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Pre-gravid oral contraceptive use in relation to birth weight: a prospective cohort study

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Abstract

Few studies have evaluated the association between pregravid oral contraceptive (OC) use and birth weight, and findings have been conflicting. We conducted a prospective cohort study of 5921 pregnancy planners in Denmark to evaluate recency, duration, and type of OC used before conception in relation to infant birth weight. Participants completed online questionnaires and reported detailed information on contraceptive history and covariates at baseline. Participants completed bimonthly follow-up questionnaires to update their pregnancy status for up to 12 months or until conception occurred. Birth weight data were ascertained from the Danish Medical Birth Registry for 4046 live births delivered by study participants between 2008 and 2010. We used multivariable linear and log-binomial regression analyses to control for confounding. Mean birth weight was higher among women who had used OCs within 0–1 months (mean difference = 97 g, CI: 26, 168) or 2–6 months (mean difference = 40 g, CI: –5, 85) before conception, compared with more than 12 months before conception. Mean birth weight was lower among women who had used OCs for long durations (mean difference comparing 12 with <4 years of OC use = –85 g, CI: –158, –11). Our findings indicate that pregravid OC use within 6 months of conception may be associated with a small increase in birth weight, but that long duration of use may have the opposite effect. Results were stronger among male infants, among 2nd and 4th generation OC users, and among users of OCs with a higher estrogen dose.

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Disclosure of Interests

The authors declare no conflicts of interest.

Contribution to Authorship

EEH conceptualized the study and directed and interpreted the analysis. KAH, KJR, AHR, HTS, and LAW made substantial contributions to the analysis and interpretation of data, and drafting and revising the article. EMM made substantial contributions to acquisition of data, interpretation of analysis, and drafting and revising the article. All authors have read and approved the final version of the manuscript.

Details of Ethics Approval

IRB approval was obtained from the Boston University Medical Center (IRB number H25361, approved December 19, 2011) and the Danish Data Protection Board.

Introduction

In developed countries, oral contraceptives (OCs) are the most common type of contraception, used by 50–80% of women at some point during their reproductive years. (1, 2) While health effects of OCs on women are well-described, possible effects on offspring conceived after the cessation of OCs are less well-studied. Some studies have reported lower risks of miscarriage and stillbirth, (3, 4) and a higher prevalence of twins among former OC users. (5) Several studies have evaluated the birth weight of infants born to mothers who used OCs before conception, with some studies suggesting an increase in mean birth weight (6) or lower prevalence of low birth weight (7) following recent OC use, while others reported no effect (4, 5, 8, 9) or a greater risk of low birth weight. (10, 11)

OCs prevent pregnancy by suppressing gonadotrophin release, which in turn inhibits follicular development and ovulation. OCs also impede sperm transport by thickening cervical mucus, and thin the endometrial lining to lessen rates of implantation. The possible mechanism of action by which pre-gravid OC use could affect birth weight is unclear, but may be due to metabolic and/or hormonal changes that persist following OC cessation. Menstrual cycle changes have been documented to persist for at least six months following OC cessation. (12) Current OC has been associated with increases in C-reactive protein (13) and insulin levels, (14, 15) lower serum hormone binding globulin (SHBG)(16) and androgens and decreased libido, (17) and a few studies suggest that some changes may persist after women discontinue OCs. (18–20) Birth weight is associated with many adult-onset health outcomes, including cancer, (21, 22) metabolic syndrome, (23, 24) and obesity; (25, 26) extremes on either end of the birth weight spectrum may have detrimental effects. Because OCs are used by a majority of reproductive age women in developed countries, even small changes in average birth weight may be meaningful on the population level if they reflect a shift in the proportion of infants born with either very low or very high birth weight.

There are few data on more recent formulations of OCs in relation to their possible effect on size at birth. We used data from a prospective cohort study of pregnancy planners to evaluate the association between recency, duration, and type of OC used before conception in relation to birth weight and related measures of growth.

