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Complete List of Authors:	Charlton, Brittany; Harvard School of Public Health, Department of Epidemiology; Boston Children's Hospital, Division of Adolescent and Young Adult Medicine Mølgaard-Nielsen, Ditte; Statens Serum Institut, Department of Epidemiology Research Svanström, Henrik; Statens Serum Institut, Department of Epidemiology Research Wohlfahrt, Jan; Statens Serum Institut, Department of Epidemiology Research Pasternak, Björn; Statens Serum Institut, Department of Epidemiology Research Melbye, Mads; Dept of Epidemiology Research
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Maternal use of oral contraceptives and risk of birth defects

Brittany M. Charlton, ScD[a], Ditte Mølgaard-Nielsen, MSc[b], Henrik Svanström, MSc[b], Jan Wohlfahrt, DMSc [b], Björn Pasternak, MD[b], Mads Melbye, MD[b]

[a]Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA, USA & Division of Adolescent and Young Adult Medicine, Boston Children's Hospital, Boston, MA, USA & Department of Pediatrics, Harvard Medical School, Boston, MA USA

[b]Department of Epidemiology Research, Statens Serum Institut, Copenhagen S, Denmark

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Address correspondence to: Brittany M. Charlton, Department of Epidemiology, Harvard T.H. Chan School of Public Health, 677 Huntington Avenue, 9th Floor, Boston, MA 02115. Telephone: (617) 432-1050 Fax: (617) 566-7805 Email address: bcharlton@mail.harvard.edu

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ABSTRACT

Objectives: To investigate whether recent OC use (up to three months before) or continued OC use after pregnancy onset was associated with an increased risk of major birth defects.

Design: A prospective observational cohort study.

Setting: Multiple Danish registries, data collected between 1997 and 2011.

Participants: 880,694 live births prospectively followed for 14 years; OC use was collected from the National Prescription Register and we conservatively assumed that a woman was exposed up to the date of her most recently filled prescription.

Main Outcome Measures: Cases of major birth defects were ascertained from the National Patient Register allowing for a 1-year follow-up after birth. Major birth defects were defined according to the European Surveillance of Congenital Anomalies (EUROCAT) classification excluding minor defects. Logistic regression was used to estimate prevalence odds ratios of any major birth defect as well as categories of birth defect subgroups.

Results: The prevalence of major birth defects (per 1,000 births) was consistent across each OC exposure group: 25.1 for never users, 25.0 for OC use >3 months before pregnancy onset (reference), 24.9 for OC use 0 to ≤3 months before pregnancy onset ("recent"), and 24.8 for OC use after pregnancy onset. There was no higher prevalence of any major birth defect associated with OC exposure among women with recent use before pregnancy onset [prevalence odds ratio, 95% confidence interval: 0.98 (0.93 to 1.03)] or use after pregnancy onset [0.95 (0.84 to 1.08)] as compared with use >3 months before pregnancy. Also, there was no higher prevalence of any subgroup of birth defects (e.g., limb).

Conclusions: OC exposure just before or during pregnancy was not associated with a significantly increased risk of major birth defects; this should reassure patients and physicians.

INTRODUCTION

Oral contraceptives (OCs) are the most popular contraceptive method in many parts of the world[1,2]. While OCs are over 99% effective with perfect use, an estimated 9% of OC users become pregnant in their first year of use[3] due to missed or delayed doses, drug interactions, or illness[4] in what is known as a breakthrough pregnancy. Many more women will stop using OCs when planning a pregnancy and conceive within a few menstrual cycles. In both of these instances, a woman may inadvertently expose her fetus to exogenous sex hormones (e.g., progestins)[5,6].

Yet, despite decades of research on the safety of OC use, little is known about the association of OC use just before or during pregnancy with the offspring's health. In particular, it is unclear if these circulating exogenous sex hormones can harm the fetus and how long potential effects of circulating exogenous sex hormones may last. The literature has primarily focused on birth defects, but findings conflict and their interpretation is challenging due to methodologic limitations. For example, most of these studies were conducted over 30 years ago and relied on self-reported, retrospective exposure assessment in small case-control samples and examined a single outcome (e.g., limb defects)[7]. Some of these findings suggest that OC use is associated with certain birth defects—including hypoplastic left heart syndrome[8], gastroschisis[8], limb defects[9], and urinary tract anomalies[10]—while others found no such association[11-19].

With regard to mechanisms, exogenous sex hormones have been shown to increase vitamin A plasma levels[20], which can be teratogenic[21]. Studies also suggest that serum folate concentrations decrease after OC use and remain reduced up to three months after discontinuation; this could lead to a range of birth defects[5,6].

Using multiple Danish registries, we conducted a nationwide cohort study to investigate whether recent OC use (less than three months before pregnancy) or use during early pregnancy was associated with an increased risk of major birth defects.

