Effects of Elevated Maternal Adiposity on Offspring Reproductive Health: A Perspective From Epidemiologic Studies

Maria E. Cinzori and Rita S. Strakovsky

Department of Food Science and Human Nutrition, Michigan State University, East Lansing, Michigan 48824, USA
Institute for Integrative Toxicology, Michigan State University, East Lansing, Michigan 48824, USA
Department of Epidemiology and Biostatistics, Michigan State University, East Lansing, Michigan 48824, USA

Correspondence: Rita S. Strakovsky, PhD, RD, Department of Food Science and Human Nutrition, Michigan State University, 238C Trout Bldg, 469 Wilson Rd, East Lansing, MI 48824, USA. Email: strakovs@msu.edu.

Abstract

One in seven couples in developed countries suffers from infertility. Maternal overweight or obesity have detrimental and lasting effects on offspring cardiometabolic health, and although substantially more data are needed, hormonal imbalances in utero resulting from excessive maternal adiposity could also disrupt reproductive programming and affect the future reproductive health of offspring. Therefore, this mini-review evaluates the human epidemiologic evidence that maternal obesity/overweight could be associated with poor reproductive health outcomes in offspring. We searched PubMed for relevant studies using terms such as “maternal obesity” and “reproductive development.” While the human epidemiologic literature is limited, studies have thus far observed that maternal obesity is associated with disrupted external genital development and several other markers of reproductive health across the lifespan. Specifically, maternal obesity is associated with higher risk of hypospadias and cryptorchidism in males and disrupted anogenital distance both in males and females. Maternal obesity has also been linked to earlier age at menarche in daughters, and precocious puberty in both sons and daughters. Finally, daughters of women with overweight or obesity have higher risks of developing polycystic ovarian syndrome, which has implications for fertility. This body of research suggests that in utero exposure to maternal obesity could disrupt reproductive system development, but substantially more evidence is needed, as almost no human epidemiologic studies have evaluated the long-term consequences of maternal obesity with regard to offspring fertility/fecundity.

Key Words: obesity, adiposity, reproduction, programming, maternal

Abbreviations: AMH, anti-Müllerian hormone; AGD, anogenital distance; BMI, body mass index; DHEA, dehydroepiandrosterone; DHEAS, dehydroepiandrosterone-sulfate; DHT, dihydrotestosterone; EDC, endocrine-disrupting chemical; FSH, follicle-stimulating hormone; HPA, hypothalamus-pituitary-adrenal; HPG, hypothalamic-pituitary-gonadal; HR, hazard ratio; HFD, high-fat diet; HFDI, high-fat diet-induced; GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone; OR, odds ratio; PCOS, polycystic ovarian syndrome; RR, relative risk.

Fertility rates are rapidly declining, as one in seven couples in developed countries suffers from infertility [1, 2]. Exposure to endocrine-disrupting chemicals (EDCs), unresolved reproductive tract infections, and advanced age during pregnancy are well-established environmental and physiological factors driving this trend. Despite these known factors, nearly 30% of infertility cases are attributed to unknown causes [3]. The in utero environment has both short- and long-term consequences for fetal development [4–6], and studies are just beginning to understand the role of the fetal period in the reprogramming of the reproductive system and the implications of this hormonally sensitive period for future reproductive health.

Hormonal disruption in utero is one factor that could have short-term implications for fetal reproductive development and long-term consequences for offspring reproductive capacity. Initial determination and differentiation of the reproductive tract and gonads are guided by hormone-independent genetic factors [7]; at the sixth week of development in humans, the sex-determining region Y (SRY) gene in chromosomal males is expressed and activates SRY box 9, triggering a cascade that results in differentiation of the Sertoli cells [8, 9]. Once this key differentiation is complete, the fetal testes are the primary sites of testosterone and anti-Müllerian hormone (AMH) synthesis, respectively [7]. Subsequent secretion of testosterone and AMH are the leading drivers of gonadal and reproductive tract development in males [10, 11]; androgens (primarily) maintain the testes, whereas AMH (produced by Sertoli cells) inhibits the development of the female reproductive tract [12–14]. The absence both of testosterone and AMH permits growth of the female reproductive tract and differentiation of the somatic granulosa cells in the ovary [9, 13]. This hormonal responsiveness of the developing gonads makes them vulnerable to any perturbations in the maternal-placental hormonal milieu. For instance, female sheep exposed to excessive androgens in utero—in the forms of testosterone or dihydrotestosterone (DHT)—had altered ovarian morphology, particularly the rete ovarii and more frequent appearance of hemorrhagic antral follicles [16]. A later sheep study observed that prenatal exposure to excess testosterone or DHT resulted in larger ovarian
artery and wall areas, and thicker ovarian walls in exposed ewes compared to controls [17]. Excessive androgen exposure may also be detrimental to male gonadal development. In male sheep, rams prenatally exposed to testosterone or DHT had morphological alterations in testicular development compared to untreated rams [18]. Given the importance of the maternal hormonal milieu for reproductive development, it is crucial to identify modifiable factors that affect maternal hormone balance, since hormonally dependent changes in gonad development may have long-term implications for offspring lifelong reproductive health.

