HHS Public Access

Author manuscript

Int J Obes (Lond). Author manuscript; available in PMC 2015 March 19.

Published in final edited form as:

Int J Obes (Lond). 2014 October ; 38(10): 1275–1281. doi:10.1038/ijo.2014.114.

Maternal hormonal contraceptive use and offspring overweight or obesity

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Abstract

Objective—Experiments in animal models have shown a positive association between *in utero* exposure to pharmacologic sex hormones and offspring obesity. The developmental effects of such hormones on human obesity are unknown.

Methods—Using data from a large, prospective pregnancy cohort study (n=19,652), with linkage to a national prescription registry, we evaluated the association between use of hormonal contraceptives before and after conception (defined from dispensed prescription data and characterized by last date of use relative to conception, 12 – >4 months before (n=3,392), 4 – >1 months before (n=2,541), 1 – > 0 months before (n=2,997), and 0–12 weeks after (n=567)) in relation to offspring overweight or obesity at age 3 years.

Results—We observed a weak, inverse association between early pregnancy use of a combination oral contraceptive and offspring overweight or obesity at age 3 (adjusted OR: 0.75,

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Disclosures: None of the other authors have any disclosures.

Author contributions (all authors approved the final draft):
Jensen: Project conception, design, analyses, interpretation, manuscript draft
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Supplementary information is available at the journal's website.

95% CI: 0.53, 1.08) and a positive, but imprecise, association with use of a progestin-only oral contraceptive in early pregnancy (adjusted OR: 1.26, 95% CI: 0.79, 2.02). In general, no association was observed between use of a hormonal contraceptive before conception and offspring overweight or obesity. A sensitivity analysis comparing combination oral contraceptive users in early pregnancy to other unplanned pregnancies without hormonal contraceptive use further strengthened the inverse association (adjusted OR: 0.70, 95% CI: 0.48, 1.02). Other sensitivity analyses were conducted to evaluate the robustness of the associations observed given varying assumptions.

Conclusion—Pharmacologic sex hormones in early pregnancy may be inversely or positively associated with offspring overweight or obesity at age 3, depending on the specific formulation used. The present study provides support for the potential for environmental sources of hormonally active agents to exert developmental effects.

Keywords

Hormonal contraceptives; Estrogen-mimicking compounds; Pediatric overweight and obesity; Developmental origins of health and disease; The Norwegian mother and child (MoBa) cohort study

Introduction

Worldwide, the prevalence of childhood overweight and obesity increased from 4.2 percent in 1990 to 6.7 percent in 2010.[1] Children who are overweight or obese are more likely to be overweight in adulthood and to suffer from obesity-related morbidity and mortality.[2, 3] The obesity epidemic has been primarily attributed to changes in dietary and physical activity behaviors,[4, 5] but exposure to estrogen-mimicking compounds during developmentally sensitive periods may contribute.[6, 7]

Estrogenic agents can affect adipogenesis *in vitro*. 17-β estradiol has resulted in increased preadipocyte proliferation, likely though up-regulation of PPAR-γ.[8] Preadipocyte formation can occur as early as the blastocyst stage,[9] although upregulation of mesenchymal stem cell recruitment to preadipocytes is highest in the second trimester of pregnancy.[10]

In a previous study of the association between oral contraceptive (OC) and diethylstilbestrol (DES) use in pregnancy and offspring obesity,[11] the strongest magnitude of association for OCs was in months 1 and 2 and, for DES, in months 3–4. This study was executed at a time when the potency of OCs was considerably stronger (1959–1974).

Experiments in animal models have shown a positive association between *in utero* and neonatal exogenous estrogen exposure and metabolic disruption in the offspring, including offspring overweight or obesity.[6, 7] However, *in utero* exposure to androgens has also been associated with offspring obesity.[12–14] Hormonal contraceptives can be androgenic, depending on the progestin component included.[15] The developmental effects of exogenous sex hormones on growth may be sex-dependent, with associations primarily in male offspring.[16]

