Maternal use of oral contraceptives and risk of birth defects in Denmark: prospective, nationwide cohort study

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ABSTRACT

STUDY QUESTION

Is oral contraceptive use around the time of pregnancy onset associated with an increased risk of major birth defects?

METHODS

In a prospective observational cohort study, data on oral contraceptive use and major birth defects were collected among 880 694 live births from Danish registries between 1997 and 2011. We conservatively assumed that oral contraceptive exposure lasted up to the most recently filled prescription. The main outcome measure was the number of major birth defects throughout one year follow-up (defined according to the European Surveillance of Congenital Anomalies classification). Logistic regression estimated prevalence odds ratios of any major birth defect as well as categories of birth defect subgroups.

STUDY ANSWER AND LIMITATIONS

Prevalence of major birth defects (per 1000 births) was consistent across each oral contraceptive exposure group (25.1, never users; 25.0, use >3 months before pregnancy onset (reference group); 24.9, use 0-3 months before pregnancy onset (that is, recent use); 24.8, use after pregnancy onset). No increase in prevalence of major birth defects was seen with oral contraceptive exposure among women with recent use before pregnancy (prevalence odds ratio 0.98 (95% confidence interval 0.93 to 1.03)) or use after pregnancy onset (0.95 (0.84 to 1.08)), compared with the reference group. There was also no increase in prevalence of any birth defect subgroup (for example, limb defects). It is unknown whether women took oral contraceptives up to the date of their most recently filled prescription. Also, the rarity of birth defects made disaggregation of the results difficult. Residual confounding was possible, and the analysis lacked information on folate, one of the proposed mechanisms.

WHAT THIS STUDY ADDS

Oral contraceptive exposure just before or during pregnancy does not appear to be associated with an increased risk of major birth defects.

FUNDING, COMPETING INTERESTS, DATA SHARING

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WHAT IS ALREADY KNOWN ON THIS TOPIC

An estimated 9% of oral contraceptive users become pregnant in the first year of use; many more women will stop using oral contraceptives when planning a pregnancy and conceive within a few menstrual cycles

In both instances, the offspring could be exposed to exogenous hormones

Little is known about the association of oral contraceptive use just before or during pregnancy with the offspring's health

WHAT THIS STUDY ADDS

We observed no increased risk of any major birth defect associated with oral contraceptive exposure just before or during pregnancy

This observation should reassure patients and healthcare providers

Introduction

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

Yet, despite decades of research on the safety of oral contraceptive use, little is known about the association of oral contraceptive use just before or during pregnancy with the offspring's health. In particular, it is unclear whether these circulating exogenous sex hormones can harm the fetus and how long potential effects of circulating exogenous sex hormones might last. The literature has primarily focused on birth defects, but findings conflict and their interpretation is challenging owing to methodological limitations. For example, most of these studies were conducted over 30 years ago; relied on self reported, retrospective exposure assessment in small case-control samples; and examined a single outcome (for example, limb defects).[7] Some of these findings suggest that oral contraceptive 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 plasma concentrations of vitamin A,[20] which can be teratogenic.[21] Studies also suggest that serum folate concentrations decrease after oral contraceptive use and remain reduced for 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 oral contraceptive 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 Danish Medical Birth Register that included all singleton live births delivered from 1 January 1997 to 31 March 2011. We excluded births with a missing or implausible gestational age. After excluding infants with birth defects with known causes (such as fetal alcohol syndrome) or chromosomal aberrations (n=2714), the final cohort included 880 694 live-born infants. Individual level data were linked between registries by use of the Danish Civil Registration System's unique personal identification number assigned to all Danish residents.

Data sources

The Medical Birth Register was established in 1968 and contains information on all Danish births, including date of birth, multiple births, gestational age, and various newborn characteristics, as well as maternal characteristics such as parity and smoking status.[22] The Danish National Patient Register includes information on outpatient and emergency department visits and inpatient admissions to all Danish hospitals.[23] From this register, 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 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 Danish National Prescription Register contains information on drug prescriptions filled at Danish pharmacies since 1995, such as the anatomical therapeutic chemical code (G03A for all oral contraceptives, including less common forms such as progestin only pills and emergency contraception) 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. Each woman was categorised according to her oral contraceptive use regardless of other hormonal contraceptive use (for example, progestin intrauterine device).

