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Hormonal contraceptive use before and after conception in relation to preterm birth and small for gestational age: an observational cohort study

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Abstract

Objective—To evaluate whether hormonal contraceptives, used before or in early pregnancy, confer increased risk of preterm birth or reduced fetal growth.

Design—Population-based cohort study conducted by the Norwegian Institute of Public Health (Mother and Child Cohort Study, 1998-2008) with linkage to the Norwegian Prescription Registry and to the Medical Birth Registry of Norway.

Setting—Norway

Population—Of the 48,615 pregnancies meeting study inclusion criteria, 44,734 pregnancies were included in the complete case analysis.

Methods—We characterized hormonal contraception by type (combination oral, progestin only oral, vaginal ring, transdermal, and injectable) and specific progestin component. We used generalized estimating equations to estimate the odds of adverse outcome according to formulation used. Several sensitivity analyses were conducted.

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ETJ, JLD, and MPL contributed to the project conception and all authors contributed to the research design. All analyses were conducted by ETJ and the manuscript was drafted by ETJ. ETJ, JLD, TS, WRR, CJW, KV, PM, and MPL all contributed substantively to interpretation of study results and development of the manuscript.

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The University of North Carolina at Chapel Hill (10.3.12) and the National Institute of Environmental Health Sciences Institutional Review Boards (4.22.02) and the Norwegian Southeastern Regional Ethics Committee (1.28.13) reviewed and approved this study.

Main outcome measures—Preterm birth, small for gestational age

Results—We observed a positive association between use of a combination oral contraceptive and preterm birth for all exposure periods (e.g., adjusted OR: 1.21, 95% CI: 1.04, 1.41 for last use 12 to >4 months before conception); combination contraceptives containing the progestin norethisterone were consistently related to risk. Other types of hormonal contraception were generally not associated with preterm birth; none were related to small for gestational age. Observed associations were robust to sensitivity analyses.

Conclusion—Hormonally active agents may exert dose-, agent-, and timing-specific effects on growth and development. We found that the particular progestin component is important when assessing the potential for adverse effects among former users of hormonal contraceptives.

Keywords

Mother and child Cohort Study (MoBa); preterm birth; small for gestational age; hormonal contraceptives

Introduction

Exposure to hormonally active agents during pregnancy has been inversely associated with duration of gestation and fetal growth[1-3]. Much of the literature concerning exposure to hormonally active agents has been centered on exposure to environmental compounds that may have endocrine effects. However pharmacologic agents may also contribute. For example, in women undergoing fresh embryo-based transfer for *in vitro* fertilization, increased levels of endogenous estrogen at the time of blastocyst implantation, as a result of ovarian hyperstimulation from gonadotropins, may contribute to an increased risk of preterm birth [4, 5]. In sows, administering 17β-estradiol throughout pregnancy suppressed offspring growth in early life; in mice [6], administering diethylstilbestrol in early neonatal life resulted in an initial decrease in offspring growth [7].

Possible adverse effects, resulting from use of hormonal contraceptives in pregnancy have been studied, with mixed evidence as to whether use is associated with preterm birth or altered fetal growth. These former studies generally had limited statistical power and most used older statistical methods for data analyses [8-11]. Some of the variability in results from these studies may also be attributable to differences in the contraceptives assessed. The effects of hormonal contraceptives vary and are largely driven by the progestin component and the pharmacodynamics of progestin and ethinyl estradiol taken in combination. For example, some progestin formulations, such as levonorgestrel, are androgenic, while others, such as drospirenone, have no affinity for androgen receptor binding.[12, 13] The capacity of the progestin to bind to androgen, mineralocorticoid, and glucocorticoid receptors is thought to be a major determinant of the differential actions of progestins in eliciting adverse metabolic effects in women.[12, 14-18] These effects are similar to the metabolic changes that occur in women who are overweight or obese.[19,20] In the animal models, maternal obesity has led to an increase in the number of apoptotic follicles in the ovaries, smaller and fewer oocytes, and smaller pups at birth.[21, 22] To our knowledge, there are no studies of the association between hormonal contraceptive use and birth outcomes whereby exposure to

hormonal contraceptives was evaluated according to progestin type. We are also not aware of any studies evaluating birth outcomes for users of the progestin-only oral contraceptive. Given the differences in metabolic effects from hormonal contraceptive formulations with varying progestin components, and the relationship between maternal metabolic factors and offspring birth outcomes, evaluating the association between hormonal contraceptive by progestin type is warranted. These associations may not be limited to exposures incurred during pregnancy. In animal models, developmentally sensitive periods begin even before conception. Specifically, the recruitment of a follicle for selection as a dominant follicle and oocyte maturation can be influenced by exposure to hormonally active agents.[23-27].

In the present study we used the Norwegian Mother and Child Cohort Study (MoBa), a population-based cohort study conducted by the Norwegian Institute of Public Health,[28, 29] to evaluate the association between hormonal contraceptive use before and in early pregnancy, and birth outcomes. The MoBa data were linked to the Medical Birth Registry of Norway (MBRN) and to the Norwegian Prescription Registry (NorPD). In linking to the prescription registry, the formulation of hormonal contraceptive could be evaluated with finer detail than has been described previously.