The maternal metabolic milieu is also associated with offspring overweight or obesity.[17, 18] Hormonal contraceptives have, for many women, unintended metabolic effects, including elevated levels of very low-density lipoprotein cholesterol and total triglycerides.[15, 19–21] Hormonal contraceptives increase plasma insulin and cortisol,[21] and induce a state of insulin resistance.[15, 19, 20] Some of these metabolic changes, including increased total cholesterol[22] and insulin resistance,[23] are similar to those in women who are overweight or obese.. Whether these metabolic effects persist after cessation of use is unclear; however more androgenic formulations may subsequently increase risk of gestational diabetes.[24]

The half-lives of hormonal contraceptives are generally <24 hours;[25] however in some instances drug components may be detectable for several months post cessation. For example, Medroxyprogesterone Acetate has been detectable in serum at 8 months post cessation of administration.[15] Previous hormonal contraceptive use may have long-term effects on endogenous hormone levels, including altered hormone levels both during pregnancy[26] and after menopause.[27]

Given the data suggesting that hormonal compounds cause changes in follicular,[28, 29] embryonic, and fetal development,[30, 31] that they may cause an obesity-like metabolic milieu,[32] and that they may exert long-term effects on endogenous sex hormone levels,[27, 33] additional studies of hormonal contraceptive exposure and offspring development in humans are needed.

Because use of pharmacologic sex hormones in early pregnancy is relatively uncommon, most cohort studies lack the power to evaluate the association. Hormonal contraceptive failure occurs in about 3% of users.[34] With over 40,000 children followed to age 3, the Norwegian Mother and Child Cohort Study (MoBa)[35] offers an unusual opportunity to assess the influence of *in utero* exposure to exogenous sex hormones, through hormonal contraceptive use in early pregnancy, on childhood overweight or obesity. In the present study, through linkage of MoBa data with the Norwegian Prescription Registry (NorPD), we evaluated the association between hormonal contraceptive use and offspring overweight or obesity at 36 months of age.

Methods

MoBa study participants were recruited in Norway from 1999 through 2008, as described in detail elsewhere.[35] Women were identified for eligibility when scheduling the routine prenatal ultrasound offered free of charge to all pregnant women in Norway at 17–20 weeks of gestation. Women were mailed an invitation to participate before the scheduled ultrasound, with informed consent and enrollment taking place at the ultrasound examination. Approximately 42 percent of all pregnant women in Norway were invited to participate in the study. Of these, 39 percent consented to participate. At enrollment, participants were asked to complete a self-administered questionnaire to collect data on demographic characteristics, reproductive health history, disease and medication history, lifestyle factors, and socioeconomic status. Follow-up is conducted through self-administered questionnaires.

Prescription data from NorPD contains individual-level data on all medications prescribed and dispensed through pharmacies to non-institutionalized individuals in Norway. By Norwegian law, as of January 1, 2004, all pharmacies must provide electronic data for all prescriptions dispensed. Data quality measures are in place for assuring the NorPD is accurate and complete.[36] A validation study of hormonal contraceptive use in the NorPD was conducted in adolescents and indicated a sensitivity of 99% and a specificity of 76% for the NorPD as compared to self-reported use.[37] In adolescents, hormonal contraceptives may be provided at no cost to the individual, but in adults, hormonal contraceptives are not a reimbursable prescription. This may increase the likelihood that a dispensed prescription will be used by the individual.

There were 107,308 MoBa pregnancies registered in the Medical Birth Registry of Norway (MBRN). All MBRN data are collected on a standardized birth notification form completed by the midwife or physician attending the birth. For the present analysis, we included pregnancies resulting in a singleton live birth, with no record of death in the first year of life, and with no documentation, on either the MoBa 17-week questionnaire or the MBRN, of having received infertility treatment for the index pregnancy. We additionally excluded pregnancies to women with pre-pregnancy chronic hypertension (n=527). As the NorPD registry was not initiated until January 1, 2004, we further restricted our study population to pregnancies of women enrolled at least 12 months after the date on which the NorPD registry began collection of data (n=48,615). For the primary analyses, we also excluded pregnancies with missing covariate data (n=3,966), and for loss to follow-up at age 3 (n=24,997). The final study population included 19,652 pregnancies to 18,759 women (17,867 women with 1 offspring in the cohort, 1,782 with 2, and 1 with 3 offspring) (Figure 1). The University of North Carolina at Chapel Hill, the National Institute of Environmental Health Sciences Institutional Review Board, and the Norwegian Southeastern Regional Ethics Committee reviewed and approved this study.

