternal personal identification number. Associations between codeine therapy and pregnancy outcomes were identified using logistic regression analyses.
Results No significant differences were found in the survival rate [adjusted odds ratio (OR) 0.9, 95% confidence interval (CI) 0.6–1.5] or the congenital malformation rate (adjusted OR 0.9, 95% CI 0.8–1.1) between codeine-exposed and unexposed infants. Codeine use anytime during pregnancy was associated with planned Cesarean delivery (adjusted OR 1.4, 95% CI 1.2–1.7; $P<0.0001$). Third-trimester use was associated with acute Cesarean delivery (adjusted OR 1.5, 95% CI 1.3–1.8; $P<0.0001$) and postpartum hemorrhage (adjusted OR 1.3, 95% CI 1.1–1.5; $P<0.0001$). No significant associations with other adverse pregnancy outcomes were found.
Conclusions No effects of maternal codeine intake during pregnancy were observed on infant survival or congenital malformation rate. Our findings are reassuring; however, the association with acute Cesarean delivery and postpartum hemorrhage may justify a certain level of caution when administering codeine toward the end of pregnancy.

Keywords Codeine · Delivery complications · Pregnancy outcome

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Introduction

Few studies address the safety of codeine use during pregnancy despite its extensive use as an analgesic and antitussive in the general population. The frequency of codeine use during pregnancy has been shown to range between 1% and 3.5% [1–3]. Studies specifically targeting

codeine safety during pregnancy are either small case–control studies or case reports with inherent methodological limitations that generally warrant cautious interpretation. No data from cohort studies are available to date. One case–control study of 504 children with neuroblastoma found an association with in utero exposure to codeine [odds ratio (OR) 3.4, 95% confidence interval (CI) 1.4–8.4] [4]. Another of 599 infants found that mothers who gave birth to infants with cleft palate or cleft lip with or without cleft palate used opioid analgesics (mainly codeine) much more frequently than the control group; the largest difference was seen for codeine use during the first trimester (8.6% compared with 2.1% of infants in the control group; $P<0.01$) [5]. In a third case–control study of 1,370 infants, 12 infants with major congenital malformations had been exposed to codeine during the first trimester compared with seven in the control group (OR 3.7, Fisher's one-tailed P value 0.004) [6]. Neonatal abstinence syndrome has been described in two cases in which codeine was used by the mother over a period of several days close to term [7]. Two other reports described an association between neonatal abstinence syndrome and possibly cerebral infarction after maternal intake of codeine close to term [8].

Evidently, most of studies and case reports focus either on the possible teratogenicity of codeine or neonatal abstinence syndrome. The latter has mainly been shown to be associated with other opioids [9]. Other pregnancy outcomes, including postpartum complications, have only been studied in populations using opioid analgesics in general and those of addicted pregnant women [10–12] and not in pregnant women taking codeine in therapeutic doses. It is likely that these studies were subject to bias due to inclusion of populations with very specific sociodemographic and lifestyle characteristics, and the effects of codeine use as such would thus be difficult to evaluate [10–12]. Notwithstanding, leading literature sources on the safety of drug use during pregnancy suggest that sporadic use of codeine is safe except toward the end of pregnancy [9, 13].

Using data from a large prospective cohort study, our aim was to evaluate the potential teratogenicity of codeine and investigate possible associations with other adverse pregnancy outcomes that have not been studied so far.