METHODS

We used data from The Medical Birth Register that included all singleton live births delivered from January 1, 1997 to March 31, 2011. Births with a missing or implausible gestational age were excluded. After excluding infants with

birth defects with known causes (e.g., fetal alcohol syndrome) or chromosomal aberrations (N=2714), the final cohort included 880,694 live-born infants. Individual-level data were linked between registries using the Danish Civil Registration System's unique personal identification number assigned to all Denmark residents. The study was approved by the Danish Data Protection Agency and ethics approval was not required for Danish registry-based research.

Data Sources

The Medical Birth Register was established in 1968 and contains information on all Danish births, including the date of birth, multiple births, gestational age, and various newborn characteristics, as well as maternal characteristics such as parity and smoking status[22]. The National Patient Register includes information on outpatient and emergency department visits and inpatient admissions to all Danish hospitals[23]. From this we obtained diagnostic information on birth defects and maternal medical conditions. Information on age, place of residence, and place of birth of the women was obtained from the main administrative register known as the Central Person Register[24]. Statistics Denmark provided data on maternal education level, gross household income, and civil status.

In the Medical Birth Register, gestational age is calculated by the first day of the last menstrual period (LMP) and subsequently corrected in most pregnancies by ultrasonographic measurements. For this study, we estimated pregnancy onset by subtracting the gestational age from the date of birth.

Oral Contraceptive Exposure

The National Prescription Register contains information on drug prescriptions filled at Danish pharmacies since 1995, including the anatomical therapeutic chemical code (G03A for oral contraceptives) and the date the prescription was filled[25]. We conservatively assumed that a woman was exposed up to the date of her most recently filled prescription. We defined never users as those who never filled an OC prescription since the introduction of the prescription register. Given the high prevalence of OC use, never users are likely a highly selected group of individuals and therefore may not be the best reference group. Based on the previous literature, particularly on the proposed mechanism of decreased folate up to three months after stopping use[5 6], we modeled OC exposure using the following categories: >3 months before pregnancy onset (reference), 0 to ≤3 months before ("recent"), and after

pregnancy onset. The two primary exposures of interest were after pregnancy onset and recent use before pregnancy onset.

Major Birth Defects Outcome

Cases of major birth defects were ascertained from the National Patient Register allowing for a 1-year follow-up after birth. Validation studies of this registry showed that 88% of birth defects diagnoses[26] were correct when confirmed by medical record review. Major birth defects were defined according to the European Surveillance of Congenital Anomalies (EUROCAT) classification excluding minor defects (see Table S1 in the supplementary appendix)[27]. The primary outcome was any major birth defect and secondary outcomes were subgroups of major birth defects categorized by organ system. Some previous studies have observed associations between OC exposure and hypoplastic left heart syndrome[8], gastroschisis[8], limb defects[9], and urinary tract anomalies[10]. Analyses of limb and urinary tract defects were included in our secondary outcomes; we also added analyses of specific birth defects including gastroschisis and hypoplastic left heart syndrome.

Statistical Analyses

Logistic regression was used to estimate prevalence odds ratios of any major birth defect as well as categories of birth defect subgroups. For these category analyses, an infant could contribute to several analyses. For instance, if a child had one defect categorized as "nervous system" and another categorized as "eye," that pregnancy was categorized as a case in both analyses.

A priori knowledge on the risk factors for birth defects and determinants of OC use were used to select potential confounders for adjustment. Covariates included demographics (maternal age at pregnancy onset, calendar year, place of birth, county of residence, married/living with partner, level of education, and household income), parity, history of birth defects in a previous pregnancy, smoking in pregnancy, and health care utilization (prescription drug use in last six months, hospitalizations in the last five years, and outpatient contacts in the last five years). We imputed any missing covariate values with each variable's respective mode (see Table S2).

We conducted sensitivity analyses with propensity score matching. Using logistic regression, we estimated propensity scores as the probability of exposure to OCs after pregnancy onset given baseline characteristics at pregnancy onset. The propensity score also included all two-way interactions between demographic variables in the regression. Exposed women, defined as those who used OCs after pregnancy onset, were then matched, in a 1:4 ratio, to unexposed women, defined as those who stopped OC use >3 months before pregnancy onset, using the nearest neighbor–matching algorithm (a caliper width equal to 0.1 of the standard deviation of the logit score)[28 29].

We also ran further sensitivity analyses by also including birth defects identified among induced abortions after 12 gestational weeks [International Classification of Diseases-10 (ICD-10): O05.3 and O05.4] and stillbirths, as described in detail previously[30]. However, the registration of birth defects among induced abortions and stillbirths have not been validated. Data for this sensitivity analysis were available for January 1, 2004 to March 31, 2011 (N=429,940, see Table S3**)**.

SAS software (version 9.2) was used for all analyses.