We defined never users as those who never filled an oral contraceptive prescription since the introduction of the prescription register. Given the high prevalence of oral contraceptive 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 modelled oral contraceptive exposure into distinct categories (>3 months before pregnancy onset (reference group), 0-3 months before pregnancy onset (that is, recent use), and after pregnancy onset). The two primary exposures of interest were use after pregnancy onset and recent use before pregnancy onset.

Major birth defects outcome

Major birth defects were identified from the National Patient Register, allowing for a one year follow-up after birth. Validation studies of this registry showed that 88% of birth defect diagnoses[26] were correct when confirmed by medical record review. Major birth defects were defined according to the European Surveillance of Congenital Anomalies classification, excluding minor defects (web table S1).[27]

The primary outcome was any major birth defect, and secondary outcomes were subgroups of major birth defects categorised by organ system. Previous studies have observed associations between oral contraceptive exposure and hypoplastic left heart syndrome,[8] gastroschisis,[8] limb defects,[9] and urinary tract anomalies.[10] We included analyses of limb and urinary tract defects in our secondary outcomes; we also added analyses of specific birth defects including gastroschisis and hypoplastic left heart syndrome.

Statistical analyses

We used logistic regression 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 categorised as "nervous system" and another categorised as "eye," that pregnancy was included in both analyses.

A priori knowledge of the risk factors for birth defects and determinants of oral contraceptive use were used to select potential confounders for adjustment. We imputed any missing covariate values with each variable's respective mode (web table S2) and most covariates had less than 0.01% missing values. Covariates included:

- Demographics (maternal age at pregnancy onset, calendar year of pregnancy onset, place of birth, county of residence, married or living with partner, level of education, and household income)
- Parity
- History of birth defects in a previous pregnancy
- Smoking in pregnancy

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- Healthcare use (prescription drug use in the past six months, hospital admissions in the past five years, and outpatient contacts in the past five years).

We conducted sensitivity analyses with propensity score matching. Using logistic regression, we estimated propensity scores as the probability of exposure to oral contraceptives 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 oral contraceptives after pregnancy onset) were then matched in a 1:4 ratio to unexposed women (defined as those who stopped oral contraceptive use more than three months before pregnancy onset). Matching was done by use of the nearest neighbour 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 including birth defects identified among induced abortions after 12 gestational weeks (ICD-10 (international classification of diseases, 10th revision) codes O05.3 and O05.4) and stillbirths, as described in detail previously.[30] However, the registration of birth defects among induced abortions and stillbirths was not validated. Data for this sensitivity analysis were available for the period from 1 January 2004 to 31 March 2011 (n=429 940, web fig**)**. We used SAS software (version 9.2) for all analyses.

Patient involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for recruitment, design, or implementation of the study. No patients were asked to advise on interpretation or writing up of results. There are no plans to disseminate the results of the research to study participants or the relevant patient community.

Results

Of 880 694 liveborn infants in our study cohort, 2.5% (n=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 oral contraceptives but stopped more than three months before pregnancy onset, while 21% (n=183 963) never used oral contraceptives. However, 8% (n=74 542) had recently stopped using oral contraceptives (0-3 months before pregnancy onset), and 1% (n=11 182) used oral contraceptives beyond pregnancy onset, both categories we had considered as exposed.

Table 1 shows the characteristics of cohort mothers according to oral contraceptive exposure timing. Compared with women who had stopped using oral contraceptives more than three months before pregnancy onset (reference group), both groups of exposed women were generally younger, less likely to be married or 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 1000 births) was consistent across each of the oral contraceptive exposure groups: 25.1 for never users, 25.0 for oral contraceptive use more than three months before pregnancy onset (reference), 24.9 for oral contraceptive use 0 to three months before pregnancy onset (recent), and 24.8 for oral contraceptive use after pregnancy onset.

Our primary analyses showed no increased risk of any major birth defect associated with oral contraceptive exposure (table 2); this included women who had recently stopped using oral contraceptives (prevalence odds ratio 0.98 (95% confidence interval 0.93 to 1.03)) and women who used oral contraceptives after pregnancy onset (0.95 (0.84 to 1.08)). Corresponding results in sensitivity analyses, which included the addition of pregnancies ending as stillbirths and induced abortions to the cohort, were consistent (0.95 (0.89 to 1.02) and 0.99 (0.84 to 1.16), respectively; table 3). The result for mothers using oral contraceptives after pregnancy onset was also consistent in a sensitivity analysis using propensity score matching (0.95 (0.83 to 1.09), table 4).

