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In utero exposure to 17α-hydroxyprogesterone caproate and risk of cancer in offspring

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Abstract

Background: 17α-hydroxyprogesterone caproate (17-OHPC) is a synthetic progestogen initially approved in the 1950s to treat gynecological and obstetrical conditions. Despite repeated concerns of safety and short-term efficacy regarding the use of 17-OHPC for the prevention of preterm birth in pregnant women, little is known about long-term effects of 17-OHPC on health of offspring.

Objective: To examine the association between *in utero* exposure to 17-OHPC and risk of cancer in offspring.

Study Design: The Child Health and Development Studies is a population-based cohort of more than 18,000 mother-child dyads receiving prenatal care in the Kaiser Foundation Health Plan (Oakland, California) between 1959 and 1966. Clinical information was abstracted from mothers' medical records beginning six months prior to pregnancy through delivery. We identified the number and timing of 17-OHPC injections during pregnancy. Incident cancers diagnosed in offspring were ascertained through 2019 by linkage to the California Cancer Registry. We used Cox proportional hazards models to estimate adjusted hazard ratios (aHR) and their 95% confidence intervals, with follow-up time accrued from date of birth through date of cancer diagnosis, death, or last contact.

Results: 1,008 offspring were diagnosed with cancer over 730,817 person-years of follow-up. About 1.0% of offspring (n=234) were exposed *in utero* to 17-OHPC. Exposure in the first trimester was associated with increased risk of any cancer (aHR 2.57, 95% CI 1.59, 4.15), and risk increased with number of injections (1–2 injections: aHR 1.80, 95% CI 1.12,2.90; ≥3 injections:

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aHR 3.07, 95% CI 1.34, 7.05). Exposure in the second or third trimester conferred an additional risk for male (aHR 2.59, 95% CI 1.07, 6.28) but not female (aHR 0.30, 0.04, 1.11) offspring. Risk of colorectal (aHR 5.51, 95% CI 1.73, 17.59), prostate (aHR 5.10, 95% CI 1.24, 21.00), and pediatric brain (aHR 34.72, 95% CI 7.29, 164.33) cancer was higher in offspring first exposed to 17-OHPC in the first trimester compared to offspring not exposed.

Conclusions: Caution using 17-OHPC in early pregnancy is warranted, given the possible link with cancer in offspring.

Condensation

In a population-based cohort of more than 18,000 mother-child dyads, *in utero* exposure to 17α-hydroxyprogesterone caproate was associated with cancer in offspring.

Introduction

17α-hydroxyprogesterone caproate (17-OHPC) is a synthetic progestogen initially approved in 1956 to treat several gynecological and obstetrical conditions, including habitual and threatened abortion in pregnant women. 17-OHPC was administered at a high dose (250 mg/mL intramuscular injection) to millions of pregnant women in the U.S. (Delalutin® by Bristol-Myers Squibb) and Europe (Proluton® by Schering) during the 1950s and 1960s. In October 1973, the U.S. Food and Drug Administration (FDA) noted a lack of substantial evidence to support 17-OHPC for the prevention of habitual and threatened abortion and raised concerns of an association with congenital heart defects in offspring.[1, 2] They subsequently removed all pregnancy-related indications from its label, citing the possibility of teratogenic effects associated with systemic use.[1] Although labeling requirements of progestogens were later modified,[3] the FDA withdrew their approval of 17-OHPC in September 2000 at the request of the manufacturer and because it was no longer being marketed.[4]

As part of its Accelerated Approval Program, the FDA again approved 17-OHPC in February 2011 (Makena® by AMAG Pharmaceuticals) for pregnant women with a history of spontaneous preterm birth, based on a randomized trial[5] demonstrating reductions in the incidence of preterm birth at 37 weeks. Detailed analyses of that trial (reviewed by Calda[6]) raised concerns regarding fetal toxicity, noting a small, although not statistically significant, increase in fetal deaths and stillbirths among women who received 17-OHPC. Two large trials of 17-OHPC in multiple gestations similarly showed an excess of serious adverse fetal or neonatal events.[7–10] Signals for embryo-fetal toxicity associated with 17-OHPC were later confirmed in rhesus monkeys[11] and rodents[12] in a review of experimental studies.[13]

The FDA required a confirmatory trial as part of their accelerated approval of 17-OHPC; the PROLONG trial was completed in March 2019 and demonstrated no reduction in the incidence of preterm birth at 35 weeks or neonatal morbidity and mortality.[14] As a result, the Center for Drug Evaluation and Research recommended in October 2020 to withdraw approval[15] and maintained this position after the Evaluating Progestogens for Preventing Preterm birth International Collaborative (EPPPIC) meta-analysis[16] was published. Conflicting perspectives[15, 17–19] highlight the ongoing controversy surrounding 17-OHPC.