RESULTS

Our study cohort was made up of 880,694 live-born infants of whom 22,013 were diagnosed with a major birth defect within the first year of life. Over two-thirds of the cohort mothers (69%, N=611,007) had used OCs but stopped >3 months before pregnancy onset, while 21% (N=183,963) never used OCs. However, 8% (N=74,542) had recently stopped using OCs (0 to ≤3 months before pregnancy onset) and 1% (N=11,182) used OCs beyond pregnancy onset, both categories we considered "exposed."

Table 1 shows the characteristics of cohort mothers according to OC exposure timing. Compared to women who had stopped using OCs >3 months before pregnancy onset (reference), both groups of exposed women were generally younger, less likely to be married/living with a partner, less educated, had a lower income, were less likely to be parous, and smoked more often during pregnancy.

The prevalence of major birth defects (per 1,000 births) was consistent across each of the OC exposure groups: 25.1 for never users, 25.0 for OC use >3 months before pregnancy onset (reference), 24.9 for OC use 0 to ≤3 months before pregnancy onset ("recent"), and 24.8 for OC use after pregnancy onset.

In our primary analyses, there was no increased risk of any major birth defect associated with OC exposure (see Table 2); this included women who had recently stopped using OCs [prevalence odds ratio, 95% confidence interval (CI): 0.98 (0.93 to 1.03)] and women who used OCs after pregnancy onset [0.95 (0.84 to 1.08)]. These results were consistent in sensitivity analyses, which included the addition of pregnancies ending as stillbirths and induced abortions to the cohort [0.95 (0.89 to 1.02) and 0.99 (0.84 to 1.16), see Table 4]. The result for use of OCs after pregnancy onset were likewise consistent in a sensitivity analysis using propensity score-matching [0.95 (0.83 to 1.09), see Table 4]. None of our findings varied by levels of age, smoking during pregnancy, or education (all *p* values for interaction terms with OC use >0.05, variables categorized as in Table 1), and our results proved to be robust when restricted to women who were 25-34 years of age and Danish born [never OC use: 1.05 (0.99 to 1.10), recent OC use to pregnancy onset: 0.99 (0.94 to 1.05), and OC use after pregnancy onset: 0.91 (0.78 to 1.04)].

In our secondary analyses, there was no significantly increased risk of any subgroup of major birth defects associated with OC exposure (see Table 3). All prevalence odds ratios for the two OC exposure groups were less that 1.15 with the exception of abdominal wall defects. We also examined more specific birth defects including gastroschisis [0.84 (0.26 to 2.68)] and hypoplastic left heart syndrome [2.47 (0.77 to 7.97)] without any significantly increased risk; both of which had three cases that were exposed to OC use after pregnancy onset.

Never use of OCs was associated with a slight increase in risk of any major birth defect [1.06 (1.02 to 1.10)] compared to the reference group of women who had stopped using OCs >3 months before pregnancy onset (Table 2). When grouped by type of major birth defect, never use of OCs was associated with increased risk of genital defects as well as those in the nervous and digestive systems and with decreased risk of abdominal wall defects (see Table 4).

DISCUSSION

We assessed the association between maternal OC exposure during or shortly before pregnancy and major birth defects. Overall, we found no significant increase in risk of birth defects or subgroups of defects.

Comparisons across the literature are challenging since the time windows of OC exposure and the reference groups vary widely across studies. Few studies have been statistically powered to examine exposure after pregnancy onset. A meta-analysis of 12 prospective studies, published in 1990, did not find any association between OC exposure after pregnancy onset and major birth defects[31]. Similarly, one of the largest studies, a case-control study with 9986 cases of various major birth defects, 312 of which were exposed to OCs after pregnancy onset, concluded that there is no overall association[8] but did report an increased risk for two specific birth defects—hypoplastic left heart syndrome [2.3 (3.0 to 4.3)] and gastroschisis [1.8 (1.3 to 2.7)]— following OC use after pregnancy onset. The authors caution this may be attributed to multiple testing.

A few studies have found maternal OC use to be associated with specific major birth defects. For example, a case-control study reported a 1.7-fold significant increase[9] in risk with 537 cases of limb defects, 97 of which were exposed at some point throughout the periconceptional period (within 2 months before or any time after pregnancy onset). Another study with 118 cases of urinary tract anomalies, 9 of which were exposed to OCs after pregnancy onset, identified a significant 4.8-fold increase[10]. Other studies have also observed increased risk among particular groups of women, such as smokers[11]. One limitation of case-control studies of birth defects is the potential for recall bias. Women who have children with birth defects may recall their OC exposure differentially than women whose children do not have such malformations[32]. However, there is some literature that demonstrates recall bias may not arise in case-control studies of contraceptive use[33].

Overall, our study confirms the bulk of the previous work documenting no increase in birth defects following OC exposure. Because previous studies have reported increased risks for specific defects including hypoplastic left heart syndrome[8], gastroschisis[8], limb defects[9], and urinary tract anomalies[10], we did examine each of these separately. Our results did not corroborate these findings though we did not have many cases of each. We did observe slight increases in risk among women who had never used OCs. Because OC use at some point across the life span is so common, women who have never tried OCs are likely a highly selected group in several aspects; therefore,

unmeasured confounding may explain the small increases in risk. This unmeasured confounding might include factors like obesity, which is contraindicated for OC use and a risk factor for birth defects[34]. Additionally, we did not confirm the elevated risk among smokers.