Methods

Data for this study were retrieved from The Norwegian Mother and Child Cohort Study [den norske Mor & barn-undersøkelsen (MoBa)] data set (version four) released in December 2008 and from records from the Medical Birth Registry of Norway(MBRN). MoBa [14] is a prospective cohort study conducted by the Norwegian Institute of Public Health. The overall aim of the study is to examine the effect of a vast number of exposures on pregnancy outcome and maternal and fetal health during pregnancy and postpartum. Data were obtained from three self-administered questionnaires answered by pregnant women who participated in the study between 1999 and 2006. Pregnant women received a postal invitation with an informed consent form and the first questionnaire prior to their first ultrasound scan during gestational weeks 17 or 18. This first questionnaire covered the time period between the 6 months prior to pregnancy and the 18th gestational week. The second questionnaire covered the time period between the 19th and 29th gestational week, and the third questionnaire covered the time period from the 30th gestational week until birth. The questionnaires covered sociodemographic and lifestyle data, maternal medical history, maternal health during the pregnancy, drug use, and neonatal health. The overall response rate was 43.5% [15]. The MBRN [16] encompasses all births in Norway and has been prospectively collecting data on all deliveries since 1967. Approximately 60,000 infants are born in Norway every year, corresponding to an annual birth rate of 1.2 infants per 100 inhabitants. Data stem from mandatory standardized forms filled out by midwives, obstetricians, and/or pediatricians at each delivery and from the mother's pregnancy medical records. The standardized forms cover sociodemographic and lifestyle information on the mother and medical information including maternal health prior to and during pregnancy as well as delivery and postpartum complications and interventions. Data from the two sources were linked via the woman' personal identification number, which is assigned to every legal resident in Norway. The study was approved by the Regional Committee for Ethics in Medical Research, Region South, and the Norwegian Data Inspectorate.

Study population

The original quality-assured data file released for research in 2008 (version 4) consisted of data on 72,934 women. All these women had a pregnancy outcome registered in the MBRN. Prior to release of this data file, 3.5% of the women in the study did not have a pregnancy outcome registered, mainly due to spontaneous abortions that happened early on in pregnancy. Of the 72,934 women, 3,005 who did not complete the first questionnaire were excluded. A total of 69,929 pregnant women with records both in both data sets were eligible for inclusion (95.9% of the original data file). In addition, women using opioids other than codeine (i.e., ethylmorphine, morphine, ketobemidone, tramadol, pethidine, dextropropoxyphene, oxycodone, buprenorphine, and methadone) ($n=1,664$) and women using both codeine and one or several of the

aforementioned opioids (n=283) were excluded. The final study population therefore consisted of 67,982 women (93.2% of the original data file). Multiple pregnancies were included; however, only data on the first-born infant were used, as only these were linked to maternal data.

Explanatory variables

Explanatory variables consisted of the following subsets: (i) pregnant women who used codeine (alone or in a fixed combination with paracetamol) during pregnancy (total) (yes/no); (ii) pregnant women who used codeine (alone or in a fixed combination with paracetamol) during the first trimester (gestational weeks 0–12) (yes/no); (iii) pregnant women who used codeine (alone or in a fixed combination with paracetamol) during the second trimester (gestational weeks 13–28) (yes/no); (iv) pregnant women who used codeine (alone or in a fixed combination with paracetamol) during the third trimester (gestational week 29 until delivery) (yes/no). Drug therapy was classified and grouped according to the Anatomical Therapeutic Chemical (ATC) classification system developed by the World Health Organization (WHO) [17]. ATC codes used were R05DA04 (codeine alone) and N02AA59 (codeine in a fixed combination with paracetamol). Codeine in fixed combinations with acetylsalicylic acid or other nonsteroidal antiinflammatory drugs is not available in Norway. The explanatory variable subsets were created using answers to questions regarding both codeine use and maternal illness in questionnaires one and two as long as the ATC code for codeine and the timing of either codeine use or the medical condition was specified. Subanalyses were performed to investigate possible associations between the extent of codeine use (number of days used, categorized as 1–7 days, 8–14 days, and >14 days) and pregnancy outcome.

Confounding factors

Confounding factors included sociodemographic, lifestyle, and medical characteristics (Tables 1 and 2), concomitant drug use (Table 3) (this information was derived from theMoBa questionnaires), and factors related to delivery (this information was derived from the MBRN). Different potential confounding factors, the majority of which are listed in Tables 1–4 were selected for each pregnancy outcome. (Please find the complete list of confounding factors used in the analyses in Electronic supplementary material (ESM) 1: Confounding factors.)