Methods

Study population

The Snart Gravid study is an internet-based prospective cohort study of Danish women who have recently stopped using birth control to become pregnant. Study methods have been described in detail previously. (27–29) Briefly, enrollment began in June 2007 with the launch of the study Web site (www.Snart-Gravid.dk) and continued through August 2011. Potential participants learned about the study via an advertisement on a popular Danish health-related Web site (www.netdokter.dk), or through publicity in other media. Women provided informed consent through the study website and then filled out an eligibility questionnaire. Eligible women were Danish residents, aged 18–40 years, in a stable relationship with a male partner, and not currently using any form of birth control or fertility

drugs. To enroll, women had to provide their Civil Registration Number (CPR) and e-mail address. A total of 11,248 women filled out the screening questionnaire, of whom 8745 were eligible. A further 5921 women provided their CPR number and email address and enrolled in the study by filling out an extensive, baseline questionnaire. Every eight weeks, women were sent reminder emails to complete a short follow-up questionnaire via the study website. This questionnaire was intended to ascertain pregnancies and to update exposures. We followed participants until they reported a pregnancy, stopped trying to become pregnant, began fertility treatment, or had been in the study for 12 menstrual cycles (a maximum of 6 follow-up questionnaires). We restricted the current analysis to women who had a live birth while in the study.

Using the CPR number, we linked study participants with the Danish National Birth Registry (30) to obtain data on their infant's birth weight, placental weight, and gestational age. We restricted our analysis to the first live singleton birth recorded after enrollment in Smart Gravid (n=4046) through December 2010. We excluded 70 women who reported diabetes (n=12) or thyroid disease (n=58) before pregnancy, 43 who had used other hormonal methods, such as a hormone patch or injection, as their last method of birth control, and 57 who reported using more than six brands of OCs. With these exclusions, 3896 women and infant pairs remained. A total of 3772 women had used OCs at some point in the past, and 124 women had never used OCs.

Assessment of oral contraceptive use

On the baseline questionnaire, women reported all contraceptive methods ever used, as well as the last method used before attempting pregnancy. (31) Women who had ever used OCs reported the number of different brands, and the age at first use and duration of use (in months and years) of each type of OC, up to a total of six brands. To enhance recall, the questionnaire included a list of all OC brand names available in Denmark. Women who used OCs as their last method of birth control were also asked if they had intentionally delayed their pregnancy attempt, and if so, for how many cycles.

Our primary exposure variable was recency of OC use before pregnancy. We restricted our main analyses to the 3772 women who had ever used OCs. We defined recency as the number of months between the last use of OCs and the last menstrual period (LMP) before pregnancy. Among women who used OCs as their most recent method of birth control, we calculated recency in months using the following formula: $((\text{date of LMP} - \text{date of the baseline questionnaire}) + (\text{months trying to get pregnant before baseline} * 30)) / 30$. For women who delayed their pregnancy attempt after stopping OCs, we added the number of months of waiting time to the formula above. Among women who had used OCs in the past, but not as their most recent method of birth control, we calculated recency in months by subtracting the approximate age of last use of OCs (using the age started and duration of use of the most recent brand of OCs) from the age at LMP and multiplying by 12. We created two categorical variables for recency: use within 12 months before pregnancy versus more than 12 months before pregnancy, and 0–1, 2–6, 7–12, >12 months before pregnancy.

We estimated total duration of OC use for each participant by summing duration (months) of OC use across different OC brands. We categorized duration as: <4 years, 4–7 years, 8–11 years, and 12 or more years.

We classified the most recent brand of OCs by the amount of estrogen it contained: none (progestin-only pill), low-dose (<30 micrograms), and high-dose (≥30 micrograms), and also by ‘generation’ defined by progestin content: first generation (norethindrone), second generation (norgesterel and levonorgesterel), third generation (desogestrel and gestodene), and fourth generation (drospirenone).⁽³²⁾ We combined first generation and second generation pills into one category because very few women (n=72) had used first generation OCs as their most recent brand.