Hormonal contraceptive use, before conception and in early pregnancy, was characterized according to the Anatomical Therapeutic Chemical (ATC) Classification System.[38] We characterized exposure by type and route of administration (combination OC, progestin-only OC, vaginal ring, transdermal, injectable, implant, and hormonal-based intrauterine device) and by progestin formulation. All hormonal contraceptives with an estrogen component (combination OC, vaginal ring, and the transdermal contraceptive) contained ethinyl estradiol, but there were eight different progestin types used solely or in combination with ethinyl estradiol, including desogestrel, drospirenone, levonorgestrel, norelgestromin, norethisterone, lynestronol, medroxyprogesterone, and etonogestrel. Any exposures with fewer than 10 exposed cases we combined into a single “other” category (Supplementary Table S1).

Although our primary interest was to explore the association between exposure in early pregnancy and offspring overweight or obesity, we also characterized exposure into discrete windows of hormonal contraceptive exposure according to last date of use relative to conception, e.g. 12 – >4 months before, 4 – >1 months before, 1 – > 0 months before, and 0–12 weeks after. These periods of exposure were selected as they correspond to possibly distinct developmental periods of susceptibility, specifically the primordial follicular phase

(FSH independent) (12 to 4 months before conception), the secondary to antral phase of follicular development (FSH dependent) (4 to 1 month before conception), the emergence of a dominant follicle and release of the oocyte (1 month before conception), and post conception, early pregnancy (weeks 0–12), when endogenous levels of estradiol and progesterone are still relatively low and exogenous sources of exposure may contribute a relatively higher dose (relative to endogenous levels).[39]

Date of conception was estimated by subtracting 17 days[40] from the number of days of gestational length at birth (to account for the follicular phase prior to conception) and then subtracting this value from the date of birth. We used the last menstrual period (LMP)-based estimated gestational length unless the LMP-based gestational length was missing (5.1%) or ≥2 weeks from the ultrasound-based estimate of gestational length (5.2%), in which case we used the ultrasound based measure.[41] We then constructed an exposure window for each hormonal contraceptive prescription filled using the date that the prescription was filled and the number of defined daily doses dispensed (day's supply). Most OCs were dispensed in a 3 month supply (82%) or a 6 month supply (15%). For pregnancies with more than one type of hormonal contraceptive prescribed, we assigned exposure type according to the type of contraceptive used closest to the estimated date of conception. Because many women may choose to stop taking their hormonal contraceptive in order to achieve conception, we characterized women as exposed in early pregnancy only if they reported that the pregnancy was unplanned and had ≥ 1 day supply of hormonal contraceptive at or after the day of conception.

Offspring overweight or obesity was defined by first calculating the offspring body mass index (BMI) (kg/m^2) at age 3 years from questionnaire-reported height and weight measures. In Norway, families are provided a health card to record information about their children. Mothers were asked to transcribe the health care data on height, weight, and date onto a MoBa questionnaire when the children were three years old. Offspring were characterized as overweight or obese using the age- and sex-specific cut points developed by the International Obesity Taskforce (IOTF) (17.89 kg/m^2 for boys and 17.56 kg/m^2 for girls).[42] To evaluate the accuracy of the child height and weight data, we conducted a validation substudy. We assessed the correlation between BMI obtained from the questionnaire and BMI based on measures taken for the Bergen Growth Study.[43] The correlation was examined among measures obtained within 90 days of one another.[44]

Covariate selection was informed through construction of a directed acyclic graph.[45] The adjustment factors selected (and data source) were maternal age (MBRN) (14–19, 20–29, 30–39, 40–49), prepregnancy BMI (MoBa pregnancy questionnaire) (kg/m^2)(<18.5, 18.5–24.9, ≥25.0), parity (MBRN) (0, 1, ≥2), smoking (composite from MoBa questionnaires and the MBRN) (none, quit during pregnancy, smoker), and education (MoBa pregnancy questionnaire) (>4 years of university or technical, 4 year university or technical degree, 3 years of college preparatory high school, 3 years of technical high school, 1–2 years of high school, <9 years of secondary school, other).