Despite repeated concerns of safety and short-term efficacy, little is known about the long-term effects of 17-OHPC on health of offspring. The potential for synthetic hormones to disrupt embryological development and manifest as adverse health outcomes is well-established by epidemiologic studies of the synthetic estrogen, diethylstilbestrol (DES), as well as a large literature of experimental studies.[20–24] *In utero* exposure to DES increases risk of cancer in offspring across the life course.[23, 25–28] Similarly, exposure to synthetic progestogens during fetal development may permanently alter organ morphology and function.[29–31] This is consistent with evidence that 17-OHPC crosses the placental barrier[32] and the fetus and placenta are capable of metabolizing 17-OHPC,[33, 34] as well as embryo-fetal toxicity signals identified in trials and experimental studies.[6] And, as with DES, early exposure to 17-OHPC may lead to cellular, molecular, and epigenetic changes that play a role in carcinogenic processes later in life.[21, 35]

Here, we examine the association of *in utero* exposure to 17-OHPC and cancer in offspring in the Child Health and Development Studies (CHDS), a population-based cohort of more than 18,000 mother-child dyads receiving care in the Kaiser Foundation Health Plan (Oakland, CA) in the 1960s and followed for 60 years.

Materials and Methods

Study Population

Established in 1959, the CHDS enrolled nearly all (98%) pregnant women receiving prenatal care from the Kaiser Foundation Health Plan (Oakland, CA) between June 1959 and September 1966, with deliveries through June 1967 (n=18,751 live births excluding neonatal deaths among 14,507 mothers). Additional details of the CHDS and methodology are available elsewhere.[36–38]

We monitor CHDS participants by annual linkage to the California Department of Motor Vehicles, California Department of Vital Statistics, and California Cancer Registry. Mothers and their families are matched to these sources using an accumulated name and address history, routinely identifying more than 80% of families.

Primary Outcome

We ascertained incident cases of cancer in offspring through 2019 by linkage with the California Cancer Registry. The California Cancer Registry is one of the largest cancer registries in the U.S. and meets the highest quality data standards set by the National Program of Cancer Registries and U.S. Centers for Disease Control and Prevention.[39, 40] We used a rigorous protocol to verify cases, comparing fixed (e.g., birth date, sex, race) and changeable (e.g., address) identifiers by manual review.

In Utero Exposure to 17-OHPC

Clinical information, including prenatal visits, diagnosed conditions, and prescribed medications, was abstracted from mothers' medical records beginning six months prior to pregnancy through delivery. All medications are linked to the date and conditions for which they were prescribed. We identified mothers who received 17-OHPC during pregnancy and measured *in utero* exposure as the trimester of first exposure (first trimester: 0 – 90 days; second trimester: 91 – 180 days; third trimester: ≥181 days). We also measured total number of 17-OHPC injections (1–2 or ≥3 injections).

Statistical Analysis

We used Cox proportional hazards models to estimate hazard ratios (HRs) and their 95% confidence intervals (CIs) for associations of *in utero* exposure to 17-OHPC and any cancer in offspring, overall and by trimester of first exposure and number of injections. To account for correlation between observations from siblings (n=4,244), we used robust sandwich estimators. Follow-up time was accrued from date of birth through date of cancer diagnosis, date of death, or date of last contact. Because participants are regularly monitored for residence and vital status, we used year of last contact from all sources to create date of last contact. We assessed the proportional hazards assumption in all models by visually examining plots of the survival function vs. survival time, as well as log(-log(survival)) vs. log(survival time). The assumption was not violated in any model.

Because the distribution of cancer types differed in offspring exposed and not exposed to 17-OHPC, we explored some of these cancers in more detail, including prostate, colon and rectum, and pediatric brain cancers. We selected these cancers because there were multiple diagnoses in exposed offspring. We used Cox proportional hazards models to estimate HRs and their 95% CIs for the associations of *in utero* exposure to 17-OHPC and cancer in offspring, overall and in the first trimester. As above, follow-up time was accrued from date of birth through date of cancer diagnosis, date of death, or date of last contact (or age 18 years for the model of pediatric brain cancer).

We examined interaction between *in utero* exposure to 17-OHPC and offspring sex. For purposes of this analysis, we defined *in utero* exposure as first exposure in early (first trimester) or late (second or third trimester) pregnancy. We compared nested models with and without early pregnancy*sex and late pregnancy*sex product terms using a likelihood ratio test; we calculated contrasts from linear combinations of the product terms to estimate associations of exposure in early pregnancy vs. no exposure and exposure in late pregnancy vs. no exposure, jointly for male and female offspring. We also estimated stratum-specific HRs.