Birth outcomes

We evaluated birth weight, placental weight, and ponderal index (birth weight (kg)/length (m)³), an estimate of infant adiposity, as continuous variables. We also evaluated the following dichotomous outcomes: small and large for gestational age (SGA and LGA), low birth weight (<2500 g) and macrosomia (≥4000 g). SGA and LGA were calculated using the lowest and highest 10% of birth weight by gestational age as classified by ultrasonically-estimated fetal weights from a Scandinavian population. ⁽³³⁾

Potential confounders

Potential confounders were initially identified by a review of the literature and an assessment of a causal graph. Maternal age (categorized as 18–24, 25–29, 30–34, and 35–40 years), pre-pregnancy weight and height, education/vocational training (no vocational training, semi-skilled/basic training, <3 years of higher education, 3–4 years of higher education, >4 years of higher education), monthly income (<25,000 Danish Kroner (DKK), 25,000–39,999 DKK, 40,000–65,000 DKK, and >65,000 DKK) and parity (0 versus 1 or more) were collected on the baseline questionnaire. Body mass index (BMI), (weight (kg))/height (meters²), was categorized into 4 levels: <18.5, 18.5–24, 25–29, and ≥30. We classified a woman as having smoked during pregnancy if she reported current smoking on the early pregnancy questionnaire or if maternal smoking was indicated in the birth registry. We adjusted for recency and duration of use of OCs simultaneously in all models. We also adjusted for gestational age and infant sex in secondary analyses. To assess the possible confounding effect of a woman’s underlying fertility, which could be related to both contraceptive choice and birth weight, we performed sub-analyses restricted to women who conceived within 1 month, 3 months, and 6 months of stopping birth control. Within these three strata, we computed adjusted mean birth weight differences among women who used OCs as their most recent method of birth control compared with women who used barrier and other methods.

Statistical analysis

The proportion of missing values for covariates was low (<1%) for most variables, ranging from 0% (age) to 9.8% for income. Data on OC history were less complete. We compared the total number of brands each woman reported with the number of values filled in for duration of individual OCs and found that 31% had missing information for one or more

brands. A total of 17.9% were missing data on estrogen dose and generation of OC. We used simple imputation to impute duration for individual brands of OCs by substituting the median duration reported by all women with complete information for each particular brand number (brand 1–6). For example, if a woman reported a total of three brands but did not have complete information on duration of use for the second brand, we substituted the median duration for the second brand among all women who reported a total of three brands. We used multiple imputation methods to impute missing recency, last reported brand of OC and covariate values. (34) In SAS software (SAS Institute, Inc., Cary, North Carolina; Version 9.3), we used PROC MI to create 5 imputed data sets and then combined results across the imputed data sets using PROC MIANALYZE (SAS User's guide). All potential confounders were included in the imputation model along with all exposures and outcomes.

We used multivariable linear regression to estimate adjusted mean differences in birth weight, ponderal index, and placental weight by recency and duration of OC use before conception. We also evaluated birth weight in relation to recency and duration within types of OCs, stratifying by progestin type (1st/2nd, 3rd and 4th generation) and estrogen content (none, <30 vs. ≥30 mg) of the last brand used. We adjusted for maternal age, education, income, BMI, smoking, parity (none vs. one or more), and stratified the analyses according to maternal age (<30 vs. ≥30), parity, BMI (<25 vs. ≥25), smoking during pregnancy, and infant sex. We used log binomial regression to estimate risk ratios for macrosomia (≥4000), and logistic regression to estimate risk ratios for SGA, LGA and low birth weight, adjusting for the same variables as above. All multivariate models for duration and recency were mutually adjusted for each other.

We repeated our analyses excluding women who had ever used 'other hormonal' methods of birth control, including injections, implants, and vaginal rings. We also compared birth weights among ever versus never users of OCs.