Methods

Primary analyses

Study population—MoBa study participants were recruited from 1999 through 2008. 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 then mailed an invitation to participate before the scheduled ultrasound, with informed consent and enrollment taking place at the ultrasound examination. All hospitals with at least 100 births per year participated in the study recruitment and enrollment. 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 provide a blood sample and to complete an initial, self-administered questionnaire to provide data on demographic characteristics, reproductive health history, disease and medication history, lifestyle factors, and socioeconomic status. Follow-up is ongoing and is conducted through self-administered questionnaires at regular intervals and by linkage to national health registries.

All MBRN birth registry data are collected on a standardized birth notification form completed by the midwife or physician attending the birth. 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.

There were 107,308 pregnancies in the MoBa cohort (cohort Version 6). For the present analysis, we included pregnancies resulting in a singleton live birth and excluded pregnancies with documentation of infertility treatment for the index pregnancy, on either the MoBa 17-week questionnaire or the MBRN. We additionally excluded pregnancies to women who had documented 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 on prescription fills (n=48,615). We excluded pregnancies with missing covariate data (n=4,191). The final study population included 44,734 pregnancies to 42,155 women (Figure 1).

All Norwegian residents are assigned a personal identifier number. Linkage of the MoBa questionnaire, MBRN, and NorPD data files were possible through this identifier. The University of North Carolina at Chapel Hill and the National Institute of Environmental Health Sciences Institutional Review Boards and the Norwegian Southeastern Regional Ethics Committee reviewed and approved this study.

Exposure

Dispensing of hormonal contraceptives prior to conception and in early pregnancy was ascertained via linkage to the Norwegian Prescription Registry Database. These contraceptives were characterized according to the Anatomical Therapeutic Chemical (ATC) Classification System. We characterized exposure by type and route of administration (combination oral contraceptive, progestin-only oral contraceptive, vaginal ring, transdermal, injectable, implant, and hormonal-based intrauterine device), the approach most similar to previous studies evaluating the relationship between hormonal contraceptive use and adverse pregnancy outcomes. Because of the heterogeneity in hormonal contraceptive progestins in their specificity for binding to the progesterone receptor, we also characterized exposure by type, route, and progestin component. All hormonal contraceptives with an estrogen component (combination oral contraceptives, 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. Date of conception was estimated by subtracting 17 days [30] from the total number of days of gestation (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 or ≥2 weeks different from the ultrasound-based estimate of gestational length, in which case we used the ultrasound-based measure [31]. 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). We characterized exposure into discrete categories relative to conception: last use 12 - >4 months before, 4 - >1 months before, and 1 - >0 months before, and 0 -12 weeks after. Women using hormonal contraceptives in early pregnancy were also using hormonal contraceptives before pregnancy. In our analyses, we evaluated outcomes among those within a category of date of last use as compared to those with no hormonal contraceptive use within any of the other exposure periods assessed.

Most oral contraceptives were dispensed in 3-month supply (82%) or 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 on the 17-week questionnaire that the pregnancy was unplanned and they had ≥1 day(s) supply of hormonal contraceptive at or after the day of conception as defined above.

Outcome

Preterm birth was defined as delivery before 37 completed weeks of pregnancy [32]. Small for gestational age (SGA) was characterized as having been born at <3rd percentile for weight for gestational age [33, 34]. Birthweight z-score was calculated by subtracting the observed birthweight from the expected birthweight based on the population standard distribution (at that gestational age) and then dividing this value by the standard deviation for each gestational age.

Covariates

We used a Directed Acyclic Graph (DAG) approach[35] to identify a minimally sufficient set of adjustment factors. The selected covariates included in the DAG were factors demonstrated to be antecedents of both hormonal contraceptive use and preterm birth or weight for gestational age, including maternal age (14-19, 20-29, 30-39, 40-49) [36, 37], maternal pre-pregnancy BMI (kg/m^2)(<18.5, 18.5-24.9, ≥25.0) [37, 38], parity (0, 1, ≥2) [39], maternal smoking (none, quit, smoker) [37, 40], and maternal education (>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) [41,42]. In the analyses we restricted the study population to women without chronic hypertension and adjusted on BMI, age, parity, smoking, and education.

Analysis

Our primary analyses were concerned with assessing the association between hormonal contraceptive use, by type (combination versus progestin-only) and route (oral, vaginal, transdermal, and injectable), and preterm birth or SGA within the discrete categories of period of last use as listed above. For each exposure period, any contraceptive with <10 exposed cases were combined into a single “other” exposure category. We used generalized linear models with a logit link, and generalized estimation equations (GEE) with an independent correlation matrix [43] to estimate associations between exposures and outcomes using robust standard errors, accounting for lack of independence between siblings.