Pregnant women with obesity (or more precisely, excessive adiposity) have altered levels of sex-steroid hormones, primarily testosterone, which could be detrimental for fetal reproductive development [19–21]. The consequences of maternal obesity with regard to offspring metabolic health are well established [22], but experimental studies have also demonstrated that maternal obesity causes reproductive dysfunction in offspring. In mice, maternal high-fat diet-induced (HFD)-induced obesity caused infertility in female offspring by impairing ovarian development via a reduction of primordial and antral follicles and elevated levels of genes involved in apoptosis [23]. Another study in HFD obese rat dams observed that male offspring had lower levels of luteinizing hormone (LH) and testosterone, reduced sperm concentration, viability, and motility, as well as more sperm abnormalities and testicular reactive oxygen species compared to controls [24]. Maternal obesity also has the potential to disrupt the hypothalamus–pituitary–gonadal (HPG) axis, as its activity in the fetal period is largely driven by maternal hormones [25, 26]. Importantly, the HPG axis is activated throughout the lifespan, including the neonatal period, when gonadotropin-releasing hormone (GnRH) is released in discrete bursts to stimulate secretion of LH and follicle-stimulating hormone (FSH) [25]. Experimental studies have demonstrated that the adipokine leptin secreted by adipose tissue stimulates GnRH release [25], and in vitro studies have demonstrated that insulin and leptin can also activate the HPG axis and modulate GnRH release [27]. Because pregnant women have altered concentrations of leptin and insulin [28, 29], there is strong potential for maternal obesity/adiposity to affect the fetal HPG axis, which could alter gonadal and reproductive development.

While the human epidemiologic literature is somewhat sparse, currently available studies have broadly supported the potential for maternal obesity to affect offspring reproductive development in utero, using various markers of reproductive health across the lifespan. Specifically, in the present review, we discuss human epidemiologic studies that considered associations of maternal obesity or adiposity with newborn markers of gonadal development, precocious menarche in daughters, puberty onset in daughters and sons, and markers of reproductive capacity in adult children. We conclude by providing insight into potential challenges related to evaluating the long-term implications of these findings in human epidemiologic studies and provide brief recommendations for future directions in the field.

Search Strategies
We searched PubMed using combinations of various keywords including “maternal obesity,” “fetal reproductive programming,” “gonadal development,” “precocious puberty,” “age at menarche,” “cancer,” and “infertility.” Studies were included if they assessed associations between maternal obesity (either as a clinical cutoff or as a continuous variable using body mass index; BMI) and reproduction-related end points in offspring (eg, cryptorchidism, hypospadias, age at menarche, puberty onset, disrupted steroid hormone levels, biomarkers of reproductive capacity, or development of reproductive organ–specific cancer). This review focuses on studies in human populations, but we discuss experimental studies when observational studies were not available or if additional support was needed for interpretation or mechanistic insight into findings from human epidemiologic studies.