Results

Women who had used OCs within the year before conception tended to be younger, nulliparous, and were less likely to be obese compared with women who had not used OCs during that time period (Table 1). Overall, we found that infant birth weight was slightly higher among women who had used the pill within 0–1 months (mean difference=97 g, CI: 26, 168) or 2–6 months (mean difference=40 g, CI: –5, 85) before conception, compared with women who had last used OCs over one year before conception (Table 2). Babies born to women with a longer duration of OC use before the pregnancy tended to have a lower birth weights; adjusted mean birth weights were –3 g (CI: –70, 636), –45 g (CI: –108, 19) and –85 g (CI: –158, –11) for 4<8, 8–<12, and 12 or more years of OC use respectively compared with <4 years of use (Table 2). Adjustment for maternal age, parity, cigarette smoking, income, vocational training, and BMI resulted in only small changes in our effect estimates. (Unadjusted estimates for comparison with those in Table 2 are provided in a supplemental on-line table.) We saw similar associations between patterns of OC use and ponderal index, which was higher for recent use of OCs (mean differences=0.04 (CI: 0.01, 0.08), 0.03 (CI: 0.01, 0.05), and 0.02 (CI: –0.01, 0.04), for use within 0–1, 2–6, and 7–12 months compared with over 12 months before conception. Duration of use of OCs was

inversely related to ponderal index (Table 2). We found little association between either recency or duration of OC use and placental weight (data not shown).

Adjusting for gestational age (GA) attenuated the results for recency of use within one month of conception (adjusted mean difference=55.2 g (CI: -0.6, 110.9), but the estimates for other categories for recency of use changed only slightly. Similarly, adjustment for GA slightly attenuated the estimates for longer duration of OC slightly (data not shown). Adjustment for infant sex had little effect (data not shown).

Results were also similar when we excluded the 202 women who had ever used another type of hormonal method of birth control (vaginal ring, hormone injection or patch) from the analysis (data not shown). The small number of women (n=124) who had never used OCs or other hormonal methods had heavier infants than women who had ever used OCs, regardless of recency or duration of use (adjusted mean difference=70.4 g (CI: - 42.1, 183.0)).

The higher birth weight among infants of very recent OC users, who have conceived quickly, may reflect greater reproductive fitness among more fertile women. We evaluated this possibility by restricting our analysis to women who conceived very quickly and comparing OC users with women stopping other methods of contraception. When we restricted the analysis to women who conceived within 1 month of stopping contraception, the adjusted mean birth weight was 81.3 g higher (CI: -44.3, 207.0) in women who had last used OCs compared with those who last used all other non-hormonal methods. Among women conceiving within 3 and 6 months, the adjusted mean birth weight differences were 31.9 g (CI: - 57.7, 121.4) and 11.9 g (CI: -56.9, 80.7) respectively for oral contraceptive users compared with women stopping other methods.

When we analysed the data using dichotomous outcomes, the results were broadly similar to those using continuous birth weight. We found a reduction in the risk of low birth weight among recent OC users (RR=0.69, (95% CI: 0.47, 1.01)) for use of OCs within one year before pregnancy compared to longer ago) (Table 2). There was little association between macrosomia and OC use within the past twelve months, but there was a small association between very recent OC use and macrosomia (RR=1.29, 95% CI: 1.02, 1.64) for use within 0–1 months compared with use more than 12 months before conception), but no consistent trend across categories of recency (Table 2). Longer duration of OC use tended to be associated with a lower risk of macrosomia but there was no consistent trend between duration of use and low birth weight (Table 2). There were few discernible patterns between recency or duration of OC use in relation to SGA or LGA (Table 2).

The results for recency and duration of OCs were broadly consistent across categories of several covariates including smoking status, age, parity and BMI (data not shown). The effects for recency of use appeared to be slightly stronger among male infants. For males, adjusted mean birth weight differences were 128.6 g (95% CI:28.8, 228.3) and 85.3 g (95% CI:20.2,150.3) among women who had used OCs within 0–1 month and 2–6 months, respectively, compared with those who used OCs more than one year before conception. Among female infants, the corresponding birth weight differences were 77.8 g (95% CI:

–21.0, 176.7) and 3.1 g (95% CI: –58.4, 64.5). Similarly, the inverse association of duration of use of OCs on birth weight was slightly stronger among male infants (data not shown).