We conducted likelihood ratio tests to assess whether the model fit for preterm birth or SGA was improved by characterizing exposure with increasing detail. We used generalized linear models to obtain the log likelihood for three, nested models; first modeling any hormonal contraceptive use in each of the exposure periods as compared to no use at any of the exposure periods, second, hormonal contraceptive use by type and route as compared to no use, and third, contraceptive use by type, route and progestin formulation as compared to no use. All analyses were conducted using SAS v9.3 (SAS Inc., Cary, North Carolina).

Sensitivity analyses

Examination of the covariate distribution among pregnancies with hormonal contraceptive use in early pregnancy, as compared to non-users, indicated that women with hormonal contraceptive use were generally older and more parous than non-users (Table S1). There were also differences in the characteristics of women using different types of hormonal contraceptives. For example, while 71% of combination oral contraceptive users were nulliparous, just 17.2% of progestin-only oral contraceptive users were nulliparous. These differences suggest that prescribing patterns may differ based on individual factors, thus raising concern about confounding by indication. We explored the robustness of our results through sensitivity analyses designed to mitigate the potential for confounding by indication.

First, because combination oral contraceptive users were much likely to be nulliparous than progestin-only oral contraceptive users, we restricted our analysis to nulliparous pregnancies only. Next, we compared the association comparing combination oral contraceptive use to vaginal ring use (Table S1), because these two groups were socio-demographically similar. Also, to assess whether factors associated with having an unplanned pregnancy (e.g. prenatal care or other behavioral factors) could be confounding the results observed, we restricted our analysis of exposure at 0 -12 weeks after conception to women reporting an unplanned pregnancy, specifically, users of a hormonal contraceptive as compared to unplanned pregnancies not using a hormonal contraceptive. Finally, we conducted a propensity score analysis to reduce residual confounding associated with use of combination oral contraceptives as compared to no use of a hormonal contraceptive.

To construct the propensity scores, we evaluated several models to estimate the predicted probability of obtaining a combination oral contraceptive prescription (propensity for treatment scores). We included in the models those factors believed to be associated with both use of the combination oral contraceptive and preterm birth (parity, maternal pre-pregnancy body mass index, maternal age, maternal education, maternal smoking), but that preceded the use of a combination oral contraceptive. We compared the distribution of propensity scores among those prescribed a combination hormonal contraceptive to those not prescribed any hormonal contraceptive, to evaluate evidence of common support, and trimmed any observations where there was no corresponding propensity score. We then ranked the scores into deciles and assigned each observation a corresponding rank. We used GEE models to assess the relationship of combination oral contraceptive use with preterm birth, with inclusion of an indicator term for rank, and obtained a pooled estimate of the association across strata. In addition to the term for rank, these models included all of the potential confounders from the primary analyses models [44-46]. The distribution of study covariates for the exposed and unexposed was similar within propensity score rank (Table S2).

Results

As noted above, 44,734 pregnancies met the inclusionary criteria. Of these, nearly all were to women between the ages of 20-39 (97%), approximately half were first pregnancies (47.1%), and the majority had at least some college education (81.4%). Roughly a third of the pregnancies (30.7%) were in women who were overweight or obese (Table 1).

There were 1,969 (4.4%) births before 37 completed weeks of gestation and 1,167 (2.6%) infants were SGA. Relative to conception, 7,470 pregnancies were last exposed 12 to >4 months before, 5,740 were exposed 4 to >1 months before, 6,465 were exposed 1 to >0 months before, and 1,638 were exposed 0 to 12 weeks after.

In evaluating hormonal contraceptive use by type and route of administration, we observed a positive association between use of a combination oral contraceptive and preterm birth, with the magnitude of the association remaining relatively consistent regardless of the exposure period (Table 2). For the progestin-only oral contraceptive, we observed an inverse association with preterm birth for use 1 to >0 months before conception (aOR: 0.67, 95% CI: 0.46, 0.97) and a positive, but statistically non-significant association for each of the other exposure periods. Other associations with preterm birth were not observed, except use of an injectable contraceptive at 12 - >4 months before conception was positively associated with preterm birth (aOR: 1.83, 95% CI: 1.06, 3.18). Data were too sparse to evaluate the association between the injectable and preterm birth for any of the other exposure periods. The direction of the association between use of a hormonal contraceptive and gestational length, in days, was generally consistent with the estimates obtained from modeling the association with preterm birth.

When characterizing exposure by type, route, and progestin component, likelihood ratio tests indicated improved model fit ($p<0.05$) for exposure 4 to >1 months before, 1 to >0 months before, and 0 to 12 weeks after conception. For example, for exposure 0 - 12 weeks after conception, the magnitude of the association for use of a combination oral contraceptive with norethisterone was much stronger (aOR: 3.33, 95% CI: 1.69, 6.57) than the magnitude of the association for the combination oral contraceptive containing drospirenone (aOR: 1.17, 95% CI: 0.76, 1.80). Similarly, by evaluating the progestin-only oral contraceptive by progestin type, we observed a strong association between use of the norethisterone progestin-only oral contraceptive 0 - 12 weeks after conception and preterm birth (aOR: 2.02, 95% CI: 1.03, 1.79). Data were too sparse to evaluate other forms of the progestin-only oral contraceptive by progestin type for exposure 0 - 12 weeks after conception.