Our study had some limitations, including needing to group the major birth defects into categories due to being rare outcomes. Data on filled prescriptions was available from 1995, which limited our ability to examine different aspects of OC exposure that were not available in the registry, such as different OC formulations. Other health outcomes, such as breast cancer[35], have varied by formulation—with triphasic levonorgestrel formulations driving the increased breast cancer risk. However, there is no literature demonstrating any heterogeneity in the risk of birth defects by OC formulations; this may be worth exploring in future research since prescribing practices could be easily altered if any one formulation were associated with defects. Our operationalization of basing OC exposure on filling a prescription is not without some misclassification, but this is likely more accurate than previous work that primarily relied on self-reported recalled data. Nonetheless, we do not know if women took the OCs they had picked up at the pharmacy, which would result in bias towards the null. Residual confounding was possible but we addressed this by conducting propensity score matched sensitivity analysis, which provides more extended control for potential confounders[36]. We also lacked information on folate, one of our proposed mechanisms, so we could not examine this further. If there is a causal link between OC use and birth defects, it's possible that differential folate exposure could explain our null finding. However, our null findings were consistent across birth defects that are folate-dependent (e.g. orofacial clefts) as well as those that are not. Overall, the rarity of birth defect subgroups makes it difficult to disaggregate the results across the literature, including in the present analysis.

We expand on this literature by levering statistical power from registry and prospectively collected prescription data on OC use; this allowed us to include a large number of potential confounders, finer categories of OC exposure, and a broad range of birth defect subgroup categories. Potential confounders included detailed demographic information and medical information. The statistical power, while lacking for OC formulations and certain birth defect subgroups, was ample for studying the importance of timing of OC use. Some studies have examined exposure after pregnancy onset but few have been able to examine use before, in a number of different categories, as well as after pregnancy onset. In addition to our primary analyses among pregnancies ending in live births, we were able to

confirm our findings in a sub-cohort of pregnancies ending as induced abortions and stillbirth, which is a novel approach.

In conclusion, we did not observe a significantly increased risk of major birth defects associated with OC use in the months before or after pregnancy onset. For women who do experience a breakthrough pregnancy during OC use or even intentionally become pregnant within a few months of stopping OC use, any exposure is unlikely to cause her fetus to develop a major birth defect.

Table 1. Characteristics of Pregnancies According to Maternal OC Use Before and After Pregnancy Onset 1997-2011 (N=880,694).