When we evaluated the association between recency of OC use and birth weight according to the last type of OC used (by generation and estrogen dose), we found stronger effects among women who had last used 1st or 2nd and 4th generation OCs compared with 3rd generation OCs (Table 3a). Women who used 1st or 2nd generation OCs within 12 months of conception gave birth to babies who were 85.6 g (95% CI: –77.6, 152.9) heavier compared with infants whose mothers who had last used 1st/2nd generation OCs 12 or more months before conception. Among 3rd or 4th generation users, mean birth weight differences were 16.2 and 61.7 g respectively, comparing women who had last used OCs within 12 months with those who used them longer ago. There were few consistent associations by duration of use for 1st/2nd generation and 3rd generation. Longer durations of OC use among women who used 4th generation pills most recently were associated with decreased birth weight though estimates were very imprecise.

Results also differed according to the estrogen dose of the last brand used (Table 3b); among high dose users (≥ 30 mg), the mean birth weight difference comparing recent (≤ 12 months) with more distant (>12 months) OC use was 96.4 g (95% CI: –6.7, 199.5) and among low and medium dose users (<30 mg) the mean difference was 29.3 g (95% CI: –16.0, 74.5). The same tendency was apparent when the finer categories of recency were examined. Few women used progestin only pills and results were unstable.

Discussion

Main Findings

In this prospective cohort study of pregnancy planners, we found a positive association between recency of OC use and mean infant birth weight and ponderal index. Associations appeared to vary depending on the type of OC that was used most recently, with higher birth weights being more strongly associated with recent use of 1st or 2nd and 4th generation OCs and higher estrogen dose pills. It seems plausible that some physiologic effects may persist for a few months after discontinuing OCs, since women tend to be less fertile for the first few cycles following OC cessation. (14, 31)

In contrast to the results for recency of OC use, longer durations of OC use were associated with slightly lower mean birth weight. The inverse associations between duration of OC use and birth weight were most pronounced for 1st or 2nd generation, 4th generation, and high estrogen dose pills.

Previous findings on birth weight following pre-gravid OC use are mixed. One study found an increase in mean birth weight comparing ever with never users of OCs, as well as with more recent and longer duration of OC use, (6) and another study found a slightly lower prevalence of low birth weight (<2500 g) in former OC users (4.8%) compared with non-users (7.1%), but potential confounding was not evaluated. (7) Several studies found little difference in birth weight, (4, 5) while two studies suggested an increase in low birth weight among periconceptional (10) and very recent (<30 days LMP) OC users. (11) Two prior

studies evaluated findings by infant sex. Similar to our findings, Polednak et al. found higher birth weights in males according to recency of OC use, but only in older mothers. (8) Another study found no effect of OC use within three years of conception in either male or female infants. (5) As did Mucci et al., (6) we found a small increase in birth weight associated with recency of use, particularly when restricted to recent users of 1st and 2nd generation OCs. In contrast to Mucci's study, we found higher mean birth weight among the small proportion (3%) of women who had never used OCs, and reductions in birth weight among women who had used OCs for 4 years or more. Few other studies have evaluated duration of OC use in relation to birth weight.