None of our findings varied by levels of age, smoking during pregnancy, or education (P>0.05 for all interaction terms with oral contraceptive use, variables categorised as in table 1), and our results proved to be robust when restricted to women aged 25-34 years and Danish born (never oral contraceptive use, prevalence odds ratio of birth defect 1.05 (95% confidence interval 0.99 to 1.10); recent oral contraceptive use to pregnancy onset, 0.99 (0.94 to 1.05); and oral contraceptive use after pregnancy onset, 0.91 (0.78 to 1.04)).

Our secondary analyses showed no significantly increased risk of any subgroup of major birth defects associated with oral contraceptive exposure (table 5). All prevalence odds ratios of major birth defects for the two groups exposed to oral contraceptives were less than 1.15, apart from abdominal wall defects. We also examined more specific birth defects, including gastroschisis (prevalence odds ratio of birth defect 0.84 (95% confidence interval 0.26 to 2.68)) and hypoplastic left heart syndrome (2.47 (0.77 to 7.97)) without any significantly increased risk; both subgroups included three women who were exposed to oral contraceptive use after becoming pregnant.

Never use of oral contraceptives was associated with a slight increase in risk of any major birth defect (prevalence odds ratio 1.06 (95% confidence interval 1.02 to 1.10)) compared with the reference group of women who had stopped using oral contraceptives more than three months before becoming pregnant (table 2). When grouped by type of major birth defect, never use of oral contraceptives 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 (table 5).

Discussion

Principal findings

We assessed the association between maternal oral contraceptive exposure shortly before or during

Table 1 | Characteristics of pregnancies according to maternal oral contraceptive use before and after pregnancy onset in 1997-2011 (n=880 694). Data are no (%) of pregnancies

	Oral contraceptive use before and after pregnancy onset (1997-2011)			
Pregnancy characteristics at pregnancy onset*	Never (n=183 963, 21%)	More than 3 months before (reference; n=611 007, 69%)	0-3 months before (n=74 542, 8%)	After (n=11 182, 1%)
Demographics				
Age at pregnancy onset (years)				
<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				
1996-98	62 781 (10.3)	53 381 (29.0)	9711 (13.0)	1599 (14.3)
1999-2001	117 936 (19.3)	53 266 (29.0)	15 609 (20.9)	2550 (22.8)
2002-04	132 129 (21.6)	33 459 (18.2)	15 945 (21.4)	2271 (20.3)
2005-07	142 904 (23.4)	22 304 (12.1)	16 643 (22.3)	2336 (20.9)
2008-11	155 257 (25.4)	21 553 (11.7)	16 634 (22.3)	2426 (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 (divided into five equal groups)				
Group 1	42 310 (23.0)	74 668 (12.2)	11 998 (16.1)	3047 (27.2)
Group 2	43 699 (23.8)	109 159 (17.9)	15 578 (20.9)	2794 (25.0)
Group 3	30 935 (16.8)	142 143 (23.3)	17 538 (23.5)	2296 (20.5)
Group 4	30 766 (16.7)	147 049 (24.1)	16 086 (21.6)	1656 (14.8)
Group 5	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)
Healthcare use				
Prescription drugs, past 6 months.				
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, past 5 years				
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, past 5 years				
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)

*Most covariates had less than 0.01% missing values (web table S2) but any missing values were imputed with each variable's respective mode

Table 2 | Risk of major birth defects in live births by maternal oral contraceptive use before and after pregnancy onset in 1997-2011 (n=880 694)

Latest oral contraceptive use before and after pregnancy onset	No of live births	No of birth defects	Prevalence odds ratios (95% CI)	
			Unadjusted	Adjusted¶
Never*	183 963	4609	1.00 (0.97 to 1.04)	1.06 (1.02 to 1.10)
>3 months before†	611 007	15 271	Reference	Reference
0-3 months 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)

*Individuals who never filled a prescription for an oral contraceptive since the National Prescription Register began in 1995.
†Reference group, including individuals whose latest prescription was filled more than three months before pregnancy onset.
‡Individuals whose latest prescription was filled 0-3 months before pregnancy onset.
§Individuals whose latest 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 healthcare use (prescription drug use in last six months, hospital admissions in last five years, and outpatient contacts in last five years).