Pregnancy characteristics at pregnancy onset	OC Use before and after pregnancy onset			
	Never (N=183,963, 21%)	>3 mo. before (ref.) (N=611,007, 69%)	0 to ≤3 mo. before (N=74,542, 8%)	After (N=11,182, 1%)
Demographics	N (%)			
Age, pregnancy onset				
<18	1769 (1.0)	1843 (0.3)	746 (1.0)	424 (3.8)
18-24	28,238 (15.3)	94,256 (15.4)	18,671 (25.0)	3701 (33.1)
25-29	49,995 (27.2)	240,517 (39.4)	31,117 (41.7)	3531 (31.6)
30-34	62,989 (34.2)	203,455 (33.3)	19,246 (25.8)	2530 (22.6)
35-39	34,561 (18.8)	63,887 (10.5)	4437 (6.0)	885 (7.9)
40+	6411 (3.5)	7049 (1.2)	325 (0.4)	111 (1.0)
Year				
1996-1998	62,781 (10.3)	53,381 (29.0)	9,711 (13.0)	1,599 (14.3)
1999-2001	117,936 (19.3)	53,266 (29.0)	15,609 (20.9)	2,550 (22.8)
2002-2004	132,129 (21.6)	33,459 (18.2)	15,945 (21.4)	2,271 (20.3)
2005-2007	142,904 (23.4)	22,304 (12.1)	16,643 (22.3)	2,336 (20.9)
2008-2011	155,257 (25.4)	21,553 (11.7)	16,634 (22.3)	2,426 (21.7)
Place of birth				
Denmark	115,709 (62.9)	559,617 (91.6)	67,588 (90.7)	9674 (86.5)
Europe	12,437 (6.8)	13,814 (2.3)	1726 (2.3)	292 (2.6)
Rest of the world	55,817 (30.3)	37,576 (6.1)	5228 (7.0)	1216 (10.9)
County of residence				
Capital	69,253 (37.6)	194,310 (31.8)	22,146 (29.7)	3158 (28.2)
Mid Jutland	41,249 (22.4)	143,321 (23.5)	17,257 (23.2)	2445 (21.9)
North Jutland	16,540 (9.0)	61,859 (10.1)	8020 (10.8)	1292 (11.6)
Zealand	21,983 (11.9)	81,804 (13.4)	10,322 (13.8)	1720 (15.4)
South of Denmark	34,938 (19.0)	129,713 (21.2)	16,797 (22.5)	2567 (23.0)
Married/living with partner	160,586 (87.3)	540,072 (88.4)	62,815 (84.3)	8200 (73.3)
Level of education				
Primary	37,304 (20.3)	105,867 (17.3)	16,247 (21.8)	3861 (34.5)
Secondary	13,542 (7.4)	59,909 (9.8)	8459 (11.3)	1229 (11.0)
Vocational/short tertiary	81,458 (44.3)	236,591 (38.7)	29,675 (39.8)	4094 (36.6)
Medium/long tertiary	51,659 (28.1)	208,640 (34.1)	20,161 (27.0)	1998 (17.9)
Gross household income (quintiles)				
Q1	42,310 (23.0)	74,668 (12.2)	11,998 (16.1)	3047 (27.2)
Q2	43,699 (23.8)	109,159 (17.9)	15,578 (20.9)	2794 (25.0)
Q3	30,935 (16.8)	142,143 (23.3)	17,538 (23.5)	2296 (20.5)
Q4	30,766 (16.7)	147,049 (24.1)	16,086 (21.6)	1656 (14.8)
Q5	36,253 (19.7)	137,988 (22.6)	13,342 (17.9)	1389 (12.4)
Pregnancy history				
Parity				
0	75,091 (40.8)	279,367 (45.7)	38,184 (51.2)	5192 (46.4)
1	64,398 (35.0)	231,930 (38.0)	24,219 (32.5)	3072 (27.5)
2	31,568 (17.2)	77,637 (12.7)	9481 (12.7)	2088 (18.7)
≥ 3	12,906 (7.0)	22,073 (3.6)	2658 (3.6)	830 (7.4)
Birth defects history	11,123 (6.0)	30,223 (4.9)	3243 (4.4)	617 (5.5)
Smoking in pregnancy	29,162 (15.9)	110,135 (18.0)	15,501 (20.8)	3407 (30.5)
Health care utilization				
Prescription drugs, last 6 mo.				
0	128,321 (69.8)	377,897 (61.8)	27,632 (37.1)	5647 (50.5)
≥ 1	55,642 (30.2)	233,110 (38.2)	46,910 (62.9)	5535 (49.5)
Hospital admissions, last 5 yrs				
0	67,778 (36.8)	217,637 (35.6)	30,445 (40.8)	4032 (36.1)
1-3	26,558 (14.4)	83,720 (13.7)	10,803 (14.5)	1780 (15.9)
4-5	16,361 (8.9)	41,866 (6.9)	5100 (6.8)	776 (6.9)
6+	73,266 (39.8)	267,784 (43.8)	28,194 (37.8)	4594 (41.1)
Outpatient hospital contacts, last 5 yrs				
0	66,979 (36.4)	155,698 (25.5)	22,680 (30.4)	3034 (27.1)
1-5	81,450 (44.3)	262,225 (42.9)	31,841 (42.7)	4775 (42.7)
6+	35,534 (19.3)	193,084 (31.6)	20,021 (26.9)	3373 (30.2)

Table 2. Prevalence Odds Ratio of Birth Defects in Live Births by Maternal OC Use Before and After Pregnancy Onset 1997-2011 (N=880,694).

Latest OC Use Before and After Pregnancy Onset*	Live Births No.	Birth Defects No.	Unadjusted Prevalence Odds Ratios (95% CI)	Adjusted† Prevalence Odds Ratios (95% CI)
Never	183,963	4609	1.00 (0.97 to 1.04)	1.06 (1.02 to 1.10)
>3 mo. before	611,007	15,271	ref.	ref.
0 to ≤3 mo. before	74,542	1856	1.00 (0.95 to 1.05)	0.98 (0.93 to 1.03)
After	11,182	277	0.99 (0.88 to 1.12)	0.95 (0.84 to 1.08)

*Never users are individuals who have never once filled an OC prescription since the study period began in 1997. The reference group includes those whose last prescription was filled >3 months before pregnancy onset, the exposure group "0 to ≤3 mo. before" includes those whose last prescription was filled 0-≤3 months before pregnancy onset, and the exposure group "After" includes those whose last prescription was filled after pregnancy onset.

†Adjusted for demographics (maternal age at pregnancy onset, calendar year, place of birth, county of residence, married/living with partner, level of education, and household income), parity, history of birth defects in a previous pregnancy, smoking in pregnancy, and health care utilization (prescription drug use in last six months, hospitalizations in last five years, and outpatient contacts in last five years).

Table 3. Prevalence Odds Ratio of Subgroups of Birth Defects in Live Births by Maternal OC Use Before and After Pregnancy Onset 1997-2011 (N=880,694).