Outcome variables

Outcome variables were retrieved from both MoBa and MBRN. The choice of outcome variables was based on current information on codeine safety during pregnancy and studies on the effect of opioid analgesics on pregnancy outcome and labor progress, with special focus on prolonged labor and neonatal complications. The chosen variables consisted of any congenital malformations detected at birth, major congenital malformations detected at birth, survival (live birth, miscarriage/stillbirth, perinatal death, death during the first 12 months of life), birth weight <2,500 g, gestational age <37 weeks, Apgar scores <7 at 1 and 5 min, neonatal respiratory depression, neonatal hypoglycemia, newborn admitted to intensive care unit, acute Cesarean delivery, planned Cesarean delivery, atonic uterus, prolonged labor, and postpartum hemorrhage >500 ml. All outcome variables were dichotomized into yes or no categories.

Statistical analysis

Logistic regression analyses were performed to identify significant associations between codeine therapy and pregnancy outcome. Subsets of confounding factors were selected for each pregnancy outcome depending on clinical plausibility, statistical significance, and size of outcome event rates (a full list of confounding factors controlled for in each analysis is available in the ESM 1: Confounding factors). Confounding factors controlled for in logistic regression analyses were chosen on the basis of theoretical clinical significance and initial Pearson's χ^2 analyses, where the P value was <0.25. Preliminary logistic regression analyses enabled the subsequent removal of potential confounding variables, with a P value of >0.5, with the exception of instances in which the coefficient change of the exposure variable was >20%. The final logistic regression models for pregnancy outcome included statistically significant variables and clinically plausible interactions only. The threshold for retaining these variables in the final logistic regression model was P<0.05. Potential multicollinearity among the independent variables was identified using multiple regression analysis. Tolerance values for multicollinearity were set at >0.5. Hosmer and Lemeshow goodness-of-fit tests >0.5 indicated robust models and were considered valid in the logistic regression analyses. All statistical analyses were performed with the Statistical Package for Social Sciences SPSS for Windows version 16.1 (SPSS, Chicago, IL, USA). Risk ratio estimates are given as odds ratios (OR) with 95% confidence intervals (CI).

Results

Of the 67,982 pregnant women in the study, 2,666 (3.9%) used codeine during pregnancy (exposed group), whereas 65,316 (96.1%) did not (unexposed group). In the exposed

Table 1 Maternal characteristics of the study population

	Women who used codeine during pregnancy; exposed group (n=2,666)		Women who did not use opioids during pregnancy: unexposed group (n=65,316)	
	No.	%	No.	%
Maternal age (years)				
< 20	32	1.2	714	1.1
20 – 29	1,194	44.8	28,840	44.1
30 – 39	1,380	51.8	34,530	52.9
≥ 40	60	2.2	1,234	1.9
Parity				
0	1,153	43.2	28,523	43.7
≥1	1,513	56.7	36,787	56.3
Plurality				
1	2,611	97.9	64,123	98.2
> 1	55	2.1	1,193	1.8
Ethnicity				
Of Norwegian descent	2,572	96.5	61,782	94.6
Not of Norwegian descent	94	3.5*	3,534	5.4
Marital status				
Married/cohabiting	2,553	95.8	63,484	97.2
Other	113	4.2*	1,832	2.8
Education				
Primary	80	3.0	1623	2.5
Secondary	1,005	37.7	20,803	31.8
Tertiary	1,525	57.2*	41,607	63.4
BMI prior to pregnancy (kg/m^2)				
< 18.5	65	2.4	2,002	3.1
18.5 – 25.0	1,479	55.5	41,930	64.2
> 25.0	1,050	39.4*	19,483	29.8
Folic acid intake prior to pregnancy	596	22.3	15,041	23.0
Sick leave lasting longer than 2 weeks during pregnancy	1,023	38.4*	20,505	31.4
Smoking at gestational week 30	391	14.7*	6,180	9.4
Alcohol intake during pregnancy[a]	1,421	53.3**	3,3512	51.3