Across all models, the following were evaluated *a priori* as confounders, individually and simultaneously: year of birth, sex, maternal age at pregnancy, race/ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, Asian, other), maternal education (less than high school, high school or trade school, some college or more), parity at pregnancy (primiparous, multiparous), total family income (above or below the median, adjusted for 1960 dollars), gestational age (<37 weeks, ≥37 weeks), maternal body mass index (underweight/normal, overweight, obese), and birth weight. We selected these confounders because they may be directly or indirectly related to mothers' use of 17-OHPC and offspring's risk of cancer. We used height and weight reported by mothers during in-person interviews at enrollment or recorded at the first prenatal visit to measure maternal body mass index. Gestational age was calculated by subtracting the date of the last menstrual period from the date of delivery (range 20 – 42 weeks). To select the most parsimonious model, we retained potential confounders that, if removed from the model, changed the effect estimate by >10%.[41, 42]

We also estimated incidence rates (of any cancer) and 95% confidence intervals based on the discrete probability distribution for a binomial parameter, separately by trimester of first exposure to 17-OHPC and number of injections.

Sensitivity Analyses

We conducted several sensitivity analyses to enhance the rigor of our approach, detailed below.

Confounding by Indication.—We examined the association between any cancer in offspring and conditions indicating 17-OHPC in mothers, such as threatened abortion.

Age Dependency.—Using age as the underlying time parameter, we estimated HRs and their 95% CIs from Cox proportional hazards regression models.[43] We included product terms with age at follow-up (+/− 50 years) and first exposure to 17-OHPC in the first trimester and compared models with and without product terms using a likelihood ratio test.

Probabilistic Bias Analysis.—The association between *in utero* exposure to 17-OHPC and cancer in offspring may be confounded by shared factors between mother and offspring and that were not measured in the CHDS. We conducted a probabilistic bias analysis[44, 45] to model error from unmeasured confounding.

Multiple Imputation.—Missingness ranged from 0.0% (birth weight, year of birth) to 13.3% (maternal body mass index). We used multiple imputation by fully conditional specification to estimate associations of *in utero* exposure to 17-OHPC and any cancer in offspring. Fully conditional specification[46] relaxes assumptions of joint multivariate normality and linearity and is well-suited for imputation of both categorical and continuous variables.

The Institutional Review Board at the Public Health Institute and the University of Texas Health Science Center at Houston approved this study. All analyses were conducted in SAS version 9.4 (SAS Institute, Cary, NC).

Results

Table 1 shows characteristics of 18,751 offspring. Most (48.2%) were born in the early 1960s. About one-fourth (n=4,332, 23.1%) were non-Hispanic Black, and half (52.1%) were in families with an annual income less than the median. Median follow-up was 49.5 years (interquartile range [IQR]: 25.5 – 53.5 years).

About 1.0% of offspring (n=234) were exposed *in utero* to 17-OHPC. 17-OHPC was most commonly indicated for threatened abortion (41.0%); the first 17-OHPC injection occurred at a mean of 12 weeks' gestation (median: 10 weeks, IQR: 7 – 15 weeks), and there was a

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mean of 2.4 injections (median: 1 injection, IQR: 1 – 2 injections). The majority (n=165 of 234, 70.5%) of offspring were first exposed in the first trimester. There was no difference in median follow-up between offspring exposed (50.5 years) and not exposed (49.5 years) to 17-OHPC.

Table 2 shows the types of cancers (n=1,008) diagnosed in offspring by sex and gestational day of first exposure to 17-OHPC. Among exposed offspring (n=234), 23 were diagnosed with cancer, including two diagnoses in childhood (age <18 years) and 21 in adulthood (age ≥18 years). Cancer types included: melanoma (n=2), lymphoma (n=2), leukemia (n=1), polycythemia vera (n=1), colon and rectum (n=3), prostate (n=3), brain (n=2, both in childhood), breast (n=2), thyroid (n=1), oral cavity (n=1), lung and pleura (n=1), cervix (n=1), uterus (n=1), kidney (n=1), and testis (n=1). Median age at diagnosis was similar for offspring exposed (45 years, IQR: 37 – 51 years) and not exposed (45 years, IQR: 34 – 51 years) to 17-OHPC.