Subgroup of Major Birth Defects Latest OC Use Before and After Pregnancy Onset*	Live Births No.	Birth Defects No.	Adjusted† Prevalence Odds Ratio (95% CI)
Nervous system			
Never	183,963	266	1.24 (1.05 to 1.45)
>3 mo. before	611,007	706	ref.
0 to ≤3 mo. before	74,542	78	0.84 (0.67 to 1.07)
After	11,182	16	1.09 (0.66 to 1.79)
Eye			
Never	183,963	172	1.07 (0.88 to 1.30)
>3 mo. before	611,007	596	ref.
0 to ≤3 mo. before	74,542	73	1.04 (0.81 to 1.33)
After	11,182	11	1.05 (0.58 to 1.91)
Ear, face and neck			
Never	183,963	35	0.80 (0.53 to 1.21)
>3 mo. before	611,007	158	ref.
0 to ≤3 mo. before	74,542	16	0.79 (0.47 to 1.34)
After	11,182	3	1.01 (0.32 to 3.20)
Cardiac			
Never	183,963	1342	1.06 (0.99 to 1.14)
>3 mo. before	611,007	4525	ref.
0 to ≤3 mo. before	74,542	545	0.95 (0.87 to 1.04)
After	11,182	89	0.99 (0.80 to 1.22)
Respiratory			
Never	183,963	200	1.19 (0.99 to 1.43)
>3 mo. before	611,007	604	ref.
0 to ≤3 mo. before	74,542	78	1.08 (0.85 to 1.37)
After	11,182	8	0.67 (0.33 to 1.35)
Orofacial clefts			
Never	183,963	275	0.96 (0.83 to 1.11)
>3 mo. before	611,007	984	ref.
0 to ≤3 mo. before	74,542	125	1.03 (0.85 to 1.24)
After	11,182	20	1.09 (0.70 to 1.70)
Digestive system			
Never	183,963	332	1.16 (1.00 to 1.33)
>3 mo. before	611,007	981	ref.
0 to ≤3 mo. before	74,542	118	0.93 (0.77 to 1.13)
After	11,182	21	1.10 (0.71 to 1.69)
Abdominal wall defects			
Never	183,963	28	0.51 (0.32 to 0.79)
>3 mo. before	611,007	157	ref.
0 to ≤3 mo. before	74,542	24	1.00 (0.65 to 1.55)
After	11,182	6	1.36 (0.59 to 3.10)
Urinary			
Never	183,963	474	1.03 (0.92 to 1.15)
>3 mo. before	611,007	1679	ref.
0 to ≤3 mo. before	74,542	202	1.02 (0.88 to 1.18)
After	11,182	27	0.95 (0.65 to 1.39)
Genital			
Never	183,963	511	1.17 (1.05 to 1.32)
>3 mo. before	611,007	1592	ref.
0 to ≤3 mo. before	74,542	184	0.95 (0.81 to 1.11)
After	11,182	32	1.10 (0.78 to 1.57)
Limb			
Never	183,963	742	0.97 (0.88 to 1.06)
>3 mo. before	611,007	2,511	ref.
0 to ≤3 mo. before	74,542	309	1.00 (0.89 to 1.13)
After	11,182	37	0.78 (0.56 to 1.08)
Other			
Never	183,963	232	1.04 (0.88 to 1.23)
>3 mo. before	611,007	778	ref.
0 to ≤3 mo. before	74,542	104	1.13 (0.92 to 1.40)
After	11,182	7	0.51 (0.24 to 1.07)
Specific Major Birth Defect			
Gastroischis			
Never	183,963	11	0.29 (0.15 to 0.58)
>3 mo. before	611,007	107	ref.
0 to ≤3 mo. before	74,542	17	0.93 (0.55 to 1.56)

After	11,182	3	0.84 (0.26 to 2.68)
Hypoplastic left heart syndrome			
Never	183,963	22	1.36 (0.78 to 2.36)
>3 mo. before	611,007	58	ref.
0 to ≤3 mo. before	74,542	10	1.21 (0.61 to 2.40)
After	11,182	3	2.47 (0.77 to 7.97)

*Never users are individuals who have never once filled an OC prescription since the study period began in 1997. The reference group includes those whose last prescription was filled >3 months before pregnancy onset, the exposure group "0 to ≤3 mo. before" includes those whose last prescription was filled 0-≤3 months before pregnancy onset, and the exposure group "After" includes those whose last prescription was filled after pregnancy onset.

†Adjusted for demographics (maternal age at pregnancy onset, calendar year, place of birth, county of residence, married/living with partner, level of education, and household income), parity, history of birth defects in a previous pregnancy, smoking in pregnancy, and health care utilization (prescription drug use in last six months, hospitalizations in last five years, and outpatient contacts in last five years).

Table 4. Sensitivity Analyses of the Prevalence Odds Ratio for Birth Defects by OC Use Before and After Pregnancy Onset.