Maternal Obesity and Reproduction-related Outcomes in Offspring

External Indicators of Altered Reproductive Development
The anogenital distance (AGD) may be a meaningful external biomarker of disrupted reproductive system development. AGD is a sexually dimorphic trait, as males tend to have a longer AGD compared to females, and this has been observed in experimental and human epidemiologic studies [30, 31]. Furthermore, studies in rodents have implicated the actions of androgens as the primary driving force behind the development and differentiation of the AGD [32–34]. Due to the disrupted sex-steroid hormone milieu in pregnant women with obesity [20, 35], it is plausible that exposure to maternal obesity could disrupt fetal reproductive tract development, which can be evaluated early by assessing newborn AGD. Although many human studies have considered associations of environmental factors or polycystic ovarian syndrome (PCOS) with AGD [36–39], we recently also reported that select measures of maternal obesity and adiposity were associated with changes in AGD independent of maternal PCOS diagnosis [40]. We characterized maternal obesity using several measures, including prepregnancy and early-pregnancy BMI, prepregnancy and early-pregnancy body weight, hip and waist circumferences, visceral (central) adiposity, and total adiposity. Using data from 430 mother/newborn dyads, we observed that higher prepregnancy and early-pregnancy BMI, body weight, hip circumference, and visceral fat level were associated with elongated (androgenized) anoclitoral and anofourchette AGD in newborn girls; no associations were observed in newborn boys [40]. Conversely, another recent study in 397 Chinese infants observed no association between maternal prepregnancy BMI and AGD in boys or girls [41]. Compared to our study, this study discussed having too few women with obesity to consider this group individually, whereas 22% of the women in our study had obesity. Additionally, the study by Wang et al [41] controlled for newborn birth weight in covariate-adjusted models, whereas we normalized AGD measures for birth length, as birth weight could mediate (and thus underestimate) the association of maternal BMI with AGD. Finally, the second study evaluated the combined effect of maternal BMI with gestational weight gain, whereas we did not take this approach, as gestational weight gain was not associated with AGD in our study. Our study provides evidence that maternal adiposity could affect fetal reproductive tract development, but additional studies are needed to understand whether AGD provides an early detection tool for future reproductive dysfunction.

Maternal obesity has also been implicated as a risk factor for birth defects and genital anomalies in offspring, including
hypospadias and cryptorchidism [42–44]. In males, hypospadias (urethral opening not on the tip of the penis) and cryptorchidism (undescended testes) [45] are potential external indicators of altered reproductive programming and have the potential to cause infertility due to their association with impaired semen flow [46, 47] and compromised germ cell maturation [48], respectively. A case-control study among infants born between 1997 and 2002 from the US National Birth Defects Prevention Study evaluated maternal obesity as a risk factor for structural birth defects in infants, as confirmed by clinical geneticists. The study reported that sons of women with overweight or obesity had higher odds of developing hypospadias compared to sons of women who were normal weight (odds ratio [OR]: 1.25; 95% CI, 1.01–1.54 and OR: 1.33; 95% CI, 1.03–1.72, respectively) [44]. Similarly, a Swedish register-based study of male singleton infants (n = 1,055,705) born between 1992 and 2012 also observed a positive association between maternal overweight or obesity with the risk of cryptorchidism and hypospadias [42]. Although the possible mechanisms underlying these associations remain elusive, these studies appear to confirm experimental models reporting that elevated maternal adiposity disrupts the development of the reproductive system [16–18, 23, 24, 49, 50].

**Precocious Onset of Menarche**

Menarche, the beginning of menstruation, marks the start of female fertility and relies on the coordination of the HPG axis [51]. Age at first menarche has continued to decline in the United States and other developed countries [52]. Precocious onset of menarche poses a concern for short- and long-term health because early menarche has been associated with complications such as cardiovascular disease and type 2 diabetes, as well as higher rates of ectopic pregnancies, breast cancer, and miscarriage [53–57]. The potential effects of early menarche extend beyond physical health; in human epidemiologic studies, an earlier age at menarche is associated with both depressive and antisocial behaviors in adulthood [56]. Puberty and menarche vary largely between individuals, with menarche having a known genetic component [58, 59]. However, there is an established link between lifestyle factors like adolescent obesity and an earlier age at menarche [60–62], and several studies have suggested that maternal overweight or obesity is also associated with age at menarche in daughters independent of adolescent weight status. In the 1979 US National Longitudinal Survey of Youth study, 2497 women born between 1957 and 1964 reported their age at menarche and their mother’s prepregnancy BMI. Maternal prepregnancy overweight/obesity was associated with an earlier age at menarche in the daughters (hazard ratio [HR]: 1.20; 95% CI, 1.06–1.36), even when accounting for the daughters’ prepubertal BMI [63]. Another study of 597 US women in the Collaborative Perinatal Project (enrolled 1959-1965) observed that daughters of women with prepregnancy obesity had higher odds of menarche before age 12 years (OR: 3.3; 95% CI, 1.1–10.0) compared to women whose mothers were normal weight or underweight; results were not attenuated when formal mediation models evaluated daughters’ BMI at age 7 as a mediator [64]. Further supporting this phenomenon, in a 1991 to 1992 prospective population-based birth study of 2086 mother-daughter dyads in Britain, daughters of women with prepregnancy overweight or obesity had a higher risk of early menarche (relative risk [RR]: 1.37; 95% CI, 1.08–1.91 and RR: 1.34; 95% CI, 0.93–1.91, respectively) [65], compared to daughters of women who were normal weight. Although the underlying mechanisms of these findings are poorly understood, there is reason to postulate that the effect of maternal obesity on precocious menarche stems from the response of the HPG axis to excess fuel availability in utero, which could signal the potential for earlier reproductive capacity [66]. Thus, while there is certainly a hereditary component to the onset of menstruation, external factors (including elevated maternal adiposity) could be important contributors to the downward trend in age at menarche.