Norethisterone in the combination oral contraceptive was significantly, positively associated with preterm birth across all exposure periods, with the exception of use 1 - >0 months before, which was statistically non-significant. A trend in association magnitude across the four periods was not supported ($p=0.41$). Norethisterone in the progestin-only oral contraceptive was not associated with preterm birth at any of the other exposure periods (Table 3); however a test of homogeneity of aOR across the four exposure periods suggested no difference (3 d.f., $p=0.14$).

Levonorgestrel was the most commonly prescribed progestin type in combination oral contraceptives in this data. With the exception of use at 4 - >1 month before (aOR: 1.40, 95% CI: 1.15, 1.70), there was little evidence to support an association between levonorgestrel in the combination oral contraceptive and preterm birth (Table 3).

Data were too sparse for evaluating use of desogestrel in early pregnancy, however desogestrel was significantly, positively associated with preterm birth for use 1- >0 months and 12 - >4 months before conception. Use of desogestrel 4 ->1 month before suggested a positive, but non-statistically significant association with preterm birth (Table 3).

With the exception of use 12 - >4 months before conception, the combination oral contraceptive containing drospirenone progestin was generally not associated with preterm birth. Etonogestrel, in the vaginal ring, and norelgestromin, in the transdermal hormonal contraceptive, were also not associated with preterm birth in any of the exposure periods (Table 3).

Medroxyprogesterone was the only progestin used as an injectable among women in this sample and, as described above, was moderately associated with preterm birth for exposure 12 - >4 months before conception (Table 3).

For formulations where sufficient data were available for analyses, we observed no association between use of hormonal contraceptives and increased odds of SGA or decreased birthweight z-score (Tables S3-S4). We observed an inverse relation with use of a progestin-only oral contraceptive and SGA for exposure 4 – >1 month before and 1 – >0 months before conception. Sparse data precluded evaluation of the association between early pregnancy use of a progestin-only oral contraceptive and SGA (Table S3), as well as individual progestin types for the progestin-only oral contraceptive (Table S4).

In sensitivity analyses, estimates observed in our primary analyses were robust to restriction of the study sample to nulliparous pregnancies (Table S5). When restricting the comparator population to vaginal ring users within the same exposure period, the magnitude of the association observed for combination oral contraceptive users and preterm birth strengthened (aOR 12 - >4 months: 1.78, 95% CI: 0.99, 3.21), however the wider confidence intervals reflect the markedly reduced sample size for these analyses (Table S6). The results of the sensitivity analysis evaluating early pregnancy hormonal contraceptive users as compared to unplanned pregnancies without hormonal contraceptive use attenuated the estimates observed in the primary analysis (aOR 1.22, 95% CI: 0.91, 1.63 vs aOR 1.32, 95% CI 1.01, 1.73). The estimate for the combination oral contraceptive containing norethisterone remained significantly, positively associated with preterm birth (aOR: 3.00, 95% CI: 1.53, 5.83) (Table S6). The association between the combination oral contraceptive and preterm birth, at all exposure periods, was similarly robust to approaches employing propensity scores (Table S7).

Discussion

Main findings

In the present study, use of some formulations of hormonal contraceptives, especially oral contraceptives, was associated with preterm birth. The associations observed varied by timing and progestin component, with norethisterone and desogestrel showing the strongest magnitude of association.

For preterm birth, the positive association for the combination oral contraceptive was observed across all exposure periods. The consistency in the magnitude of the association across exposure periods could be evidence of an association with long-term (>12 months) use, in which case proximity of last exposure to conception may be less important.

For inadvertent use of hormonal contraceptives early in pregnancy a few suggestive findings were seen; however, there was no convincing evidence of a causal relationship with preterm birth, and no positive association with SGA was observed.

Strengths and limitations

We used multiple approaches to explore the sensitivity of the estimates to various assumptions made in the analysis, including restriction to nulliparous pregnancies, unplanned pregnancies, and use of a propensity score to ensure covariate balance in the exposed and unexposed groups. As with all observational studies, there remains the potential that residual confounding is contributing to the estimates observed.

The association between the combination oral contraceptive and preterm birth was generally robust to several sensitivity analyses evaluating potential for uncontrolled confounding in our primary analyses. The sensitivity analysis examining use of a hormonal contraceptive in early pregnancy as compared to other women experiencing an unplanned pregnancy resulted in an attenuation of estimates, with the exception of the norethisterone-containing formulation, which remained significantly associated with preterm birth. However, there may be factors we did not include in our models -- factors not in our dataset that lead to differential use of hormonal contraceptives and that were associated with pregnancy outcomes. For example, the specific hormonal contraceptive prescribed is influenced by an individual woman's estrogen, progesterone, androgen sensitivities [12] and these could confound the association between hormonal contraceptives and preterm birth. Still, the propensity score models provide additional support for the associations observed in our primary analyses, assuming we accurately predicted prescribing of a combination oral contraceptive.