Overall, offspring exposed *in utero* to 17-OHPC had an increased risk of any cancer (aHR 1.99, 95% CI 1.31, 3.02) compared to offspring not exposed, and risk differed by trimester of first exposure (Table 3). Specifically, offspring first exposed to 17-OHPC in the first trimester had an increased risk of any cancer (aHR 2.57, 95% CI 1.59, 4.15) compared to offspring not exposed. There was no association with first exposure in the second (aHR 1.24, 95% CI 0.46, 3.32) or third (aHR 0.82, 95% CI 0.18, 3.80) trimester, although fewer offspring were first exposed later in pregnancy (n=69 of 234 exposed offspring, among whom 5 cancers were diagnosed). Incidence rates were 29.6 per 100,000 (95% CI 17.6, 46.8), 16.5 per 100,000 (95% CI 4.5, 42.3), and 10.9 per 100,000 (95% CI 0.3, 60.6) in offspring first exposed in the first, second, and third trimester, respectively.

Risk of any cancer in offspring also increased by number of 17-OHPC injections (1–2 injections: aHR 1.80, 95% CI 1.12, 2.90; ≥3 injections: aHR 3.07, 95% CI 1.34, 7.05) compared to offspring not exposed. Incidence rates were 22.3 per 100,000 (95% CI 13.2, 35.3) and 37.0 per 100,000 (95% 12.0, 86.2) in offspring exposed to 1–2 and ≥3 injections, respectively.

Supplementary Table 1 shows associations of *in utero* exposure to 17-OHPC and specific cancer types. Risk of colorectal (aHR 5.51, 95% CI 1.73, 17.59), prostate (aHR 5.10, 95% CI 1.24, 21.00), and pediatric brain (aHR 34.72, 95% CI 7.29, 164.33) cancer was higher in offspring first exposed to 17-OHPC in the first trimester compared to offspring not exposed. The large effect size for pediatric brain cancer corresponds to two cases of 234 offspring exposed *in utero* to 17-OHPC compared to seven cases of 15,517 offspring not exposed.

Associations of *in utero* exposure to 17-OHPC and any cancer in offspring differed by offspring sex (p-value from likelihood ratio test=0.04; Table 4). First exposure in early pregnancy increased risk of any cancer in both male (aHR 2.75, 95% CI 1.36, 5.54) and female (aHR 2.09, 95% CI 1.13, 3.87) offspring, and first exposure in late pregnancy was associated with risk of cancer in male (aHR 2.59, 95% CI 1.07, 6.28) but not female (aHR 0.30, 0.04, 1.11) offspring. Notably, for male offspring, risk of any cancer was similar for first exposure in early and late pregnancy.

Results of sensitivity analyses are shown in Supplementary Table 2 (multiple imputation) and the Online Supplement (probabilistic bias analysis). Results did not materially differ from those reported above. In addition, there was no association between any cancer in offspring and threated abortion (aHR 1.09, 95% CI 0.84, 1.41); there was no evidence of age dependency (p-value from likelihood ratio test=0.40).

Comment

Principal Findings

We examined the long-term and intergenerational consequences of *in utero* exposure to 17-OHPC. Offspring exposed *in utero* to 17-OHPC had a higher risk of any cancer compared to offspring not exposed, and the majority of cancers were diagnosed before age 50 years. There were particularly striking associations with exposure in the first trimester and three or more injections, and male offspring had an additional risk of cancer associated with exposure in late pregnancy.

Our findings suggest *in utero* exposure to 17-OHPC may contribute to increasing incidence rates of cancer in young adults. Incidence rates of several early-onset (age <50 years) cancers – and cancers seemingly unrelated – are increasing in younger adults in the U.S., including multiple myeloma, leukemia, and colorectal, uterine, gallbladder, kidney, gastric, thyroid, and pancreatic cancer.[47] For some of these cancers, such as colorectal and gastric cancer, incidence rates have *decreased* in older adults in parallel,[48, 49] raising questions of the as-yet-unknown risk factors contributing to increasing rates in younger adults. Importantly, incidence rates of early-onset cancers have increased successively across generations,[47, 50] and higher incidence rates observed in *Generation X* (approximately birth years 1965 – 1980) implicate exposures prevalent in their early life. This is consistent with evidence that 17-OHPC crosses the placenta, has a long half-life in maternal circulation and noted inter-individual variability,[32, 51] and in our study, more and earlier injections in pregnancy were associated with higher risk of cancer in offspring. As the cancer research paradigm shifts to studying exposures in early life,[52] our findings support the importance of the timing of exposure assessment and measuring these exposures during critical windows of growth and development.