**Premature Adrenarche**

Adrenarche is the maturational increase in the secretion of androgens in early and mid-childhood, occurring both in males and females [67]. During adrenarche, the adrenal gland increases secretion of dehydroepiandrosterone-sulfate (DHEAS) and dehydroepiandrosterone (DHEA), which can be converted into androgens in the adrenal gland, peripheral adipose tissues [68], the ovary, and the testes [67, 69]. Premature adrenarche is the early secretion of androgen precursors and occurrence of early presentation of androgen-associated signs of puberty before age 8 years in girls and age 9 years in boys [67]. While not included in the Tanner stages, adrenarche is partly responsible for the development of pubic hair (pubarche), axillary hair, and acne [70]. The intrauterine environment has lasting consequences for fetal growth and the development of the hypothalamic-pituitary-adrenal (HPA) axis [71, 72], which is key in regulating DHEA and DHEAS secretion [72, 73]. Epidemiologic studies in humans [74] and experimental studies in rats [75] and macaques [76] indicate that the programming of the HPA is sensitive to the maternal environment. For example, prior studies have observed associations between maternal PCOS status—regardless of prepregnancy BMI—and early onset of adrenarche in girls (but not boys) [70]. Similarly, phthalates have been associated with increased risk of premature adrenarche both in girls and boys [77]. These studies indicate that the maternal environment may program the premature onset of adrenarche. Although no studies (to our knowledge) have considered the relationship between maternal obesity and premature adrenarche, several studies have observed associations between birth size and timing of adrenarche [71, 73]. Given that women with overweight or obesity are either more likely to have small for gestational age [78, 79] or large for gestational age infants [80, 81], and the known role of the HPA in birth size [82–84], there is reason for future experimental and epidemiologic studies to consider the role of maternal obesity or adiposity in premature adrenarche.

**Precocious Onset of Puberty**

Beyond menarche, and potentially adrenarche, maternal obesity has been associated with precocious puberty both in sons and daughters. Pubertal onset is clinically characterized using the Tanner stages in the following categories: pubic hair development (boys and girls), breast development (girls), and growth of the external genitalia (boys), with stages one and five defined as “prepubertal” and “adult-form”, respectively [85]. Additional puberty-adjacent criteria—like acne and nocturnal emissions—have also been evaluated [86, 87]. Early onset of puberty is concerning because it could increase the risk
of developing breast and endometrial cancer in women, and prostate cancer in men [88]. Additionally, precocious puberty has been associated with poorer psychosocial adjustment in boys and girls, and behavioral problems in boys [89]. A 2010 study of 2661 daughters of women recruited in Great Britain from 1991 to 1992 observed that daughters of women with overweight or obesity tended to enter Tanner stages two and three of breast development before those born to normal-weight women [90]. Interestingly, daughters of women with prepregnancy overweight, but not obesity, tended to develop pubic hair earlier than daughters of normal-weight women [90]. Another study recruited 15 602 children born between 2000 and 2003 from the Danish National Birth Cohort to evaluate the relationship between maternal prepregnancy obesity and the timing of puberty in offspring. The authors reported daughters of women with prepregnancy obesity tended to achieve all pubertal milestones earlier and tended to start puberty overall −3.2 (95% CI, −2.1 to −4.2) months before daughters of normal-weight women [86]. Daughters of women with prepregnancy overweight experienced similar outcomes to daughters of women with obesity for all pubertal milestones and tended to start puberty −2.6 (95% CI, −1.8 to 3.3) months before daughter of normal-weight women [86].