Some data do not add up to the total due to missing values

* Pearson's χ^2 test $P<0.001$ when compared with the unexposed control group,

** Pearson's χ^2 test $P<0.05$ when compared with the unexposed control group

[a] Including data on sporadic intake and intake before the women were aware of their pregnancy

group, 45 women used codeine alone and 2,621 used codeine in a fixed combination with paracetamol. A higher proportion of exposed women had attained lower levels of education, were not married or cohabiting with their partner, were overweight (had a body mass index >25 kg/m^2) prior to pregnancy, and smoked throughout pregnancy (Table 1). Moreover, these women were more likely to suffer from medical complications both prior to and during pregnancy (Table 2). Concomitant nonsteroidal antiinflammatory drug and psychotropic agent use was also significantly higher in the exposed group than in the unexposed group (Table 3). No significant difference was found in the survival rate of infants when comparing the exposed (99.4% live births) with the unexposed (99.2% live births) groups (adjusted OR 0.9, 95% CI 0.6–1.5] (Table 4). No significant difference in overall congenital malformation rate was found when comparing the exposed (4.9%) with the unexposed (5.0%) group (adjusted OR 0.9, 95% CI 0.8–1.1). No significant difference in the major congenital malformation rate was found between the exposed (2.9%) and unexposed (2.9%) group (adjusted OR 0.9, 95% CI 0.7–1.2) (Table 4).

Codeine use anytime during pregnancy was significantly associated with an increased risk of acute Cesarean delivery (12.8% in the exposed group compared with 8.9% in the

Table 2 Maternal health and pregnancy complications

	Women who used codeine during pregnancy: exposed group (n=2,666)		Women who did not use opioids during pregnancy: unexposed group (n=65,316)	
	No.	%	No.	%
Maternal health during pregnancy				
Acute musculoskeletal pain	2,534	95.0*	58,005	88.8
Migraine and/or headache	1,536	57.6*	23,115	35.4
Proteinuria	766	28.7*	13,262	20.3
Temperature>38.5°C fever associated with a rash	590	22.1*	10,453	16.0
Hospitalization**	270	10.1*	2,839	4.3
Urinary tract infection and/or pyelonephritis	258	9.7%***[a]	5,371	8.2
Preeclampsia and/or eclampsia	157	5.9*	2,592	4.0
Involved in an accident	122	4.7*	2,003	3.1
High blood pressure during the first trimester[a]	65	2.4*	998	1.5
Maternal health prior to pregnancy				
Musculoskeletal pain (any)	1,892	71.0*	34,562	52.9
Arthritis/Systemic Lupus Erythematosus/ Fibromyalgia	348	13.0*	2,504	3.8
Depression	258	9.7*	3,533	5.4
Asthma	190	7.1*	2,885	4.4
Cardiac disease	140	5.2*	2,108	3.2
Thyroid disorder	70	2.6****	1,293	2.0
Diabetes (type I or II)	44	1.6	810	1.2
Obstetric complications				
Number of ultrasound examinations				
< 2	462	17.3	15,491	23.7
2 – 4	1,255	47.1	30,366	46.5
> 5	650	24.3*	10,205	15.6
Vaginal bleeding during pregnancy[b]	601	22.5*	11,979	18.3
First trimester	498	18.7*	10,027	15.3
Second and/or third trimesters	226	8.5*	4,295	6.6
Oligohydramnios	62	2.3	1,506	2.3
Placenta previa	46	1.7****	821	1.3
Polyhydramnios	32	1.2	556	0.8
Abruptio placentae	17	0.6	271	0.4

* Pearson's χ^2 test $P<0.001$ when compared with the unexposed control group,

** Excluding hospitalization due to vaginal bleeding and high blood pressure,

*** Pearson's χ^2 test $P<0.01$ when compared with the unexposed control group

**** Pearson's χ^2 test $P<0.05$ when compared with the unexposed control group.

[a] Defined as systolic blood pressure≥140 mmHg

[b] Vaginal bleeding lasting more than 1 day or of an amount exceeding a trace or two or more episodes of bleeding or vaginal bleeding which has led to hospitalization

unexposed group) (adjusted OR 1.3, 95% CI 1.1–1.5), planned Cesarean delivery (7.4% in the exposed group compared with 5.0% in the unexposed group) (adjusted OR 1.4, 95% CI 1.2–1.7), and postpartum hemorrhage (18.3% in the exposed group compared with 14.5% in the unexposed group) (adjusted OR 1.2, 95% CI 1.1–1.4) (Table 4).