Table 3 | Sensitivity analyses of risk of major birth defects by oral contraceptive use before and after pregnancy onset, for cohort of live births, stillbirths, and induced abortions in 2004-11 (n=429 940*)

Latest oral contraceptive use before and after pregnancy onset	No of participants	No of birth defects	Prevalence odds ratio (95% CI)	
			Unadjusted	Adjusted**
Never†	51 497	1538	1.07 (1.01 to 1.13)	1.06 (1.00 to 1.13)
>3 months before‡	335 577	9375	Reference	Reference
0-3 months 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)

*Data only available for live births, induced abortions (ICD-10 O05.3 and O05.4), and all stillbirths between 2004 and 2011.
†Individuals who never filled a prescription for an oral contraceptive since the National Prescription Register began in 1995.
‡Reference group, including individuals whose latest prescription was filled more than three months before pregnancy onset.
§Individuals whose latest prescription was filled 0-3 months before pregnancy onset.
¶Individuals whose latest 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 healthcare use (prescription drug use in last six months, hospital admissions in last five years, and outpatient contacts in last five years).

Table 4 | Sensitivity analyses of risk of major birth defects by oral contraceptive use before and after pregnancy onset, for propensity matched cohort in 1997-2011 (n=880 694*)

Latest oral contraceptive use before and after pregnancy onset	No of live births	No of birth defects	Adjusted prevalence odds ratios (95% CI)
>3 months before†	44 350	1152	Reference
After‡	11 169	276	0.95 (0.83 to 1.09)

*Prevalence odds ratios were estimated in a propensity score matched cohort matching exposed women (those who used oral contraceptives after becoming pregnant) in a 1:4 ratio to unexposed women (those who stopped using oral contraceptives more than three months before pregnancy onset).
†Individuals whose latest prescription was filled more than three months before pregnancy onset.
‡Individuals whose latest prescription was filled after pregnancy onset.

pregnancy and major birth defects. Overall, we found no significant increase in risk of birth defects or subgroups of defects.

Comparison with other studies

Comparisons across the literature are challenging because the time windows of oral contraceptive 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 oral contraceptive exposure after pregnancy onset and major birth defects.[31] A recent case-control study[8] had the highest statistical power, with 9986 cases of various major birth defects, from which 312 women were exposed to oral contraceptives after pregnancy onset. The authors found no overall association but did report an increased risk for two specific birth defects—hypoplastic left heart syndrome (odds ratio 2.3 (95% confidence interval 1.3 to 4.3)) and gastroschisis (1.8 (1.3 to 2.7))—following oral contraceptive use after pregnancy onset. The authors cautioned that this finding could be attributed to multiple testing; however, we observed a prevalence odds ratio at the same level (2.47 (0.77 to 7.97)) for hypoplastic left heart syndrome, although insignificant in our less powered study.

A few studies have found maternal oral contraceptive 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, from which 97 women were exposed at some point throughout the periconceptional period (within two months before or any time after pregnancy onset). Another study of 118 urinary tract anomalies found at childbirth, in which nine mothers were exposed to oral contraceptives 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 might recall their oral contraceptive exposure differently from those 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 oral contraceptive 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 study did not find significantly increased risks for any of these four birth defect categories, although each of our analyses should be interpreted in the context of statistical precision. That is, while our analyses of limb defects and urinary tract anomalies did have narrow confidence intervals, indicating that they were not consistent with even small to moderate increases in risk, our analyses of gastroschisis and hypoplastic left heart syndrome were based on a very small sample size and should not be taken as evidence of no association.