Although use of a pharmacy-based registry offers the benefit of studying specific formulations of contraceptives dispensed at specific times, the registry data are only a proxy for actual use of the contraceptives. Data quality measures are in place for assuring the NorPD is accurate and complete [47]. 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 [48]. 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. Classification of exposure in early pregnancy was limited to pregnancies reported to be unplanned to increase the potential that prescribed contraceptives were actually being used, but for exposure in other periods before pregnancy, fewer women may have been taking a hormonal contraceptive than estimated. The consistent attenuation in adjusted associations at the 1 - >0 months before conception exposure interval, as compared to other exposure periods, may reflect the higher potential for misclassification in this exposure period. In some instances, data were too sparse to

evaluate all formulations at every exposure period, limiting our capacity to explore differences.

Interpretation

As noted above, previous studies of hormonal contraceptive use in pregnancy and gestational length at birth or size at birth had limited statistical power and were underpowered for evaluating formulation-specific effects[10, 11, 49-52]. Nonetheless, their results suggest a possible, albeit small, negative association between *in utero* exposure to hormonal contraceptives and birth weight (Table 4). Contemporary approaches to evaluating birthweight or low birthweight have shifted toward assessment of birthweight z-scores or small for gestational age as these metrics take into account gestational age [53]. Applying these contemporary approaches to assessing weight at birth, we found little evidence to support an association with birthweight z-score or small for gestational age. The association with birthweight observed in these previous studies may reflect birth after a shorter gestation. For two of these studies, investigators did not evaluate gestational length at birth. In two other studies, investigators evaluated gestational length; with one small study suggestive of a weak, positive association.

Several studies have assessed the association between use of hormonal contraceptive before pregnancy and outcomes at birth, including birthweight [10, 11, 49-52] and gestational length [50, 51]. In general, these studies suggest a small, negative association between use of an oral contraceptive before pregnancy and birthweight. For preterm birth, findings have been mixed [50, 51]. The apparent lack of consistency in results between studies may be attributable to several factors, including differences in formulations, timing of exposure, differences in outcome characterization, such as in using birthweight as opposed to birthweight z-score or weight for gestational age, small sample limitations, differential confounding patterns, or chance.

In the present study, we found that use of a combination oral contraceptive before pregnancy, for all exposure periods examined, was associated with preterm birth. The combination oral contraceptive was not associated with weight for gestational age, while use of a progestin only oral contraceptive was negatively associated with small for gestational age at birth. Compared to former studies[10, 11, 49-52], the present project had the benefit of a larger sample size, improved capacity to evaluate formulation-specific effects, better investigation of the potential for confounding by indication, and use of contemporary metrics for weight at birth.

Unusually high concentrations of endogenous estradiol due to ovarian hyperstimulation is associated with impaired fetal growth [54, 55]. In the present study, however, exogenous estrogen at the time of conception was unrelated to fetal growth. The estrogenicity of the hormonal contraceptives studied may have been too low to affect growth. The weakly estrogenic environmental contaminant bisphenol A was recently associated with impaired fetal growth [56]; that association, however, could be independent of estrogenicity. The hormonally active agent DDE, a degradation product of the insecticide DDT, has been shown to be antiprogestogenic [57] and has been associated with preterm birth [58]. The association of norethisterone-containing contraceptives with preterm birth seen here

suggests that agents disrupting normal progesterone signaling may increase risk of preterm birth, but other possibilities exist. The variation in effects of hormonal contraceptives is largely driven by the progestin component. The capacity of the progestin to bind to androgen, mineralocorticoid, and glucocorticoid receptors is thought to be a major determinant of the differential actions of progestins in eliciting adverse effects [14].

Conclusion

Pharmacologic sources of exposure to hormonally active agents are prevalent due to the frequent use of hormonal contraceptives among women of childbearing age. The results of this study suggest that certain formulations of hormonal contraceptives may increase risk for preterm birth. We found that the particular progestin component is important when assessing the potential for adverse effects among former users of hormonal contraceptives. Additional resources are needed to evaluate the reproducibility of these findings as these findings potentially have important clinical implications for women and their future pregnancies. Should the results of this study be replicated in additional studies, clinicians prescribing hormonal contraceptives may need to be selective in the formulations they prescribe for women planning to conceive at a later date.