Strengths and Limitations

Strengths of our study include the prospective assessment of pregnancy, and a detailed questionnaire assessing timing and duration of exposure. We also collected specific information on OC brand, and included a pop-up menu of brand names to enhance recall. Nevertheless, some misclassification of exposure is likely, which would tend to bias results toward the null for the extreme duration or recency categories, with less predictable influences for estimates in intermediate categories. OC duration is likely to be subject to more misclassification than recency since it requires reconstruction of the lifetime history of OC use. In addition, we evaluated recency and duration of use within different OC types (e.g. by generation and estrogen dose), but used only the most recent brand to categorize the OC formulation. Therefore, the associations for duration of use within type of OC are subject to misclassification for the women who changed brands. Finally, we did not have information on indication for OC use. If women with menstrual irregularities, including polycystic ovarian disease, are more likely to use OCs for long periods than more fertile, reproductively fit women, this difference might have affected our results, particularly for duration. We controlled for many confounders, including maternal age, BMI, parity, education, income, and smoking in pregnancy, but as in any study, confounding by unmeasured variables may have biased our results. We did not have information on maternal weight gain, diet or medication use in pregnancy, which may affect fetal growth but seem less likely to be related to OC use; these variables may be affected by OC use and thus would not be considered confounders. We controlled for gestational age and infant sex in secondary analyses and results were similar. Women who use OCs may be inherently more fertile than women who use other methods of birth control, so it is possible that the effects for recency of use of OCs may reflect greater reproductive fitness rather than any effect of OCs per se. Nevertheless, when we restricted our analysis to women who conceived promptly and compared OC users with women stopping other methods, the results were only slightly attenuated. An important consideration in this study is that selection bias due to loss to follow-up is not likely, as we linked our study participants with the Danish birth registry. Thus, we were able to identify all live births among our study population through 2010, regardless of whether women stopped responding to follow-up questionnaires. Our study recruited participants via the Internet and thus unlike traditional prospective cohort studies, we were not able to calculate response rates or compare characteristics of baseline responders and non-responders to evaluate possible selection bias. Nonetheless, we have compared associations between several factors related to birth weight (e.g. maternal smoking) in our cohort with those of the entire population of singleton live births in the

Danish Medical Birth Registry, and found similar results, indicating that selection bias in the study was small or nonexistent. (35)

Interpretation

Potential mechanisms for the association between recent pregravid OC use and higher birth weight are uncertain but may be due to persistent physiological effects, such as changes in maternal endogenous hormones, following OC cessation. Lower levels of estrogens among postmenopausal women (19) and macaque monkeys (20) have been found after long-term premenopausal use of OCs. One study found changes in insulin-like growth factor (IGF-1) levels following cessation of OCs, but the results differed according to age group, with decreased IGF-1 among young women (age 18–21) and increased IGF-1 among women aged 31–40. (18) Increased insulin resistance, (15, 36) alterations in cholesterol levels (15) and a higher incidence of hypertension (37) among OC users have been reported. Some studies have suggested that OCs may influence libido (17) via a reduction in circulating androgen levels, (38) and persistent changes in serum hormone binding globulin (SHBG) following OC cessation have been described. (16) C-reactive protein (CRP) levels are higher in current users of OCs, although it is unclear whether this elevation persists following OC cessation. We are not sure how to explain the opposing effects for recency and duration of use of OCs. Perhaps different physiologic changes, with opposing effects on fetal growth, occur with recent versus long term duration of OCs. Some synthetic progestins present in OC formulations are structurally related to testosterone. (39, 40) Higher levels of testosterone in pregnancy have been associated with lower birth weight in both humans (41) and marmosets, which might explain the association between longer duration of OC use and lower birth weights. On the other hand, long duration of OC use may be correlated with greater menstrual irregularity, which in turn could be associated with lower reproductive fitness and propensity to deliver to lower birth weight babies.

Conclusion

In summary, we found an increase in mean infant birth weight among women who had recently discontinued OCs in order to conceive, but birth weights tended to decrease with longer durations of use of OCs. Results for recency and duration were stronger among women who had last used 2nd and 4th generation OCs, and OCs with a higher estrogen dose, and among male infants. Larger prospective cohort studies with balanced numbers of women using OCs and other types of contraception would be useful to clarify the associations between recency, duration and type of pregravid OC use with birth weight. It would also be worthwhile to evaluate the association with newer forms of hormonal contraception such as the vaginal ring and extended cycle OCs. If causal, the biologic mechanisms for this association are uncertain, but might include residual physiologic effects such as endogenous hormonal changes following OC cessation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Maternal characteristics and reproductive factors by recency of oral contraceptive use