Results in the Context of What is Known

Although several trials of 17-OHPC for the prevention of preterm birth have identified signals for embryo-fetal toxicity,[6] and others have raised concerns of maternal toxicity,[53, 54] follow-up studies[55–59] of offspring exposed *in utero* to 17-OHPC suggest no association of *in utero* exposure with adverse physical (e.g., genital or reproductive tract abnormalities, congenital anomalies) or neurodevelopment (e.g., masculinization) sequelae. Similarly, the four-year follow-up[60] of the Meis et al. trial[5] found no differences in health status or physical examination in the subset of participating offspring (60% of those enrolled). Limitations of follow-up studies, most of them published in the 1980s, make it difficult to draw conclusions about long-term effects on health of offspring. Many combine several synthetic progestogens, do not consider the timing of exposure, or rely on self-reported outcomes from mothers many years after pregnancy. Further, across nearly all of these studies, fetal and neonatal deaths remain higher in the exposed, and follow-up is limited to surviving offspring. It is possible that the endocrine disrupting effects of 17-OHPC manifest as both short-term fetal toxicities reported in trials and experimental studies and long-term associations with cancer that we have observed here.

The case of *in utero* exposure to DES is instructive. Like 17-OHPC, DES was most commonly prescribed to pregnant women to prevent miscarriage.[23] Randomized trials published in the 1950s showed DES was not effective for improving pregnancy outcomes,[61] but DES continued to be prescribed in pregnancy for many years, declining after the FDA issued an advisory in 1971 to discontinue use in pregnancy.[62] Decades of subsequent research has demonstrated that DES disrupts developmental programs *in utero*, despite high levels of natural estrogen in pregnancy,[24] manifesting as both short-term and long-term health consequences for offspring. In fact, DES is considered a model endocrine disruptor, displaying many of the key characteristics that define endocrine-disrupting chemicals.[21] *In utero* exposure to DES increases risk of reproductive tract abnormalities in sons[24] and daughters,[63, 64] infertility, ectopic pregnancy, and preterm birth in daughters,[23] and breast and vaginal cancer in daughters.[28, 65]

Clinical Implications

Importantly, the timing, frequency, and pregnancy-related indications of 17-OHPC in the 1950s and 60s differ from current clinical practice. Most offspring exposed to 17-OHPC in our study were first exposed in the first trimester and exposed to 1 or 2 injections. Today, 17-OHPC is recommended starting in gestational weeks 16 – 20, and women may receive 20 injections if carried to term. Off-label use may also occur.[66] We observed an association between first exposure in early pregnancy and cancer in all offspring, but first exposure in late pregnancy increased risk of cancer in male offspring only. We cannot rule out the possibility that exposure in the second trimester or later also contributes to risk of cancer in female offspring, but our finding that risk was similar in male and female offspring exposed in early pregnancy, or during embryogenesis, is consistent with evidence that effects of exposure to endocrine disruptors depends on whether exposure occurs during critical periods of development.[67–69] The additional risk associated with first exposure in late pregnancy for male offspring may correspond to the period of sexual differentiation, whereby testosterone produced by fetal testis plays a vital role in development.[70] We also cannot disentangle effects of the timing of exposure from the number of injections because few offspring were exposed to multiple injections; however, the much higher number of injections given in today's practice, even if limited to the second or third trimester, may confer additional risk to both male and female offspring.

Although sometimes used interchangeably,[71] it is also worth noting differences between 17-OHPC, 17-α-hydroxyprogesterone (17-OHP), and progesterone.[72] Progesterone is a natural progestogen produced by the corpus luteum and subsequently the placenta. 17-OHP is a metabolite of progesterone and can be converted to cortisol and androstenedione. 17-OHPC includes a caproate (or hexanoate) ester and is not known to be metabolized to progesterone or 17-OHP or any other natural metabolite.[13] The EPPPIC meta-analysis[16] demonstrated a reduction in the incidence of preterm birth at 34 weeks for progesterone administered as a vaginal gel or suppository (relative risk 0.78, 95% CI 0.68, 0.90); there was a similar reduction for 17-OHPC, although the confidence interval contained the null value (relative risk 0.83, 95% CI 0.68, 1.01). Our study does not add to the ongoing discussion of natural vs. synthetic progestogens because vaginal suppositories were not recorded in the CHDS, and few offspring were exposed *in utero* to other synthetic progestogens (e.g., oral contraceptives[73]).