Primary analyses

Our primary analyses were concerned with assessing the association between early pregnancy hormonal contraceptive exposure, as compared to no use of a hormonal contraceptive in early pregnancy or the 12 months before pregnancy, and offspring overweight or obesity. We used generalized linear models with a logit link, and generalized estimation equations (GEE) with an independent correlation matrix[46] to estimate robust standard errors and account for lack of independence between siblings. We used similar models to assess the association between hormonal contraceptive use prior to conception and offspring overweight or obesity. Finally, we evaluated the association between hormonal contraceptive use with BMI z-score, calculated from the World Health Organization growth standards for BMI.[47]

Subgroup analyses

In subgroup analyses, we explored the association between route of administration and type of progestin agent and offspring overweight or obesity. We also explored whether there was evidence of interaction between hormonal contraceptive use and offspring sex, maternal prepregnancy overweight/obese status (≥25.0 kg/m^2; Yes/No), or maternal pre-pregnancy weight using interaction terms. *A priori*, we considered a p value <0.20 as evidence of potential interaction.[48] Given evidence of possible interaction, we examined stratum-specific estimates. All analyses were conducted using SAS v9.3 (SAS Inc., Cary, North Carolina).

Sensitivity analyses

We conducted several sensitivity analyses to address the potential for residual confounding or confounding by indication (use of different comparator groups and additional adjustment factors), the potential for selection bias from loss to follow-up (use of both multiple imputation and inverse probability weighting), and the potential for exposure misclassification (consideration of self-reported use of hormonal contraceptives). We also assessed whether a log-binomial model, for estimating relative risks, generated estimates that were materially different from estimates obtained in the logit model estimating odds ratios. The methods for these analyses are described in Supplement I, with supporting details provided in Supplementary Tables S1–S3.

Results

In general, compared to all MoBa pregnancies with baseline data collected in pregnancy and at birth, the pregnancies included in the final study sample were to women who were older, less parous, more educated, and less likely to have smoked in pregnancy (Table 1). At 36 months of age, 2,653 (13.1%) children in the analysis met the IOTF definitions for overweight or obese. We identified 3,392 pregnancies exposed 12 – >4 months before, 2,541 4 – >1 months before, 2,997 1 – >0 month before, and 567 0 – 12 weeks after conception. For the validation substudy, 77 children had height and weight data at age 3 collected in both MoBa and the Bergen Growth study. These data were obtained no more than 90 days apart from the respective studies (mean difference: 32 days, std 33 days). The correlation of

BMI between the two sources of data was high (Pearson r=0.86, 95% CI: 0.81, 0.90) and consistent with the expected correlation between BMI calculated from serial measures of height and weight in young children.[44]

Primary analyses

In early pregnancy, the combination OC was weakly, inversely associated with offspring overweight or obesity at age 3 (aOR: 0.75, 95% CI: 0.53, 1.08). The progestin-only OC was weakly, positively associated with overweight or obesity (aOR: 1.26, 95% CI: 0.79, 2.02) (Table 2). Use of a hormonal contraceptive before pregnancy was generally not associated with overweight or obesity, with the exception of use of a vaginal ring-type hormonal contraceptive, which was inversely associated, particularly for exposure estimated to have occurred 1 – >0 months before conception (aOR: 0.60, 95% CI: 0.35, 1.04) (Table 2). Data were too sparse to evaluate the association between early pregnancy use of the vaginal ring and subsequent offspring overweight or obesity. The direction of the estimates obtained when modeling BMI z-score as a continuous outcome were similar to those obtained when modeling BMI as a dichotomous outcome (data not shown).

Subgroup analyses

Among combination OC users, the association with overweight or obesity was similar across combination OCs with differing progestin components (Supplementary Tables S4–S7). In early pregnancy only, the desogestrel progestin-only OC was moderately associated with offspring overweight or obesity (aOR: 1.87, 95% CI: 1.06, 3.32) (Supplementary Table S4).

For early pregnancy use of a combination OC there was weak evidence of effect modification by offspring sex or maternal pre-pregnancy BMI. For exposure to the combination OC in early pregnancy, the observed association with overweight or obesity was present only in males (aOR: 0.56, 95% CI: 0.32, 0.97 in males vs aOR: 0.98, 95% CI: 0.63, 1.53 in females). The magnitude of association observed for use of the combination OC was also stronger in women characterized as normal BMI (BMI <25.0 kg/m^2) (aOR: 0.64, 95% CI: 0.40, 1.02 in normal BMI women vs aOR: 0.95, 95% CI: 0.56, 1.62 in overweight or obese women), although confidence intervals of the strata overlapped considerably (Supplementary Table S8). There was no evidence of interaction between hormonal contraceptive use (of any type) and maternal pre-pregnancy weight (p for interaction term >0.20).