	Used OCs within past year (N=1895) N (%)	Used OCs more than 1 year ago (N=1877) N (%)
<u>Age</u>		
18–24	355 (18.7)	248 (13.2)
25–29	935 (49.3)	822 (43.8)
30–34	504 (26.6)	625 (33.3)
35	101 (5.3)	182 (9.7)
<u>Pre-pregnancy BMI (kg/m²)</u>		
<18.5	58 (3.1)	70 (3.7)
18.5–24	1283 (67.7)	1188 (63.3)
25–29	379 (20.0)	381 (20.3)
30	175 (9.2)	238 (12.7)
<u>Smoking</u>		
Non-smoker	1519 (80.2)	1445 (77.0)
Current smoker	376 (19.8)	432 (23.0)
<u>Parity</u>		
Nulliparous	1349 (71.2)	1165 (62.1)
Parous	546 (29.8)	712 (37.9)
<u>Vocational training</u>		
No vocational training	210 (11.1)	210 (11.2)
Semi-skilled/Basic training	292 (15.4)	315 (16.8)
<3 years higher education	272 (14.4)	268 (14.3)
3–4 years higher education	665 (35.1)	665 (35.4)
>4 years higher education	456 (24.1)	419 (22.3)
<u>Income</u>		
<25,000 DKK	229 (12.1)	235 (12.5)
25,000–39,999 DKK	480 (25.3)	443 (23.6)
40,000–65,000 DKK	898 (47.4)	879 (46.8)
>65,000 DKK	288 (15.2)	320 (17.1)

Table 2

Adjusted mean birth weight (grams) and ponderal index (kg/m^3) differences and risk ratios (RR) of low birth weight and macrosomia according to characteristics of pregravid oral contraceptive use

	Birth Weight (g)		Ponderal Index		Low Birth Weight		Macrosomia		SGA		LGA	
	Total N [^]	Mean difference [†] (95% CI)	Mean difference [†] (95% CI)	N [^]	RR [*] (95% CI)	N [^]	RR ^{**} (95% CI)	N [^]	RR [*] (95% CI)	N [^]	RR [*] (95% CI)	
Recency												
	Past year	37 (1, 73)	0.03 (0.01, 0.04)	51	0.69 (0.47, 1.01)	330	1.06 (0.92, 1.22)	184	0.91 (0.73, 1.13)	188	1.05 (0.84, 1.32)	
	> 1 year ago	Referent (0)	Referent (0.0)	74	Referent (1.0)	346	Referent (1.0)	201	Referent (1.0)	194	Referent (1.0)	
	0–1 months	97 (26, 168)	0.04 (0.01, 0.08)	7	0.67 (0.30, 1.49)	63	1.29 (1.02, 1.64)	24	0.89 (0.57, 1.40)	30	1.05 (0.69, 1.61)	
	2–6 months	40 (–5, 85)	0.03 (0.01, 0.05)	22	0.63 (0.38, 1.03)	148	1.03 (0.86, 1.23)	90	0.94 (0.72, 1.24)	87	1.02 (0.77, 1.35)	
	7–12 months	11 (–37, 59)	0.02 (–0.01, 0.04)	22	0.77 (0.47, 1.27)	119	1.01 (0.83, 1.24)	70	0.87 (0.65, 1.17)	71	1.09 (0.80, 1.48)	
>12 months	Referent (0)	Referent (0.0)	74	Referent (1.0)	346	Referent (1.0)	201	Referent (1.0)	194	Referent (1.0)		
Duration												
	<4 years	Referent (0)	Referent (0.0)	11	Referent (1.0)	78	Referent (1.0)	36	Referent (1.0)	31	Referent (1.0)	
	4–7 years	–3 (–70, 63)	–0.03 (–0.06, 0.00)	33	1.02 (0.51, 2.05)	210	0.97 (0.78, 1.22)	108	1.04 (0.70, 1.56)	122	1.47 (0.97, 2.25)	
	8–11 years	–45 (–108, 19)	–0.02 (–0.05, 0.01)	59	1.04 (0.53, 2.03)	290	0.80 (0.64, 1.00)	166	0.90 (0.61, 1.32)	166	1.19 (0.79, 1.80)	
	12 years	–85 (–158, 11)	–0.03 (–0.07, 0.00)	22	0.94 (0.44, 2.03)	98	0.68 (0.52, 0.89)	75	0.99 (0.64, 1.55)	63	1.20 (0.75, 1.93)	