We did observe slight increases in risk among women who had never used oral contraceptives. Because oral contraceptive use at some point in life is so common, women who have never tried oral contraceptives are probably a highly selected group in several aspects; therefore, unmeasured confounding could explain the small increases in risk. This unmeasured confounding might include factors such as obesity, which is contraindicated for oral contraceptive use and a risk factor for

Table 5 | Risk of major birth defects in live births by maternal oral contraceptive use before and after pregnancy onset, by birth defect subgroup in 1997-2011 (n=880 694)

Latest oral contraceptive use before and after pregnancy onset*	No of live births	No of birth defects	Adjusted† prevalence odds ratio (95% CI)
Nervous system			
Never	183 963	266	1.24 (1.05 to 1.45)
>3 months before	611 007	706	Reference
0-3 months 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 months before	611 007	596	Reference
0-3 months 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 months before	611 007	158	Reference
0-3 months 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 months before	611 007	4525	Reference
0-3 months 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 months before	611 007	604	Reference
0-3 months 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 months before	611 007	984	Reference
0-3 months 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 months before	611 007	981	Reference
0-3 months 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 months before	611 007	157	Reference
0-3 months 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 months before	611 007	1679	Reference
0-3 months 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 months before	611 007	1592	Reference
0-3 months 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 months before	611 007	2511	Reference
0-3 months 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 months before	611 007	778	Reference
0-3 months before	74 542	104	1.13 (0.92 to 1.40)
After	11 182	7	0.51 (0.24 to 1.07)

birth defects.[34] With the National Prescription Register starting in 1995, it is also possible that some women who stopped using oral contraceptives by 1995 were misclassified as never users. Additionally, we did not confirm the elevated risk among smokers.

Strengths and limitations of study

Limitations included the need to group major birth defects into categories owing to these defects being rare outcomes. We also lacked the statistical power to examine different aspects of oral contraceptive exposure, such as 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 oral contraceptive formulations. This topic may be worth exploring in future research because prescribing practices could be easily altered if any one formulation were associated with defects.

Our process of basing oral contraceptive exposure on filling a prescription is not without some misclassification, but this eliminates recall bias and is likely to be more accurate than previous work that primarily relied on self-reported data. Nonetheless, we do not know if women took the oral contraceptives they had picked up at the pharmacy, which would result in bias towards the null. We tried to minimise residual confounding by conducting sensitivity analyses based on propensity score matching, which provides more extended control for potential confounders.[36]

We also lacked information on folate, one of our proposed mechanisms, and could not examine this further. If there is a causal link between oral contraceptive use and birth defects, differential folate exposure could explain our null finding. However, our null findings were consistent across birth defects that are folate dependent (for example, 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 leveraging statistical power from registry records and prospectively collected prescription data on oral contraceptive use. This information allowed us to include many potential confounders, finer categories of oral contraceptive exposure, and a broad range of birth defect subgroups. Previous studies have primarily relied on exposure assessment through maternal interview rather than through prescription registries. Potential confounders included detailed demographic information and medical information.

The statistical power, while lacking for oral contraceptive formulations and certain birth defect subgroups, was ample for studying the importance of timing of oral contraceptive use. Some studies have examined exposure after pregnancy onset but few have been able to examine use before, in several different categories, as well as after pregnancy onset. In addition to our primary analyses among pregnancies ending in

Table 5 | Risk of major birth defects in live births by maternal oral contraceptive use before and after pregnancy onset, by birth defect subgroup in 1997-2011 (n=880 694)

Latest oral contraceptive use before and after pregnancy onset*	No of live births	No of birth defects	Adjusted† prevalence odds ratio (95% CI)
Specific major birth defect			
Gastroschisis			
Never	183 963	11	0.29 (0.15 to 0.58)
>3 months before	611 007	107	Reference
0-3 months 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 months before	611 007	58	Reference
0-3 months before	74 542	10	1.21 (0.61 to 2.40)
After	11 182	3	2.47 (0.77 to 7.97)

*Never users=individuals who never once filled a prescription for an oral contraceptive since the National Prescription Register began in 1995; Reference=group of individuals whose latest prescription was filled more than three months before pregnancy onset; 0-3 months before=individuals whose latest prescription was filled 0-3 months before pregnancy onset; After=individuals whose latest 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 healthcare use (prescription drug use in last six months, hospital admissions in last five years, and outpatient contacts in last five years).

live births, we were able to confirm our findings in a subgroup of pregnancies ending as induced abortions and stillbirth.

Conclusion

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

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 analysed 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. BMC acts as guarantor of the study.

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Ethical approval: The study was approved by the Danish Data Protection Agency; ethics approval was not required for Danish registry based research.

Data sharing: No additional data available.

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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Web appendix: Supplementary material