Sensitivity analyses

In early pregnancy, for the analyses evaluating the use of different comparator groups, the inverse association between the combination OC and offspring overweight or obesity was robust to restricting the comparator population to unplanned pregnancies (aOR: 0.70, 95% CI: 0.48, 1.02) (Table 3). This inverse relationship was also materially unchanged when comparing early pregnancy combination OC users to former users of the combination oral contraceptive and when comparing the combination OC users to the progestin-only OC users (aOR: 0.75, 95% CI: 0.52, 1.06) (Table 3). Similarly, the relationship between

progestin use in early pregnancy and offspring overweight or obesity was robust to choice of comparator groups (Table 3).

The estimate comparing vaginal ring use to the combination OC (within 1 month prior to conception) was aOR 0.59 (95% CI: 0.33, 1.03) and consistent with estimates obtained when comparing vaginal ring users to non-users of a hormonal contraceptive (aOR: 0.60, 95% CI: 0.35, 1.04).

The magnitude of the estimates from models employing multiple imputation were somewhat attenuated (aOR: 0.85, 95% CI: 0.66, 1.11 for the combination OC) compared to those obtained in the primary analyses (aOR: 0.75, 95% CI: 0.53, 1.06) while estimates obtained using inverse probability weighting were somewhat strengthened (aOR: 0.68, 95% CI: 0.49, 0.99 for the combination OC) (Supplementary Tables S9–S10). Characterizing exposure by self-reported use in early pregnancy, as reported on the questionnaire administered during pregnancy, also attenuated the estimates observed and introduced additional imprecision (aOR: 0.88, 95% CI: 0.57, 1.35 for use of the combination OC and aOR 1.15, 95% CI 0.58, 2.28 for use of the progestin-only OC) (data not shown). Adjustment for diabetes type I or II, age in 5-year increments, income, and maternal weight did not substantively change the estimates (data not shown). Estimates obtained using a log-binomial model were also not materially different (Combination OC RR: 0.78 (95% CI: 0.57, 1.82) and Progestin-only OC RR: 1.23 (95% CI: 0.83, 1.82) for early pregnancy use).

Discussion

In our primary analysis of the association between early pregnancy hormonal contraceptive use and offspring overweight or obesity, we found that use of a combination OC was weakly, inversely associated with offspring overweight or obesity at age 3. Use of the progestin-only OC in early pregnancy was weakly, positively associated with offspring overweight or obesity. A moderate positive association for early pregnancy progestin-only OC use was observed for desogestrel. With the exception of an inverse association for the vaginal ring, there was no association with use of a hormonal contraceptive before pregnancy and offspring overweight or obesity. The absence of an association with use before pregnancy suggests that any developmental effect may be result of a direct effect on the embryo and fetus, as opposed to changes to follicular or oocyte development. The relevance of timing of use was further supported by an evaluation of self-reported duration which was unrelated to offspring overweight or obesity (data not shown).

All of the associations were qualitatively unchanged with selection of different comparator groups, suggesting that the characteristics of women using the contraceptive were not contributing to the estimates observed. The sensitivity analyses indicated that the results could have been affected somewhat by out-selection bias, but the direction of the bias was unclear. The sensitivity analyses also showed results were attenuated when based on self-reported hormonal contraceptive use. Self-reported data, however, lacked the detail of the NorPD data, and progestin specific associations could not be ascertained.

In experimental animal models, *in utero* and neonatal exposure to estrogenic agents (DES and 17β-estradiol) results in an initial period of depressed growth, followed by increasing adiposity at follow-up.[6,16] Although the timing of exposure for these animal studies is somewhat different (from conception through birth for pregnancy and in early neonatal life), the weak, inverse association with the combination pill in the present study may be congruent with observations of an initial period of depressed growth in these experimental studies. The evidence for depressed growth from hormonal contraceptives in human studies has been mixed, with some studies indicating no association with birthweight or low-birth-weight and others indicating a weak, positive association with low-birth-weight. The number of exposed pregnancies in these studies has been small and unable to differentiate between contraceptive formulations.[49–52] Additional follow-up of the MoBa cohort will allow investigation of associations at later ages to determine whether the growth pattern exhibited in animal models is relevant in humans.