Although this is the largest study to date, examining the association between hormonal contraceptive use and preterm birth or small for gestational age, the relatively small number of exposed cases for some formulations limited study power. The sample size was restricted by the fact that the Norwegian Prescription registry did not begin until 2004, over 5 years after the MoBa cohort enrollment began. The Danish National Birth Cohort (DNBC) would offer the opportunity to study these associations with a larger sample, as the prescription registry predates the initiation of the DNBC.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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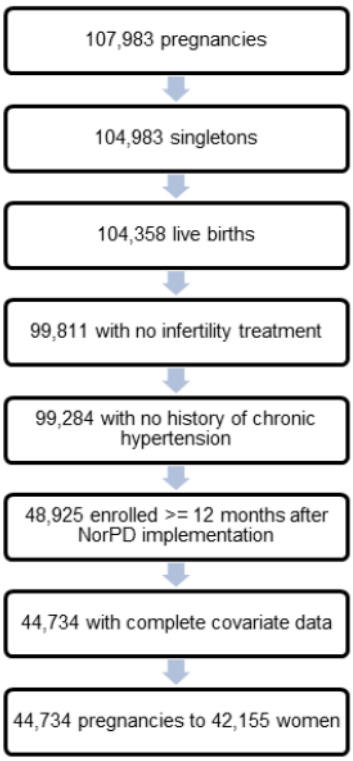

Table 1

Study population characteristics by type of hormonal contraceptive used 12 months before conception

Characteristic		Study population n=44,734 %	No hormonal contraceptive n=23,727 %	Combination oral contraceptive n=14,012 %	Progestin only oral contraceptive n=4,572 %	Vaginal ring n=1,215 %	Transdermal n=832 %	Other[b] n=376 %
Maternal age (yrs)								
	14-19	0.9	0.5	1.8	0.3	0.6	1.2	0.0
	20-29	42.1	33.1	56.5	37.7	54.3	59.0	47.9
	30-39	54.9	63.1	41.3	60.6	44.0	39.4	49.7
	40-49	2.1	3.3	0.4	1.4	1.1	0.5	2.4
Maternal BMI (kg/m^2)								
	<18.5	3.2	3.3	3.1	3.3	2.8	4.1	2.9
	18.5-24.9	66.0	65.6	66.8	65.7	68.8	65.0	60.1
	25.0-29.9	21.7	21.3	21.9	22.8	22.6	21.3	28.2
	≥30.0	9.0	9.8	8.2	8.3	5.8	9.6	8.8
Parity								
	0	47.1	37.8	70.6	17.2	67.4	57.2	29.5
	1	35.5	39.6	20.9	63.9	21.0	27.5	41.2
	2	13.7	17.6	7.0	15.0	9.3	12.7	21.8
	3	2.8	3.8	1.1	3.1	1.7	1.9	5.3
	4 or more	0.9	1.3	0.4	0.8	0.7	0.6	2.1
Maternal education								
More than 4 years of university or technical		27.2	29.5	23.4	30.0	25.8	16.4	17.8
4 year university degree, regional technical		40.8	40.0	40.5	44.7	46.0	42.0	33.8
3 years high school, junior college		13.4	12.7	15.3	10.6	13.2	17.7	17.3
	Technical high school	11.2	10.3	12.8	9.5	10.5	14.7	16.8
	1-2 years high school	3.9	3.9	4.3	2.8	2.1	4.9	7.5
	9-year secondary	2.2	2.3	2.3	1.3	1.1	2.6	5.3
	Other	1.4	1.4	1.4	1.2	1.4	1.8	1.6
Maternal smoking (at 17 weeks)								
	None	79.3	80.0	76.8	85.0	77.8	75.0	70.5
	Quit	14.5	13.9	16.5	10.9	16.5	16.6	18.6

Characteristic		Study population n=44,734 %	No hormonal contraceptive n=23,727 %	Combination oral contraceptive n=14,012 %	Progestin only oral contraceptive n=4,572 %	Vaginal ring n=1,215 %	Transdermal n=832 %	Other[b] n=376 %
	Daily	1.4	1.3	1.6	1.2	1.7	2.2	2.4
	Sometimes	4.8	4.8	5.1	3.0	4.1	6.3	8.5

[a] represents unique pregnancies conceived without infertility treatments, resulting in a singleton live birth, with a date of birth ≥12 months after NorPD registry began (January 1, 2004)

[b] includes the intrauterine, injectable, emergency, and implant hormonal contraceptives

Table 2

Hormonal contraceptive use and gestational length at birth by period of last use relative to conception, progestin type, and route of administration