Upon analyzing the effects of codeine on pregnancy outcome during the three specific trimesters, an increased risk of planned Cesarean delivery was seen after exposure in the first (7.3%; adjusted OR 1.4, 95% CI 1.1–1.7), second (7.5%; adjusted OR 1.5, 95% CI 1.2–1.8), and third (8.9%; adjusted OR 1.6, 95% CI 1.3–2.0) trimesters. Third

Table 3 Frequency of concomitant nonsteroidal antiinflammatory drug and psychotropic agent use during pregnancy

Drug	Women who used codeine during pregnancy: exposed group (n=2,666)		Women who did not use opioids during pregnancy: unexposed group (n=65,316)	
	No.	%	No.	%
NSAIDs	759	28.5*	8,271	12.6
Ibuprofen	470	17.6*	6,269	9.6
Diclofenac	170	6.4*	703	1.1
Naproxen	85	3.2*	782	1.2
Other[a]	185	6.9*	1,323	2.0
Psychotropic agents	359	13.5*	3,159	4.8
Antidepressants[b]	172	6.4*	1,935	3.0
Anxiolytics[c]	132	4.9*	788	1.2
Hypnotics[d]	86	3.2*	490	0.7
Antipsychotics[e]	60	2.2*	452	0.7

NSAIDS nonsteroidal anti-inflammatory drugs

* Pearson's χ^2 test $P<0.001$ when compared with the unexposed control group

[a] Including piroxicam, meloxicam, indomethacin, acetylsalicylic acid, ketoprofen, nabumetone, and tolfenamic acid

[b] Including selective serotonin reuptake inhibitors, tricyclic antidepressants, monoamine oxidase inhibitors, mianserin, mirtazapine, and venlafaxine

[c] Including diazepam, oxazepam, alprazolam, hydroxyzine, and buspirone

[d] Including nitrazepam, flunitrazepam, zopiclone, and zolpidem

[e] Including levomepromazine, perphenazine, prochlorperazine, flupenthixol, zuclopenthixol, olanzapine, quetiapine, and risperidone

trimester use was, in addition, associated with an increased risk of acute Cesarean delivery (15.1%; adjusted OR 1.5, 95% CI 1.3–1.8) and postpartum hemorrhage (20.3%; adjusted OR 1.3, 95% CI 1.1–1.5) (Table 4). Subanalyses on the effect of codeine therapy duration on pregnancy outcomes revealed that codeine use lasting >14 days was significantly associated with planned (but not acute) Cesarean delivery (unadjusted OR 3.2, 95% CI 1.3–7.9). No dose–effect relationship was found for postpartum hemorrhage.

Discussion

Information on the safety of analgesic use during pregnancy is an important issue for all clinicians prescribing these drugs to pregnant women. It is often not feasible to prescribe the more thoroughly documented nonopioid analgesics either for safety reasons or lack of adequate pain relief. The safety profiles of as many different analgesics as possible must be known before an individual risk–benefit evaluation can be done. In this study, codeine use during pregnancy was not found to be associated with infant survival rate, congenital malformation rate, or other adverse pregnancy outcomes, except for Cesarean delivery and excessive postpartum hemorrhage. Unlike previous studies [4, 5, 7, 8] and other medical literature sources that rely either on data regardng opioid analgesic use in general or a few case studies [9, 13], we found no increased risk of congenital malformations or neonatal respiratory depression. Associations of codeine use during pregnancy and neonatal abstinence syndrome were unfortunately not feasible to evaluate, as neonatal abstinence syndrome scores were not routinely applied. However, neither low Apgar scores nor admission of the neonate to intensive care were associated with codeine use during pregnancy, and these outcomes are also partly representative of neonatal abstinence syndrome.

Of other adverse pregnancy outcomes, the strongest association was between codeine use during pregnancy and increased risk of planned Cesarean delivery. This association remained significant, even after controlling for several clinically and statistically significant potential confounders, including high birth weight, fetal malpresentation, plurality, placenta previa, and others (a full list is available in the ESM 1: Confounding factors). A dose–effect relationship between codeine and planned Cesarean delivery was also detected. Nevertheless, we believe it is highly likely that the association was due to underlying medical conditions. Thirteen percent of exposed women suffered from chronic conditions, including arthritis, systemic lupus erythematosus, and fibromyalgia, compared with only 3% in the unexposed group; almost 10% had depression compared with only 5% of the unexposed women; a significantly