We observed differences in association depending on the type of contraceptive and progestin used. The agents in different hormonal contraceptives vary with respect to their biding affinities for androgen, progestogen, and estrogen receptors. Some exert androgenic properties, others anti androgenic properties.[15] To our knowledge, studies of offspring adiposity or growth following exposure to progestogenic compounds during early fetal development have not been conducted in animals or humans. However, endogenous serum progesterone levels in pregnancy have been positively associated with offspring birthweight[53, 54] and birthweight has been associated with offspring weight at follow-up.[55] Fetal exposure to androgenic agents has resulted in metabolic abnormalities, including a polycystic ovarian syndrome-like phenotype in animal models.[12] Unopposed by ethinyl estradiol, desogestrel has high progestational and moderate androgenic activity relative to other progestin types, but when desogestrel is present in combination with ethinyl estradiol, the progestational and androgenic activities are substantively reduced.[15] Norethisterone is only weakly androgenic. This property may explain the difference in association observed between desogestrel and norethisterone progestin-only contraceptives in this study.

The inverse association between use of the vaginal ring and offspring overweight or obesity may be attributable to the pharmacokinetic properties of the vaginal ring. The vaginal ring contains etonogestrel and ethinyl estradiol. Hormonal constituents of the vaginal ring are absorbed through the vaginal epithelium and provide steady release of etonogestrel and ethinyl estradiol for the three week period after the ring is inserted.[15] Pharmacokinetic studies comparing the vaginal ring to the combination OC indicate that the dose of ethinyl estradiol, as measured in blood serum and represented by the area under the curve, is lower than that of doses experienced in combination OC users.[56] The agents in the vaginal ring do not experience first pass metabolism. The ring provides a consistent release of hormones unaffected by dietary or gastrointestinal factors and is less subject to fluctuation in delivered dose when compared to oral or transdermal-administered forms of contraception.[57]

Sparse data limited the ability to assess variation in effects by different progestin types in early pregnancy. We found possible evidence of effect modification by offspring sex and maternal prepregnancy BMI for the combination OC; however, sample size limitations may have also precluded the ability to detect effect modification for the progestin-only

formulation. The possible effect modification observed for early pregnancy is consistent with animal data suggesting that developmental effects of estrogenic compounds may be stronger among male offspring.[16] The associations observed could be attributable to residual confounding or confounding by indication. Women may be prescribed different contraceptive formulations based on factors for which we cannot control in our data. Notwithstanding, estimates obtained from sensitivity analyses, conducted to assess the potential for confounding by indication, were robust to choice of comparator group. Use of methods to explore the potential for bias from loss to follow-up is effective only insofar as we have correctly assumed that we were able to successfully impute missing values from the covariates in our imputation models (multiple imputation approach) or correctly predict the probability of staying in the study from the covariates in our predicted probability models for generating weights (inverse probability weighting approach). There was also a potential for misclassification of the timing of exposure.

The overall proportion of overweight or obese children at age 3 in this study (13.1%) is relatively consistent with national prevalence estimates for overweight or obesity at age 3 that were obtained from height and weight data collected by research staff (11.3%).[58] Nonetheless, BMI is less specific for identifying clinically relevant adiposity in children when compared to other measures of assessing childhood adiposity.[59]

Overweight and obesity may be influenced by developmental exposure to exogenous sex hormones. The present data suggest that pharmacologic sex hormone agents may be associated with offspring overweight or obesity at age 3. The direction of the relationships appears contingent upon hormone formulation. Little is known about long-term, formulation-specific effects on offspring weight status.

Data from experiments on animals suggest that early life exposure to hormonally-active agents may affect offspring growth. Given the evidence that early life anthropometric indicators are associated with adult adiposity,[2, 3] the investigation of determinants of early life anthropometrics is warranted. The results presented provide support for the assertion that *in utero* exposure to hormonally active agents, during developmentally sensitive periods, may contribute to alterations in offspring growth.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

We are grateful to all the participating families in Norway who take part in this ongoing cohort study.