Research Implications

Mechanisms contributing to the elevated risk of cancer in offspring exposed to 17-OHPC *in utero* are not yet known, given the lack of data concerning the range of endocrine activity of 17-OHPC, particularly during embryonic life. A case report published in 1983 suggested a link between *in utero* exposure to 17-OHPC and adrenocortical carcinoma in infants.[74] Carcinogenic effects of synthetic progestogens (including 17-OHPC and others) were subsequently evaluated by the International Agency for Research on Cancer (IARC) in 1987;[75] that report concluded synthetic progestogens are possibly carcinogenic to humans but noted inadequate evidence for listing 17-OHPC as a carcinogen, as only two relevant studies had been conducted at that time.[76, 77] More recent IARC reports of progestin-only contraceptives are relevant to effects in adulthood but do not consider *in utero* exposure.[78] 17-OHPC is known to bind the progesterone receptor, and depending on their structure, synthetic progestogens can have other endocrine activity and activate several hormone receptors, including the estrogen receptors, androgen receptor, glucocorticoid receptor, and mineral corticoid receptor.[79] Progesterone and other hormone receptors are widely distributed;[80] the intricate developmental program that likely evolved in concert with high maternal and fetal exposure to naturally occurring progesterone supports the hypothesis that a synthetic progestogen, like17-OHPC, may disrupt multiple organ systems during development. The metabolic pathways for progesterone are not the same as for synthetic progestogens,[81] and downstream metabolites may also play a role in developmental disruption.

Our finding that *in utero* exposure to 17-OHPC in late pregnancy increased risk of cancer in male but not female offspring was unexpected but plausible. Sexual dimorphism is evident in nearly all diseases (e.g., cardiovascular disease, cancer,[28, 82] neurological disorders), and for many of these diseases, susceptibility begins in early development.[83, 84] Normal development of male offspring depends on fetal testis' production of testosterone during embryonic life,[70] and this process may be subject to disruption. For example, a series of three experimental studies in male rats exposed *in utero* to 17-OHPC identified several reproductive abnormalities in adulthood, including decreases in: steroidogenic enzymes, sperm count, sperm motility, sperm viability, and sperm function.[85–87] The same laboratory later reported alterations in hepatic metabolism, such as increased activity of antioxidant enzymes and lipid peroxidation, in adult rats exposed *in utero* to 17-OHPC.[88] Others have suggested fetal origins of prostate cancer,[89] consistent with our finding that *in utero* exposure to 17-OHPC increases risk of prostate cancer. Human prostatic development spans five stages and extends late into the second trimester, as well as the third trimester;[90] another possibility is that exposure in late pregnancy increases susceptibility of the developing prostate gland to carcinogenesis following additional exposures in adulthood. Additional, well-conducted experimental studies will be critical to substantiate the association between *in utero* exposure and cancer in offspring we have reported here.

Strengths and Limitations

A strength of our study is the multi-generational cohort. Prospective, robust follow-up of the CHDS, with detailed information on both mothers and offspring, offers a unique opportunity to study effects of 17-OHPC in the 60 years after offspring were born. 17-OHPC was ascertained by medical record review and cancer cases by linkage with a high-quality cancer registry, minimizing the possibility of bias due to measurement error. There was also no difference in follow-up between offspring exposed and not exposed to 17-OHPC, and it is unlikely that differential ascertainment of cancer in offspring explains our findings.

There are some limitations of our study. We could not directly examine the effect of first exposure at weeks 16 – 20, as currently administered in clinical practice, because most offspring exposed during this time were also exposed earlier in pregnancy. However, we observed an elevated risk of cancer in male offspring first exposed in late pregnancy (at gestational days 114, 149, and 236) – more comparable to today's practice. In observational studies of drug exposure, it is possible that observed associations are related to the underlying medical conditions indicating the drug. We observed no association of conditions indicating 17-OHPC (e.g., threatened abortion) and cancer in offspring, providing some confidence that effects are not explained by indications for use. Associations between *in utero* exposure to 17-OHPC and cancer in offspring may be confounded by factors shared between mother and offspring, which were not measured in the CHDS. We addressed unmeasured confounding by conducting a probabilistic bias analysis; the median bias-corrected association from all simulations was slightly attenuated but similar to the observed association. These results suggest an unmeasured confounder could only explain the *entire* observed association if the confounder was a strong predictor of cancer in offspring, and its distribution substantially differed between exposed and unexposed offspring, scenarios that are both unlikely. Finally, the number of cancers diagnosed in offspring is small, as is expected in this relatively young population; the estimates we report here are not overly imprecise, likely reflecting the large, prospective sample and the duration of follow-up that did not differ by exposure.