In the same Danish study, compared to sons of normal-weight women, sons of women with obesity experienced axillary hair development, acne, and voice cracks −4.4 (95% CI, −6.1 to −2.7), −2.5 (95% CI, −4.0 to −0.9), and −2.2 (95% CI, −3.8 to −0.6) months earlier, respectively, and tended to enter the third, fourth, and fifth Tanner pubic hair stages −1.7 (95% CI, −3.1 to −0.4), −1.7 (95% CI, −3.0 to −0.4), and −2.0 (95% CI, −3.6 to −0.3) months earlier, respectively [86]. Finally, another Danish study used data from 2552 sons in a mother-child cohort established between 1984 to 1987 to evaluate the association between high maternal BMI and onset of puberty in sons, which was characterized by experiencing acne, shaving facial hair, voice cracks, and nocturnal emissions in place of Tanner staging [87]. The study observed that sons whose mothers had prepregnancy obesity started regularly shaving −0.69 years earlier compared to sons of normal-weight mothers (95% CI, −1.17 to −0.21) [87]. In analyses removing sons of underweight mothers, maternal obesity was also associated with an earlier age at acne development and nocturnal emission [87]. The literature suggests that maternal overweight or obesity could significantly alter the programming of puberty, so that it occurs earlier in boys and girls using both clinical Tanner stages and markers associated with the pubertal transition. Additional experimental and human epidemiologic studies will be needed to understand other potential implications of precocious puberty and whether the trend can be reversed or mitigated.

Direct and Indirect Markers of Impaired Reproductive Capacity in Females and Males

Although the evidence is limited (especially from human epidemiologic studies), maternal obesity could have lasting implications for offspring reproductive health and capacity. Experimental studies have reported that maternal obesity can impair reproductive capacity both in female and male offspring. One study in rats observed that maternal HFDI obesity was associated with signs of reduced fertility in female offspring [49]. Specifically, offspring of dams that were 28% overweight (compared to the controls) had higher ovarian weight compared to controls, and offspring of dams that were both 17% and 28% overweight had fewer primordial and primary follicles, fewer healthy oocytes, and a higher ovulation rate compared to control offspring [49]. In a later study, the male offspring of HFDI obese rats displayed decreased fertility and poor sexual maturity [50]. Specifically, male offspring of dams that were 35% overweight had fewer spermatozoa and spermatogonia, as well as a higher percentage of sperm with amorphous head curvature compared to the control males [50]. Another study in rats observed similar sperm abnormalities in males of overweight dams compared to those of control dams, and also reported that male offspring of overweight dams had decreased fertility rates (number of sired litters) compared to male offspring of control dams [24]. Results from these experimental studies suggest that excessive maternal adiposity may disrupt the development of the reproductive system, potentially with deleterious consequences for future reproductive capacity due to suboptimal gonadal function and morphology.

To our knowledge, only one human epidemiologic study has investigated whether maternal adiposity is associated with an elevated risk of offspring infertility. The Danish Healthy Habits for Two study included 9232 children of women enrolled between 1984 and 1987, with fertility status data collected from 2 patient registries through 2018 [91]. Authors reported that sons of women with overweight had higher odds of infertility compared to sons of normal-weight women (OR: 1.4; 95% CI, 1.0-1.9). Surprisingly, despite the experimental evidence, there were no associations of maternal overweight or obesity with infertility in daughters (OR: 0.9; 95% CI, 0.7-1.2) [91]. Similarly, in a study of 367 Danish women born between 1988 and 1989, maternal overweight/obesity was not associated altered follicle count in daughters—an indirect measure of fertility [92]. However, daughters of women with overweight did have lower levels of DHEAS and estradiol than women born to normal-weight mothers [92]. Although depleted follicle count, decreased oocyte health, hormonal disruption, poor sperm quality, and low sperm count are not definitive predictors of infertility, they could be markers of decrease fecundity [93–94]. In view of the deterrent evidence from human epidemiological studies, more research is needed to corroborate or refute previous findings, especially given the growing prevalence of obesity among pregnant individuals.