			Preterm birth		Gestational length (days)	
Exposure	**Exposed (n)**	**Preterm (n)**	**OR (95% CI)**	**aOR[a] (95% CI)**	**β (95% CI) unadjusted**	**β (95% CI) adjusted***
None	23,421	964	referent	referent	referent	referent
0 - 12 weeks after						
Combination OC	1,062	71	1.67 (1.30, 2.14)	1.32 (1.01, 1.73)	−1.19 (−2.08, −0.29)	−0.73 (−1.63, 0.18)
Progestin only OC	359	18	1.23 (0.76, 1.98)	1.26 (0.78, 2.04)	−0.52 (−1.75, 0.71)	−0.47 (−1.70, 0.76)
Other[b]	217	5	0.55 (0.23, 1.34)	0.49 (0.20, 1.21)	1.28 (−0.29, 2.85)	1.48 (−0.11, 3.06)
1 - >0 months before						
Combination OC	4,660	225	1.18 (1.02, 1.37)	1.13 (0.97, 1.31)	0.11 (−0.30, 0.51)	−0.09 (−0.50, 0.33)
Progestin only OC	1,204	30	0.60 (0.41, 0.86)	0.67 (0.46, 0.97)	0.87 (0.26, 1.48)	0.66 (0.05, 1.27)
Vaginal ring	356	13	0.88 (0.51, 1.54)	0.86 (0.49, 1.51)	0.18 (−1.06, 1.43)	−0.10 (−1.35, 1.16)
Other[b]	245	7	0.69 (0.32, 1.46)	0.66 (0.31, 1.42)	0.16 (−1.16, 1.48)	0.05 (−1.27, 1.36)
4 - >1 month before						
Combination OC	3,833	213	1.37 (1.18, 1.60)	1.31 (1.11, 1.53)	−0.49 (−0.93, −0.04)	−0.73 (−1.19, −0.26)
Progestin only OC	1,284	53	1.00 (0.76, 1.33)	1.15 (0.87, 1.53)	0.39 (−0.27, 1.05)	0.18 (−0.48, 0.85)
Vaginal ring	352	12	0.82 (0.46, 1.47)	0.80 (0.45, 1.43)	0.32 (−0.89, 1.52)	0.04 (−1.16, 1.25)
Other[b]	271	9	0.80 (0.41, 1.56)	0.76 (0.39, 1.49)	0.39 (−0.83, 1.61)	0.30 (−0.93, 1.52)
12 - >4 months before						
Combination OC	4,633	241	1.28 (1.11, 1.48)	1.21 (1.04, 1.41)	−0.10 (−0.51, 0.31)	−0.31 (−0.74, 0.11)
Progestin only OC	1,795	71	0.96 (0.75, 1.23)	1.10 (0.85, 1.40)	−0.38 (−0.96, 0.19)	−0.56 (−1.14, 0.001)
Vaginal ring	424	12	0.68 (0.38, 1.21)	0.68 (0.38, 1.20)	0.83 (−0.32, 1.98)	0.54 (−0.63, 1.70)
Transdermal	295	10	0.82 (0.43, 1.54)	0.78 (0.41, 1.48)	1.12 (−0.11, 2.34)	1.03 (−0.19, 2.25)
Injectable	180	14	1.96 (1.13, 3.40)	1.83 (1.06, 3.18)	−1.58 (−3.49, 0.33)	−1.72 (−3.95, 0.50)
Other[b]	143	1	0.16 (0.02, 1.17)	0.18 (0.02, 1.27)	2.47 (0.99, 3.96)	2.56 (1.07, 4.05)

[a] adjusted for parity, maternal education, maternal pre-pregnancy BMI, maternal smoking, and maternal age at birth

[b] hormonal contraceptive types with <10 exposed cases collapsed into a single “other” category

Table 3

Hormonal contraceptive use and preterm birth by period of last use relative to conception, progestin type, and route of administration

Exposure	Exposed(n)	Preterm (n)	OR (95% CI)	aOR[a] (95% CI)
None	23,421	964	referent	referent
0 - 12 weeks after				
Combination OC				
drospirenone and EE	368	22	1.48 (0.96, 2.29)	1.17 (0.76, 1.80)
levonorgestrel and EE	545	34	1.55 (1.09, 2.21)	1.20 (0.83, 1.74)
norethisterone and EE	75	11	4.00 (2.10, 7.62)	3.33 (1.69, 6.57)
Progestin only OC				
norethisterone	146	11	1.90 (1.02, 3.52)	2.02 (1.09, 3.75)
Other[b]	504	16	0.76 (0.46, 1.26)	0.69 (0.41, 1.15)
1 - >0 months before				
Combination OC				
desogestrel and EE	295	25	2.16 (1.42, 3.27)	2.09 (1.38, 3.16)
drospirenone and EE	1,472	61	1.01 (0.77, 1.31)	0.95 (0.73, 1.24)
levonorgestrel and EE	2,521	120	1.16 (0.96, 1.41)	1.11 (0.91, 1.36)
norethisterone and EE	372	19	1.25 (0.79, 2.00)	1.21 (0.76, 1.93)
Progestin only OC				
desogestrel	690	17	0.59 (0.36, 0.96)	0.65 (0.40, 1.06)
norethisterone	483	13	0.64 (0.37, 1.12)	0.74 (0.43, 1.29)
Vaginal ring				
etonogestrel and EE	356	13	0.88 (0.51, 1.54)	0.86 (0.49, 1.51)
Other[b]	276	7	0.61 (0.29, 1.29)	0.60 (0.28, 1.28)
4 - >1 month before				
Combination OC				
desogestrel and EE	197	11	1.38 (0.75, 2.54)	1.27 (0.69, 2.35)
drospirenone and EE	1,227	56	1.11 (0.85, 1.47)	1.07 (0.80, 1.41)
levonorgestrel and EE	2,107	125	1.47 (1.21, 1.78)	1.40 (1.15, 1.70)
norethisterone and EE	302	21	1.74 (1.11, 2.72)	1.67 (1.06, 2.62)
Progestin only OC				
desogestrel	817	34	1.01 (0.71, 1.43)	1.15 (0.81, 1.63)
norethisterone	417	16	0.93 (0.56, 1.54)	1.09 (0.66, 1.80)
Vaginal ring				
etonogestrel and EE	352	12	0.82 (0.46, 1.47)	0.80 (0.45, 1.43)
Other[b]	321	12	0.90 (0.51, 1.62)	0.89 (0.50, 1.60)
12 ->4 months before				
Combination OC				
desogestrel and EE	215	17	2.00 (1.21, 3.30)	1.86 (1.13, 3.09)
drospirenone and EE	1,475	79	1.32 (1.04, 1.67)	1.25 (0.99, 1.60)