Conclusions

In summary, earlier and more frequent exposure to 17-OHPC *in utero* increased risk of cancer in offspring, and exposure in late pregnancy conferred an additional risk in male offspring. Experimental studies elucidating the exact mechanisms contributing to risk of cancer will likely take years to complete, but in the interim, these results raise substantial concern for using 17-OHPC in pregnancy. Regardless of differences in the timing, frequency, and pregnancy-related indications of 17-OHPC in our study and current clinical practice, at least three large trials of 17-OHPC for the prevention of preterm birth have already identified signals for embryo-fetal toxicity, whereby a higher proportion of fetal and neonatal deaths occurred in women receiving 17-OHPC compared to placebo. Some have also raised concerns of maternal toxicity, citing a higher incidence of gestational diabetes in women receiving 17-OHPC.[53, 54] Now, given the possible risk of cancer in exposed offspring, additional caution using 17-OHPC during pregnancy may be warranted. Consideration for offering 17-OHPC to pregnant women should weigh this evidence on the long-term consequences of *in utero* exposure.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

17-OHPC	17α-hydroxyprogesterone caproate
CHDS	Child Health and Development Studies

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AJOG at a Glance:

Why was this study conducted?

- Despite continued use of 17α-hydroxyprogesterone caproate (17-OHPC) in pregnant women, little is known about its long-term effects on health of offspring.

What are the key findings?

- Offspring exposed *in utero* to 17-OHPC had a higher risk of any cancer compared to offspring not exposed.
- Risk was higher with exposure in the first trimester and three or more injections.
- Exposure in late pregnancy conferred an additional risk of cancer in male but not female offspring.

What does this study add to what is already known?

- Caution using 17-OHPC in early pregnancy is warranted, given the possible link with cancer in offspring.

Table 1.

Characteristics of 18,751 offspring[1] in the Child Health and Development Studies, 1959 – 1967, by *in utero* exposure to 17-OHPC

	In utero exposure to 17-OHPC (n=234)		Not exposed to 17-OHPC (n=18,517)	
	n	**%**	**n**	**%**
Offspring characteristics				
Sex				
Male	117	50.0	9465	51.1
Female	117	50.0	9052	48.9
Year of birth				
1959–61	98	41.9	5505	29.7
1962–64	116	49.6	8929	48.2
1965–67	20	8.6	4083	22.1
Race/ethnicity				
Non-Hispanic White	173	75.6	12092	66.3
Non-Hispanic Black	43	18.8	4289	23.5
Hispanic	2	0.9	611	3.4
Asian	5	2.2	714	3.9
Other	6	2.6	537	2.9
Missing	*5*		*274*	
Gestational age				
< 37 weeks	22	9.4	1438	7.9
≥ 37 weeks	212	90.6	16781	92.1
Missing	*0*		*298*	
Birth weight (grams)				
<2,500	20	8.6	1066	5.8
2,500 – 3,999	200	85.5	15847	85.6
≥4,000	14	6.0	1604	8.7
Maternal characteristics [2]				
Maternal age at pregnancy (years)				
<20	9	3.9	1668	9.1
20–24	61	26.2	5587	30.5
25–29	63	27.0	5317	29.0
30–34	59	25.3	3257	17.8
35–39	29	12.5	1895	10.3
≥40	12	5.2	620	3.4
Missing	*1*		*173*	
Parity at pregnancy				
Primiparous	66	28.3	5699	31.0
Multiparous	167	71.7	12685	69.0
Missing	*1*		*133*	

	In utero exposure to 17-OHPC (n=234)		Not exposed to 17-OHPC (n=18,517)	
	n	**%**	**n**	**%**
Body mass index (kg/m^2)[3]				
Underweight/ normal (<25)	167	79.2	12056	75.2
Overweight (25 – 29.9)	35	16.6	2970	18.5
Obese (≥30)	9	4.3	1014	6.3
Missing	*23*		*2477*	
Maternal education				
Less than high school	34	16.0	2865	18.2
High school or trade school	82	38.5	6121	38.8
Some college or college degree	97	45.5	6796	43.1
Missing	*21*		*2735*	
Annual family income[4]				
< median	60	32.6	4759	36.5
≥ median	124	67.4	8280	63.5
Missing	*50*		*5478*	

[1]Live births excluding neonatal deaths among 14,507 women

[2]Because mothers may have had more than one live birth during the study period, maternal characteristics are reported at the level of offspring

[3]Body mass index measured using height and weight reported by mothers during in-person interviews at enrollment or recorded at the first prenatal visit

[4]Median income adjusted to 1960 dollars = $6,303

Table 2.