Additional Diseases and Syndromes Across the Lifespan

Beyond the well-characterized reproductive endpoints discussed earlier, elevated maternal adiposity could also contribute to conditions that have known detrimental effects on reproduction. PCOS—an endocrine condition in which the ovaries are enlarged and are characterized by several cysts of varying size—is often accompanied by obesity and insulin resistance [96]. Many studies have reported that daughters of women with overweight or obesity had a higher risk of developing PCOS compared to daughters of normal-weight women, even after accounting for maternal PCOS status (HR overweight: 1.52; 95% CI, 1.36-1.70 and HR obesity: 1.97; 95% CI, 1.61-2.41) [97], suggesting that maternal obesity could be an independent determinant of PCOS development in daughters. Maternal obesity could program PCOS in utero due to the compromised hormonal milieu resulting from
| Outcome                          | Exposure                                                                 | Sample size | Study design, country | Covariates                                                                 | Main findings                                                                                                                                                                                                 | Citation |
|---------------------------------|---------------------------------------------------------------------------|-------------|-----------------------|-----------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------|
| Newborn AGD                     | Maternal prepregnancy and early-pregnancy BMI and weight, waist and hip circumference, waist/hip and waist/height ratios, body fat %, visceral fat level, muscle %, body fat/muscle ratio; evaluated continuously | 450         | Prospective cohort, US | Race/ethnicity, parity, fetal sex, first trimester smoking status, age, average gestational diet quality, and perceived stress                                                                      | Daughters of women with higher prepregnancy BMI and early pregnancy weight, waist and hip circumference, and visceral fat level tended to have longer anogenital distance and anoestrous AGD                                                   | [40]     |
| Newborn AGD                     | Maternal prepregnancy BMI (overweight/obesity: BMI ≥ 24) and GWG (inadequate, adequate, excessive) | 556         | Prospective cohort, China | GWG, age, total wks gestation, education, parity, folic acid intake, passive smoking, and infant birth weight                                                                                           | Prepregnancy BMI was not associated with AGD. Sons of women with excessive GWG tended to have shorter anopenile AGD than sons of women with adequate GWG                                                                 | [41]     |
| Hypospadias                     | Maternal prepregnancy obesity (overweight: BMI 25-29.9; obesity: BMI ≥ 30) | 1146 cases 3904 controls | Case-control, US       | Age, ethnicity, parity, smoking 1 month before conception, and folic acid intake 1 month before conception                                                                                           | Sons of women with obesity had higher odds of developing hypospadias                                                                                                                                     | [44]     |
| Cryptorchidism and hypospadias  | Maternal early-pregnancy BMI (overweight: BMI 25-29.9; obesity class 1: BMI 30-34.9; obesity class 2: BMI 35-39.9; obesity class 3: BMI ≥ 40) | 1 055 705   | Prospective cohort, Sweden | Age, parity, cigarette smoking in early pregnancy, education, origin of birth, and newborn calendar y at birth                                                                               | Sons of women with overweight or obesity class 1-3 had increased risks of developing cryptorchidism and hypospadias                                                                                     | [42]     |

Abbreviations: AGD, anogenital distance; BMI, body mass index; GWG, gestational weight gain; US, United States.

Figure 1. Elevated maternal adiposity is associated with maternal hormone disruption (specifically, sex-steroid hormones), which could contribute to altered gonadal and genital development, precocious puberty and menarche, poor sperm quality, and elevated risk of polycystic ovarian syndrome and cancers in offspring. Substantially more data from experimental and human epidemiologic studies are needed to understand if these developmental disruptions contribute to offspring infertility later in life.
| Outcome                          | Exposure                                                                 | Sample size | Study design, country | Covariates                                                                 | Main findings                                                                                     | Citation |
|---------------------------------|--------------------------------------------------------------------------|-------------|-----------------------|-----------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------|----------|
| Early menarche                  | Maternal prepregnancy BMI (overweight: BMI 25-29.9; obesity: BMI ≥ 30)  | 2497        | Prospective cohort, US | Maternal socioeconomic status, maternal race/ethnicity, maternal parity, maternal smoking, maternal age at menarche, breastfeeding, BMI at age 7 | Daughters of women with overweight or obesity had higher risk of earlier menarche                  | [63]     |
|                                 | Maternal prepregnancy BMI (overweight: BMI 25-29.9; obesity: BMI ≥ 30)  | 597         | Prospective cohort, US | Maternal age at menarche, maternal parity, socioeconomic status, race, and study site | Daughters of women with obesity had higher odds of menarche before age 12                         | [64]     |
|                                 | Maternal prepregnancy BMI (continuous and overweight: BMI 25-29.9; obesity: BMI ≥ 30) and GWG (continuous and inadequate, adequate, excessive) | 2086        | Prospective cohort, UK | Maternal age, parity, socioeconomic status, smoking, maternal age at menarche, and ethnicity | Daughters of women with prepregnancy overweight or obesity had higher risks of early menarche. Daughters of women with higher GWG had higher risks of earlier menarche. Higher maternal prepregnancy BMI was associated with earlier pubarche and thelarche | [65]     |
| Precocious Puberty              | Daughters: Tanner stages and age at menarche Maternal prepregnancy BMI (overweight: BMI 25-29.9; obesity: BMI ≥ 30) | 2661        | Prospective cohort, Great Britain | Maternal menarche before age 12, maternal smoking status, and maternal parity, maternal education, maternal race, and maternal age | Daughters of women with obesity or overweight tended to attain higher breast stages and menarche earlier than daughters born to normal-weight women. Daughters of women with obesity tended to develop pubic hair earlier than daughters of normal-weight women | [90]     |
|                                 | Daughters: Tanner stages, axillary hair, acne, menarche. Sons: Tanner stages, voice break, first ejaculation, acne, and axillary hair Maternal prepregnancy BMI (overweight: BMI 25-29.9; obesity: BMI ≥ 30) | 15602       | Prospective cohort, Denmark | Maternal alcohol consumption and smoking in first trimester, highest educational class of parents, maternal age at menarche, maternal age, parity, and cohabitation of parents during pregnancy | Daughters of women with prepregnancy obesity tended to experience all pubertal milestones, and start puberty earlier overall, than daughters of normal-weight women. Daughters of women with overweight experienced similar outcomes Sons of women with prepregnancy obesity tended to experience voice break, acne, and axillary and pubic hair growth earlier than sons of normal-weight women | [86]     |
|                                 | Sons: age of regular shaving, voice break, acne onset, and first nocturnal emission Maternal prepregnancy BMI (overweight: BMI 25-29.9; obesity: BMI ≥ 30) | 2522        | Prospective cohort, Denmark | Maternal age, parental habitation status, delivery location, maternal chronic disease status, maternal smoking during pregnancy, maternal alcohol consumption during pregnancy, family socioeconomic status, and BMI in 2005 | Sons of women with prepregnancy obesity tended to start shaving earlier than others. Sons born to women with obesity tended to develop acne and experience nocturnal emissions earlier than sons of normal-weight women | [87]     |