Table 4 Adjusted Odds Ratios (OR) for pregnancy outcome in women who used codeine during pregnancy compared with the unexposed control group

Pregnancy outcome	Women who used codeine during pregnancy: exposed group																Women who did not use opioids during pregnancy: unexposed group (*n*=65,316)	
	Total pregnancy (*n*=2,666)				First trimester (gestational weeks 0–12) (*n*=1,693)				Second trimester (gestational weeks 13–28) (*n*=1,955)				Third trimester (gestational week 29 until delivery) (*n*=1,255)					
	No.	%	OR	95%CI	No.	%	OR	95%CI	No.	%	OR	95%CI	No.	%	OR	95%CI	No.	%
Congenital malformations detected at birth																		
Any	130	4.9	0.9	0.8 – 1.1	77	4.5	0.9	0.7 – 1.1	91	4.7	0.9	0.7 – 1.1	67	5.3	1.0	0.7 – 1.3	3,247	5.0
Major	77	2.9	0.9	0.7 – 1.2	40	2.4	0.8	0.5 – 1.1	50	2.6	0.8	0.6 – 1.1	45	3.6	1.1	0.8 – 1.6	1,904	2.9
Survival (live birth)	2,649	99.4	0.9	0.6 – 1.5	1,677	99.1	0.6	0.4 – 1.0	1,939	99.2	0.7	0.4 – 1.2	1,252	99.8	2.4	0.7 – 7.5	64,797	99.2
Birth weight<2500 g	124	4.7	1.1	0.9 – 1.3	78	4.6	1.1	0.8 – 1.4	94	4.8	1.1	0.9 – 1.4	63	5.0	1.1	0.8 – 1.5	2,579	3.9
Gestational age<37 weeks	209	7.8	1.1	0.9 – 1.3	132	7.8	1.1	0.9 – 1.4	151	7.7	1.1	0.9 – 1.3	106	8.4	1.2	0.9 – 1.5	3,910	6.0
Apgar score																		
< 7 at 1 min	183	6.9	1.2	1.0 – 1.5	118	7.0	1.3	1.0 – 1.6	131	6.7	1.2	1.0 – 1.5	83	6.6	1.2	0.9 – 1.6	3,506	5.4
< 7 at5 min	44	1.7	1.3	0.9 – 1.9	33	1.9	1.6	1.0 – 2.6	35	1.8	1.5	0.9 – 2.3	15	1.2	1.0	0.5 – 1.8	875	1.3
Neonatal respiratory depression	131	4.9	1.0	0.9 – 1.3	76	4.5	0.9	0.7 – 1.2	88	4.5	0.9	0.7 – 1.1	65	5.2	1.1	0.8 – 1.4	2,706	4.1
Hypoglycemia	72	2.7	1.1	0.8 – 1.4	45	2.7	1.0	0.7 – 1.4	50	2.6	1.0	0.7 – 1.4	41	3.3	1.2	0.9 – 1.7	1,415	2.2
Newborn admitted to intensive care unit	337	12.6	1.1	1.0 – 1.3	197	11.6	1.0	0.9 – 1.2	233	11.9	1.1	0.9 – 1.2	176	14.0	1.1	1.0 – 1.4	6,520	10.0
Cesarean delivery (acute)	340	12.8	1.3	1.1 – 1.5*	191	11.3	1.1	0.9– 1.3	223	11.4	1.1	0.9 – 1.3	189	15.1	1.5	1.3 – 1.8*	5,834	8.9
Cesarean delivery (planned)	198	7.4	1.4	1.2 – 1.7*	124	7.3	1.4	1.1– 1.7*	147	7.5	1.5	1.2 – 1.8*	112	8.9	1.6	1.3 – 2.0*	3,265	5.0
Atonic uterus	137	5.1	1.2	1.0 – 1.5	88	5.2	1.3	1.0 – 1.6	97	5.0	1.2	1.0 – 1.5	69	5.5	1.3	1.0 – 1.7	2,808	4.3
Prolonged labor[a]	217	8.1	1.1	0.9 – 1.2	128	7.6	1.0	0.8 – 1.2	149	7.6	1.0	0.9 – 1.2	99	7.9	1.0	0.8 – 1.2	4,542	7.0
Postpartum hemorrhage[b]	489	18.3	1.2	1.1 – 1.4*	301	17.8	1.2	1.1 – 1.4*	344	17.5	1.2	1.0 – 1.4	255	20.3	1.3	1.1 – 1.5*	9,488	14.5