Exposure	Exposed(n)	Preterm (n)	OR (95% CI)	aOR[a] (95% CI)
levonorgestrel and EE	2,605	122	1.14 (0.94, 1.39)	1.09 (0.89, 1.33)
norethisterone and EE	338	23	1.70 (1.11, 2.61)	1.61 (1.05, 2.49)
Progestin only OC				
desogestrel	1,031	42	0.99 (0.72, 1.36)	1.13 (0.82, 1.55)
norethisterone	640	22	0.83 (0.54, 1.28)	0.95 (0.62, 1.47)
Vaginal ring				
etonogestrel and EE	424	12	0.68 (0.38, 1.21)	0.67 (0.38, 1.20)
Transdermal patch				
norelgestromin	295	10	0.82 (0.43, 1.54)	0.78 (0.41, 1.48)
Injectable				
medroxyprogesterone	180	14	1.96 (1.13, 3.40)	1.83 (1.06, 3.18)
Other[b]	267	8	0.72 (0.36, 1.46)	0.79 (0.39, 1.60)

[a] adjusted for parity, maternal education, maternal pre-pregnancy BMI, maternal smoking, and maternal age at birth

[b] hormonal contraceptive types with <10 exposed cases collapsed into a single “other” category

Table 4

Previous studies of in utero exposure to oral contraceptives and birth weight or gestational length as compared to the present study

Study (years)	Oral contraceptive	n[a]	Outcome(s) at birth	Association				
				Direction	Magnitude	Significance	Test/Estimate	Value
Oxford Family Planning Association cohort (1968-1974) (Vessey et al.)	any[b]	30	birthweight (kgs) low birth weight (<2,500 g)	null positive	-- strong	-- n.s.[f]	none[h] crude risk ratio	none[h] 7.0[f]
Upstate New York cohort (1974) (Polednak et al.)	any[c]	23	birthweight (kgs) low birth weight (<2,500 g) gestational age at birth (days)	inverse positive positive	weak weak weak	n.s.[g] n.s.[g] n.s.[g]	none[h] none[h] none[h]	none[h] none[h] none[h]
Chang Mai, Northern Thailand cohort (1984-1987) (Pardthaisong et al.)	any	601	low birth weight (<2,500 g)	positive	moderate	s.s	adjusted odds ratio	1.5 (95% CI: 1.2, 2.0)
Korean Motherrisk Program cohort (2001-2006) (Ahn et al.)	any[d]	120	birthweight (grams) low birth weight (<2,500 g) gestational age at birth (weeks) preterm birth (<37 weeks of gestation)	null positive null null	-- weak -- --	-- n.s. -- --	Mann-Whitney U-test Chi-square test Mann-Whitney U-test Chi-square test	p=0.95 p=0.07 p=0.20 p=0.88
Norwegian Mother Child cohort (2004-2008)	combination only progestin only	1,062 359	weight for gestational age at birth (z-scores) small for gestational age (<3rd percentile) gestational age at birth (days) preterm birth (<37 weeks of gestation) gestational age at birth (days) preterm birth (<37 weeks of gestation)	null null inverse positive null positive	-- -- weak moderate -- weak	-- -- n.s. s.s. -- n.s.	β coefficient adjusted odds ratio β coefficient adjusted odds ratio β coefficient adjusted odds ratio	0.02 (95% CI: −0.05, 0.09) 1.10 (95% CI: 0.78, 1.55) −0.73 (95% CI: −1.63, 0.18) 1.32 (95% CI: 1.01, 1.73) −0.47 (95% CI: −1.70, 0.76) 1.26 (95% CI: 0.78, 2.04)

[a] number exposed

[b] evaluated in parous women only

[c] defined as exposed after the date of last menstrual period

[d] defined as periconceptional use in 4 weeks before or 4 weeks after pregnancy began

[e] n.s. - not significant, s.s. – statistically significant

[f] based on our analysis of their data comparing, among parous women, women with unplanned pregnancies using an oral contraceptive and women with planned pregnancies and no use of an oral contraceptive

[g] our best guess

[h] no statistical test conducted