Propensity Matched Cohort 1997-2011 (N=880,694*)

Latest OC Use Before and After Pregnancy Onset†	Live Births No.	Birth Defects No.	Adjusted Prevalence Odds Ratios (95% CI)
>3 mo. Before	44,350	1152	ref.
After	11,169	276	0.95 (0.83 to 1.09)

Cohort of Live Births, Stillbirths, and Induced Abortions 2004-2011 (N=429,940‡).

Latest OC Use Before and After Pregnancy Onset§	Participants No.	Birth Defects No.	Unadjusted Prevalence Odds Ratios (95% CI)	Adjusted‖ Prevalence Odds Ratios (95% CI)
Never	51,497	1538	1.07 (1.01 to 1.13)	1.06 (1.00 to 1.13)
>3 mo. Before	335,577	9375	ref.	ref.
0-≤3 mo. Before	37,523	1024	0.98 (0.91 to 1.04)	0.95 (0.89 to 1.02)
After	5343	156	1.05 (0.89 to 1.23)	0.99 (0.84 to 1.16)

*Prevalence odds ratios are estimated in a propensity score matched cohort matching exposed women, defined as those who used OCs after pregnancy onset, in a 1:4 ratio, to unexposed women, defined as those who stopped OC use >3 months before pregnancy onset.
†The reference group includes those whose last prescription was filled >3 months before pregnancy onset and the exposure group "After" includes those whose last prescription was filled after pregnancy onset.
‡Data only available for live births, induced abortions (O05.3 and O05.4), and all stillbirths between 2004-2011.
§Never users are individuals who have never once filled an OC prescription since the study period began in 1997. The reference group includes those whose last prescription was filled >3 months before pregnancy onset, the exposure group "0 to ≤3 mo. before" includes those whose last prescription was filled 0-≤3 months before pregnancy onset, and the exposure group "After" includes those whose last prescription was filled after pregnancy onset.
‖Adjusted for demographics (maternal age at pregnancy onset, calendar year, place of birth, county of residence, married/living with partner, level of education, and household income), parity, history of birth defects in a previous pregnancy, smoking in pregnancy, and health care utilization (prescription drug use in last six months, hospitalizations in last five years, and outpatient contacts in last five years).

Supplementary Appendix

Table S1. Major Birth Defects Subgroups

Birth defect subgroup	**Major birth defects:** Pregnancy included and counted as case	**Minor defects:** Pregnancy included but not counted as case	**Defects with known causes:** Pregnancy excluded	**Excluded defects due to data collection method*:** Pregnancy excluded
	ICD-10 codes			
Nervous system	Q00-Q07			
Eye	Q10-Q15	Q101-Q103, Q105, Q135		Q1880, Q0782
Ear, face and neck	Q16-Q18	Q170-Q175, Q179, Q180-Q182, Q184-Q187, Q189		
Cardiac	Q20-Q26	Q211C, Q250		
Respiratory	Q30-34	Q314, Q315, Q320, Q331		
Orofacial clefts	Q35-37			
Digestive system	Q38-45, Q790	Q381, Q382, Q385, Q400, Q401, Q430		Q4021, Q4320, Q4381, Q4382
Chromosomal/genetic			D821, Q90-99, Q447B, Q619A, Q751, Q754, Q771, Q772, Q796, Q85, Q87	
Abdominal wall defects	Q792, Q793, Q795			
Urinary	Q60-64, Q794	Q610, Q627, Q633		
Genital	Q50-52, Q54-56	Q523, Q525, Q552F		Q5521
Limb	Q66-74	Q662-Q669, Q670-Q678, Q680, Q682A, Q683-Q685, Q740G		Q65
Other	Q750, Q77, Q780, Q782-Q788, Q798, Q80-82, Q893, Q894	Q825, Q8280	Q86, P350, P351, P352, P371	