CI confidence interval

* Pearson's $\chi 2$ test $P<0.0001$

[a] Labor lasting >18 h

[b] Hemorrhage >500 ml

higher number of exposed women had asthma and cardiac disease; about 10% were hospitalized during pregnancy compared with 4% of the unexposed group; and 5.9% had preeclampsia and/or eclampsia compared with 4% of the unexposed group. Several of these diseases and conditions, which were not feasible to control for in this particular analysis, are associated with planned Cesarean delivery [18]. Association codeine therapy duration may also be indicative of the severity of the underlying medical conditions.

Notwithstanding, we cannot definitively exclude a direct association between codeine and acute Cesarean delivery and postpartum hemorrhage. A study on 315,085 pregnancies concluded that preeclampsia was significantly associated with postpartum hemorrhage and postulated that a deprivation of angiogenic factors resulting in the preeclamptic state may also play a role in postpartum hemorrhage [19]. It is also known that opioid analgesics administered during labor in the form of epidural analgesia are implicated in uterine atony [20, 21]. Failure or weakening of myometrial contractions may result in excessive postpartum hemorrhage as well as Cesarean delivery [18]. However, atonic uterus and prolonged labor, cesarean delivery, induction of labor, epidural analgesia, third- or fourth-grade perineal tears and high birth weight, preeclampsia and/or eclampsia, placenta previa, and *abruptio placentae*, among others (a full list is available in the ESM 1: Confounding factors), were all controlled for in our analyses. It should be noted that the vast majority of women (98.3%) in the exposed group used codeine in a fixed combination with paracetamol. However, we found no evidence of a possible association between paracetamol and increased risk of acute Cesarean delivery or postpartum hemorrhage.

Several study strengths and limitations merit specific attention. Our study is the only prospective cohort study on codeine use during pregnancy. Information derived from both MoBa and NMBR provided us with an extensive array of medical and sociodemographic characteristics of the study population. This enabled us to control for a very large number of—but not all—important confounding factors. Several validity studies concluded that the accuracy of registration of major congenital malformations is satisfactorily high [22, 23]. The prospective collection of the majority of data greatly reduced the risk of recall bias. Differential reporting by the pregnant women was also avoided, as their pregnancy outcome was unknown to most of them at the time of data collection. In contrast to many other large studies, the chances of obtaining false positive associations due to multiple testing were reduced by including a minimum number of cases (more than four) in the final analysis. Moreover, all associations that were statistically significant had P values <0.0001. On the other hand, a difference in the prevalence of drug use and pregnancy outcomes in the study population compared with the general population may have occurred, as participant response rate was only 43.5%. However, it has been shown that only minor differences (<2% in absolute differences in sociodemographic variables) between MoBa participants and the general population of pregnant women exist, and no differences in the estimates of association measures were found between participants and the general population [15, 24]. Despite this, the risk of false negative associations due to underrepresentation of certain sociodemographic groups, possible underreporting of codeine use during pregnancy, and the rarity of some pregnancy outcomes such as major malformations, should be taken into account. Analyses on specific malformations could not be undertaken due to low statistical power. It was also not feasible to determine the codeine dose pregnant women used and the exact point in time it was taken.

In conclusion, the fact that codeine use during pregnancy had no effect on infant survival or congenital malformation rate is particularly reassuring considering the size and singularity of this cohort study and the accuracy of pregnancy outcome reporting. We found an association between codeine use anytime during pregnancy and planned Cesarean delivery and between third-trimester codeine use and acute Cesarean delivery and excessive postpartum hemorrhage. Whereas the increased risk of Cesarean delivery, in particular, may be caused by underlying medical conditions, a direct association between codeine use toward the end of pregnancy and acute Cesarean delivery and postpartum hemorrhage cannot be definitively excluded.

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Conflict of interest The authors declare that they have no conflict of interest.

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