Cancer diagnoses by sex and gestational day[1] of first *in utero* exposure to 17-OHPC (n=1,008)

	Male offspring (n=391)			Female offspring (n=617)		
Cancer type	**Not exposed**	**Early pregnancy**	**Late pregnancy**	**Not exposed**	**Early pregnancy**	**Late pregnancy**
Oral cavity	18		1 (115)	4		
Esophagus	5			2		
Stomach	6			2		
Small intestine	5			1		
Colon and rectum	30	2 (34, 71)		35	1 (46)	
Anus	9			4		
Liver	6			2		
Pancreas	4			1		
Nose or nasal cavity	3			3		
Larynx	2					
Lung and pleura	15	1 (50)		24		
Bone and joint	3			3		
Soft tissue	4			3		
Melanoma or other non-epithelial skin	57			45	2 (38, 53)	
Breast	--	--	--	197	2 (35, 67)	
Cervix	--	--	--	111	1 (56)	
Uterus	--	--	--	22	1 (63)	
Ovary	--	--	--	13		
Vagina or vulva	--	--	--	9		
Prostate	53	2 (45, 77)	1 (236)	--	--	--
Testis	28	1 (67)		--	--	--
Penis	3			--	--	--
Bladder	7			3		
Kidney	18			6	1 (46)	
Eye	3			1		
Brain	21	1 (62)		10	1 (76)	
Central nervous system	7			19		
Thyroid or other endocrine	8			34		1 (96)
Lymphoma	29		1 (114)	22	1 (73)	
Myeloma	8			6		
Leukemia	16	1 (60)		16		
Kaposi sarcoma	4					
Miscellaneous[2]	7		1 (149)	8		

[1]Early pregnancy defined as first trimester (day 0–90) and late pregnancy defined as second and third trimester (day ≥91); gestational day of first exposure to 17-OHPC denoted by ( )

[2]Includes polycythemia vera diagnosed in exposed offspring

Table 3.

Adjusted hazard ratios and incidence rates (per 100,000 persons) for any cancer in offspring with and without 17-OHPC exposure, overall and by trimester of first exposure and number of injections

	Person-years	n	aHR[1]	95% CI	Incidence rate (95% CI) per 100,000[2]
In utero exposure to 17-OHPC					
Not exposed	721401.5	985	1.00		13.7 (12.8, 14.5)
Any exposure	9415	23	1.99	1.31, 3.02	24.4 (15.5, 36.7)
Trimester of first 17-OHPC exposure					
Not exposed	721401.5	985	1.00		13.7 (12.8, 14.5)
First trimester	6073	18	2.57	1.59, 4.15	29.6 (17.6, 46.8)
Second trimester	2423	4	1.24	0.46, 3.32	16.5 (4.5, 42.3)
Third trimester	919	1	0.82	0.18, 3.80	10.9 (0.3, 60.6)
Number of 17-OHPC injections					
Not exposed	721401.5	985	1.00		13.7 (12.8, 14.5)
1–2 injections	8062	14	1.80	1.12, 2.90	22.3 (13.2, 35.3)
≥3 injections	1353	9	3.07	1.34, 7.05	37.0 (12.0, 86.2)

Abbreviations: aHR, adjusted hazard ratio; CI, confidence interval

[1] Adjusted for year of birth and maternal body mass index (overweight vs. else)

[2] Incidence rates and 95% confidence intervals were calculated based on the discrete probability distribution for a binomial parameter

Table 4.

Interaction between *in utero* exposure to 17-OHPC (no exposure vs. early pregnancy vs. late pregnancy) and offspring sex

Offspring sex	*In utero* exposure to 17-OHPC	Person-years	n	Incidence rate (95% CI)	Stratum-specific aHR (95% CI)[1]
Male	Not exposed	376390.5	380	10.1 (9.1, 11.2)	1.00
	Early pregnancy	3284	8	24.4 (10.5, 48.0)	2.75 (1.36, 5.54)
	Late pregnancy	1436.5	4	27.8 (7.6, 71.3)	2.59 (1.07, 6.28)
Female	Not exposed	345011	605	17.5 (16.2, 19.0)	1.00
	Early pregnancy	2789	10	35.9 (17.2, 65.9)	2.09 (1.13, 3.87)
	Late pregnancy	1905.5	1	5.2 (0.1, 29.2)	0.30 (0.04, 1.11)

NOTE: Interaction evaluated by comparing nested models with and without early pregnancy*sex and late pregnancy*sex product terms with the likelihood ratio test (p-value: 0.04); p-values of product terms: early pregnancy*sex (0.05) and late pregnancy*sex (0.58) Abbreviations: aHR, adjusted hazard ratio; CI, confidence interval

[1] Adjusted for birth year and maternal body mass index