Abbreviations: BMI, body mass index; GWG, gestational weight gain; UK, United Kingdom; US, United States.
excess maternal adiposity. One proposed mechanism is that an abundance of maternal adipose tissue could disrupt mitochondrial steroidogenic function and subsequently alter the concentrations of sex-steroid hormones in the placenta [97, 98]. Regardless of its etiology, PCOS has been implicated in subfertility or infertility in women, likely due to hyperandrogenism and oligo-anovulation [99], so it is important to understand whether maternal obesity is a potential preventable factor contributing to PCOS.

Finally, receiving a cancer diagnosis at any life stage could have implications for reproductive capacity because of the type of cancer (malignant or benign), the location (reproductive tract or not), and the therapy undertaken to treat the disease [100]. Although few studies are available in humans regarding maternal obesity and reproductive tract cancers, studies in mice have shown that maternal HFDI obesity promoted the progression of prostate cancer development in male offspring [101] and ovarian cancer in female offspring [102]. As the prevalence of maternal overweight and obesity increases, future human epidemiologic studies are needed to ascertain if the experimental findings translate to humans.

Increased risk of nonreproductive tract cancers could also affect reproductive capacity, as chemotherapy and radiation have been associated with premature ovarian failure and miscarriage due to incidental uterine radiation in women and cessation of sperm production and sperm DNA damage in men [103–106]. In epidemiologic studies, maternal obesity has been shown to increase the offspring's risk of developing cancer in childhood and adulthood [107, 108]. An analysis of longitudinal data from the Helsinki Birth Cohort Study (children born 1934–1944) and the Finnish Cancer Registry (followed through 2006) found a positive association between exposure to higher maternal BMI and risk of developing cancer in sons [107]. When maternal BMI was evaluated continuously, a 1-unit increase in maternal BMI was associated with a 2.50% higher risk (HR: 1.025) of developing cancer in sons (95% CI, 0.999–1.053) but not daughters [107]. In a more recent US study, childhood cancer cases (age ≤ 5 years) were identified from the California Cancer Registry from 1988 to 2013 and matched controls were selected using birth certificates from the same time period [109]. Overall, children of mothers with overweight had 27% higher odds (OR: 1.27; 95% CI, 1.07–1.49) of developing childhood cancer compared to children of mothers with normal BMI [109].