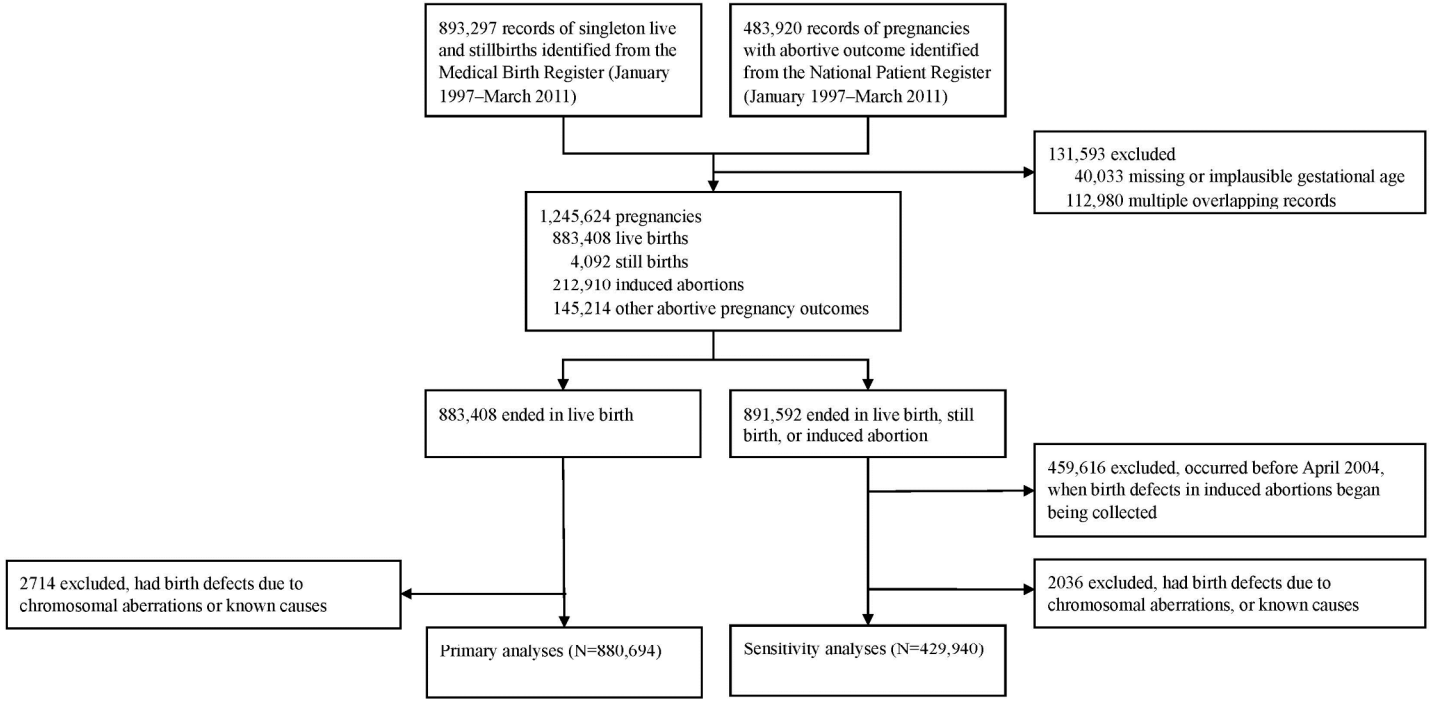
*Hip dislocation and dysplasia (Q65), were excluded due to poor validity in the National Patient Register. Some further exclusions were made because of minor inconsistencies between the ICD-10-British Pediatric Association version used by EUROCAT, and the standard ICD-10 used in Denmark including synophrys (Q1880), crocodile tears (Q0782), functional gastrointestinal disorders (Q4021, Q4320, Q4381 and Q4382), and bifid scrotum (Q5521).

Table S2. A Priori Chosen Confounders with Categories and Sources of Data

A Priori Chosen Confounders	Categories	Source of data	No. (%) Missing
Demographics at Pregnancy Onset			
Age at pregnancy onset	<18, 18-24, 25-29, 30-34, 35-39, 40+	Central Person Register	85 (0.01)
Place of birth	Denmark, Europe, Rest of the world	Central Person Register	2598 (0.29)
County of residence	Capital, Mid Jutland, North Jutland, Sealand, South of Denmark	Central Person Register	1449 (0.16)
Married/living with partner	yes/no	Statistics Denmark	8677 (0.99)
Level of education	Primary, Secondary, Vocational/short tertiary, Medium/long tertiary	Statistics Denmark	54,061 (6.14)
Gross household income	quintiles	Statistics Denmark	0 (0.00)
Pregnancy history			
Parity	0, 1, 2, 3+	Medical Birth Register	0 (0.00)
History of any birth defect	yes/no	National Patient Register	0 (0.00)
Smoking in pregnancy*	yes/no	Medical Birth Register	27,258 (3.10)
Health care utilization			
Prescription drugs used, last 6 mo	0, 1-2, 3+	National Prescription Register	0 (0.00)
Hospital admissions, last 5 years	0, 1-3, 4-5, 6+	National Patient Register	0 (0.00)
Outpatient hospital contacts, last 5 years	0, 1-5, 6+	National Patient Register	0 (0.00)

*Available for analyses based on live births; smoking in pregnancy data were not available for pregnancies with abortive outcomes and were therefore not adjusted for in the sensitivity analysis with abortive outcomes included.

Table S3. Study Design of Primary (Live Births) and Sensitivity Analyses (Live Births, Stillbirths and Induced Abortions)



FOOTNOTES

An abstract of this work was presented as an oral presentation at the annual meeting of the Society for Reproductive Investigation in March 2014. The complete manuscript has not been published in any other form.

Contributors: BMC and MM were responsible for study concept and design. BMC and HS analyzed the data. BMC wrote the manuscript while all authors critically reviewed the manuscript and approved the final version. All authors also had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

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Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

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Ethical approval: Ethical approval is not required for registry-based research in Denmark.

Data sharing: No additional data available.

Transparency: The lead author (BMC) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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