[^] N is from the first imputation dataset

[†] Linear regression model adjusted for maternal age, parity, cigarette smoking, income, vocational training, and body mass index; duration and recency models are mutually adjusted for each other

^{*} Logistic regression model adjusted for maternal age, parity, cigarette smoking, income, vocational training, and body mass index; duration and recency models are mutually adjusted for each other

^{**} Log-Binomial model adjusted for maternal age, parity, cigarette smoking, income, vocational training, and body mass index; duration and recency models are mutually adjusted for each other

Table 3a

Adjusted mean differences in birth weight (grams) by generation of most recent OC used.

	1 st /2 nd generation		3 rd generation		4 th generation	
	N [^]	Mean difference [‡] (95% CI)	N [^]	Mean difference [‡] (95% CI)	N [^]	Mean difference [‡] (95% CI)
Recency						
Past year	384	86 (−78, 153)	1088	16 (−35, 67)	261	62 (−37, 160)
More than 1 year ago	407	Referent (0)	933	Referent (0)	301	Referent (0)
0–1 months	56	179 (10, 349)	157	12 (−83, 107)	35	241 (37, 444)
2–6 months	192	53 (−49, 155)	502	30 (−33, 93)	119	71 (−53, 194)
7–12 months	136	90 (68, 249)	429	2 (−69, 72)	107	−8 (−138, 122)
>12 months	407	Referent (0)	933	Referent (0)	301	Referent (0)
Duration						
<4 years	85	Referent (0)	165	Referent (0)	75	Referent (0.0)
4–7 years	200	−21 (−215, 172)	519	3 (−11, 152)	188	−51 (−206, 103)
8–11 years	353	25 (−161, 211)	971	−44 (−155, 66)	239	−89 (−241, 62)
12 years	153	−67 (−263, 129)	366	−31 (−151, 88)	60	−286 (−490, −82)

[^] N is from the first imputation dataset[‡] Linear regression model adjusted for maternal age, parity, cigarette smoking, income, vocational training, and body mass index; duration and recency models are mutually adjusted for each other

Table 3b

Adjusted mean differences in birth weight by dose of estrogen in most recent OC used.

	No estrogen		Low/Medium estrogen		High estrogen	
	N [^]	Mean difference (g) [†] (95% CI)	N [^]	Mean difference [†] (95% CI)	N [^]	Mean difference [†] (95% CI)
Recency						
Past year	111	31 (-145, 208)	1303	29 (-16, 74)	314	96 (-7, 199)
More than 1 year ago	150	Referent (0)	1167	Referent (0)	304	Referent (0)
0-1 months	18	52 (-236, 339)	176	67 (-25, 159)	52	152 (-16, 319)
2-6 months	49	-6 (-303, 291)	606	40 (-16, 97)	158	80 (-36, 197)
7-12 months	44	64 (-266, 395)	521	4 (-56, 64)	104	94 (-63, 251)
>12 months	150	Referent (0)	1167	Referent (0)	304	Referent (0)
Duration						
<4 years	42	Referent (0)	231	Referent (0)	48	Referent (0)
4-7 years	79	103 (-241, 448)	682	-13 (-100, 73)	141	-78 (-299, 142)
8-11 years	100	80 (-257, 417)	1163	-58 (-140, 23)	287	-12 (-214, 190)
12 years	40	-116 (-514, 283)	394	-80 (-174, 14)	142	-59 (-290, 171)

[^] N is from the first imputation dataset[†] Linear regression model adjusted for maternal age, parity, cigarette smoking, income, vocational training, and body mass index; duration and recency models are mutually adjusted for each other