This work was supported in part by the Intramural Research Program of the National Institutes of Health (NIH), National Institute of Environmental Health Sciences (NIEHS) (ES102985 to CJW), the University of North Carolina institutional training grant award for reproductive, perinatal, and pediatric epidemiology (grant T32HD052468 to ETJ), the National Cancer Institute (1K01CA172717-01 to WRR), and the Carolina Population Center (R24 HD050924 to WRR). The Norwegian Mother and Child Cohort Study is supported by the Norwegian Ministry of Health, contract N01-ES-75558 with the NIH/NIEHS, NIH/National Institute of Neurological Disorders and Stroke (grant 1 UO1 NS 047537-01), and the Norwegian Research Council/FUGE (grant 151918/S10).

TS receives investigator-initiated research funding and support as Principal Investigator (R01 AG023178) and Co-Investigator (R01 AG042845) from the National Institute on Aging (NIA), and as Co-Investigator (R01 CA174453) from the National Cancer Institute (NCI) at the National Institutes of Health (NIH), and as Principal Investigator of a Pilot Project from the Patient Centered Outcomes Research Institute (PCORI). He also received research funding as Principal Investigator of the UNC-DEcIDE center from the Agency for Healthcare Research and Quality. Dr. Stürmer does not accept personal compensation of any kind from any pharmaceutical company, though he receives salary support from the Center for Pharmacoepidemiology (current members: GlaxoSmithKline, UCB BioSciences, Merck) and research support from pharmaceutical companies (Amgen, Genentech, Merck, Sanofi) to the Department of Epidemiology, University of North Carolina at Chapel Hill.

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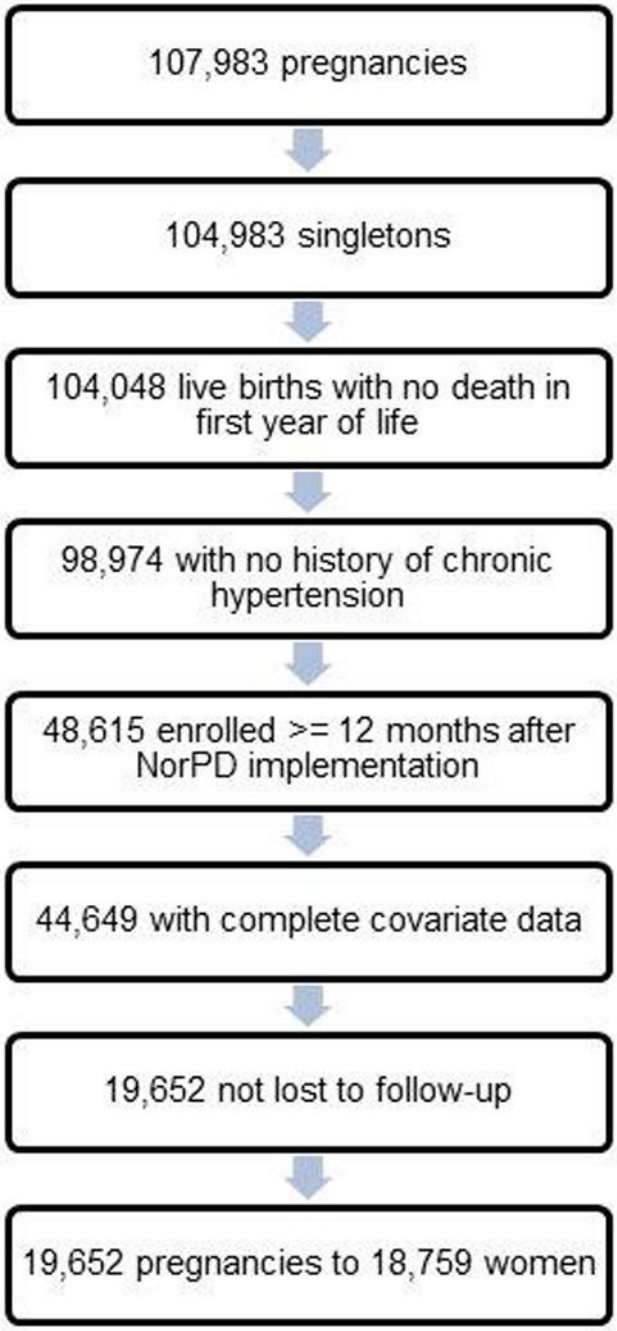

Figure 1.
Study population selection for assessing association between hormonal contraceptives and offspring overweight or obesity in the Norwegian Mother Child Prospective Cohort Study (2004–2008)

Table 1

Study and baseline population characteristics among women participating in the Norwegian Mother Child Prospective Cohort Study (2004–2008)

	Baseline population*	Study population
	n=44,649 %	n=19,652 %
Maternal age (years)		
14–19	0.9	0.4
20–29	42.1	40.3
30–39	54.9	57.1
40–49	2.1	2.3
Maternal BMI (kg/m^2)		
<18.5	3.2	2.9
18.5–24.9	66.1	67.2
25.0–29.9	21.7	21.8
≥30.0	9.0	8.1
Parity		
0	47.1	50.0
1	35.5	34.3
2	13.7	12.4
3	2.8	2.4
4 or more	0.9	0.8
Maternal education		
More than 4 years of university or technical	27.2	29.9
4 year university degree, regional technical	40.8	43.9
3 years high school, junior college	13.5	12.0
Technical high school	11.2	9.3
1–2 years high school	3.9	2.6
9-year secondary	2.2	1.1
Other	1.4	1.4
Maternal smoking (at 17 weeks)		
None	79.3	82.8
Quit	14.5	12.6
Daily	1.4	1.2
Sometimes	4.8	3.4

*Represents unique pregnancies with no use of IVF treatment, resulting in a singleton live birth and no death in the first year of life, with a date of birth ≥12 months after NorPD registry began (January 1, 2004)

Table 2

Association between hormonal contraceptive use in early pregnancy* and offspring overweight or obese

Exposure	Exposed (n)	Overweight or obese (n)	Crude OR (95% CI)	Adjusted** OR (95% CI)
None†	9,987	1,342	referent	referent
Combination OC	380	38	0.72 (0.51, 1.01)	0.75 (0.53, 1.08)
Progestin only OC	127	21	1.28 (0.80, 2.05)	1.26 (0.79, 2.02)
Other‡	60	7	0.85 (0.39, 1.88)	0.88 (0.40, 1.94)

* use within 12 weeks after conception as compared to no use of a hormonal contraceptive within the discrete categories of within 12, 4, and 1 month before conception and within 12 weeks after conception

** adjusted for maternal age, maternal smoking at 17 weeks gestation, maternal pre-pregnancy BMI, and parity

† no use of a hormonal contraceptive within the discrete categories of within12, 4, and 1 month before conception and within 12 weeks after conception

‡ hormonal contraceptives with < 10 exposed cases were combined into an “other” category

Table 3

Sensitivity analyses for early pregnancy exposure to hormonal contraceptives and offspring overweight or obesity

	n	OR (95% CI)	Adjusted** OR (95% CI)
Approach 1: Compared to former users Combination OC			
former* user of Combination OC	6,146	referent	referent
*early pregnancy Combination OC user	380	0.76 (0.54, 1.07)	0.75 (0.52, 1.06)
Progestin only OC			
former* user of Progestin OC	1,962	referent	referent
*early pregnancy Progestin OC user	127	1.20 (0.74, 1.94)	1.24 (0.75, 2.04)
Approach 2: Compared to unplanned pregnancies			
No hormonal contraception†	2,264	referent	referent
Combination OC	380	0.67 (0.46, 0.96)	0.70 (0.48, 1.02)
Progestin only OC	127	1.19 (0.73, 1.93)	1.22 (0.75, 1.98)
Other‡	60	0.79 (0.36, 1.76)	0.79 (0.35, 1.78)
Approach 3: Compared to other oral hormonal contraceptive users			
Progestin only OC	127	referent	referent
Combination OC	380	0.46 (0.23, 0.91)	0.56 (0.32, 1.00)

*former use defined as within 12 months but not within 4 months of conception and early defined as within 12 weeks of conception

**adjusted for maternal age, maternal smoking at 17 weeks gestation, maternal pre-pregnancy BMI, education, and parity

†no use of a hormonal contraceptive within 12 months before conception and 12 weeks after conception

‡hormonal contraceptives with < 10 exposed cases were combined into an “other” category