Table 3. Studies on the association between maternal obesity and direct and indirect markers of impaired reproductive capacity

| Outcome | Exposure | Sample size | Study design | Covariates | Main findings                                                                 | Citation |
|---------|----------|-------------|--------------|------------|-------------------------------------------------------------------------------|----------|
| **Rodents** |          |             |              |            |                                                                               |          |
| Females: ovarian reserve, follicle development, and ovulation | Maternal HFDI overweight | 8-10 per group | Experimental rat models using HFD or control diet | Not applicable | Offspring of dams with 28% or 17% overweight had fewer healthy oocytes and fewer primordial and primary oocytes | [49]     |
| Males: sperm quality and concentration | Maternal HFDI overweight | 8-10 per group | Experimental rat models using HFD or control diet | Not applicable | Offspring of dams with 35% overweight had fewer spermatogonia and spermatozoa compared to offspring of controls and had a higher % of sperm with amorphous head curvature | [50]     |
| **Humans** |          |             |              |            |                                                                               |          |
| Sons: infertility | Maternal prepregnancy BMI (continuous and overweight: BMI 25-29.9; obesity: BMI ≥ 30) | 9232 | Prospective cohort, Denmark | Maternal age, maternal parity, parental cohabitation status, maternal smoking and alcohol consumption during pregnancy, and parental socioeconomic status | Sons of women with overweight had higher odds of infertility compared to sons born to normal-weight women | [91]     |
| Daughters: infertility | Maternal prepregnancy BMI, evaluated continuously | 367 | Prospective cohort, Denmark | Daughters of women with high BMI tended to experience early menarche compared to others | No associations observed between maternal BMI and ovarian follicle count | [92]     |
| Daughters: age at menarche, sex steroid hormone profile, and ovarian follicle count |          |             |              | Daughters of women with higher BMI tended to have lower levels of estradiol and DHEAS than daughters of women with lower BMI |          |
# Table 4. Studies on the association between maternal obesity and reproduction-relevant diseases or syndromes

## Rodents

| Outcome | Exposure | Sample size | Study design | Covariates | Main findings | Citation |
|---------|----------|-------------|--------------|-------------|---------------|----------|
| Males: prostate cancer | Maternal HFDI overweight | 36 per group | Experimental mouse models using HFD or control diet | Not applicable | Offspring of dams fed HFD had higher prostate cancer tumor formation rates and higher mortality rates compared to offspring of controls at age 20 wk | [101] |
| Females: ovarian cancer | Maternal HDFI overweight | N/A | Experimental mouse models using HFD or control diet | Not applicable | Offspring of dams fed HFD had higher organ-specific tumor burdens compared to offspring of controls and had higher expression of CXCL13 cytokine reported in ovarian cancer cells | [102] |

## Humans

| Disease | Exposure | Sample size | Study design | Covariates | Main findings | Citation |
|---------|----------|-------------|--------------|-------------|---------------|----------|
| PCOS | Maternal prepregnancy BMI (overweight: BMI 25-29.9; obesity: BMI ≥ 30) | 3728 | Prospective cohort, Sweden | Maternal age, maternal parity, years of involuntary childlessness before index pregnancy, and maternal diabetes or preeclampsia at index pregnancy, maternal education level, country of birth, and maternal PCOS diagnosis | Daughters of women with overweight or obesity had higher risks of developing PCOS compared to daughters of normal-weight women | [97] |
| Cancer in adulthood | Maternal prepregnancy BMI, evaluated continuously | 13345 | Cohort, Finland | Maternal age, maternal parity and childhood and adult socioeconomic status, education, and income | Sons of women with high BMI had higher odds of cancer development compared to sons of normal-weight women | [107] |
| Cancer in childhood | Maternal prepregnancy BMI (overweight: BMI 25-29.9; obesity: BMI ≥ 30) | 11149 cases, 270,147 controls | Case-control, US | Birth y, maternal and paternal race/ethnicity, and maternal age | Children of women with overweight or obesity had higher odds of developing childhood leukemia compared to children of normal-weight women | [109] |

Abbreviations: BMI, body mass index; HFD, high-fat diet; HFDI, high-fat diet-induced; N/A, not available; PCOS, polycystic ovarian syndrome; US, United States.
Beyond the inherent challenges related to long-term follow-up in utero exposure (maternal obesity) and adulthood health needs to be understood about the long-term implication of BMI was included as a mediator, these results provide more maternal prepregnancy BMI and earlier menarche in daughters at the role of childhood BMI in the relationship between maternal obesity on child reproductive end points. Many of the studies we reviewed that consider relationship between maternal obesity and offspring reproductive capacity (see Table 1). Finally, daughters of women with overweight or obesity are at an elevated risk of developing PCOS, but data related to gynecologic/urologic cancers in offspring are limited to rodent models (see Table 2). Data related to frank infertility in offspring of women with overweight/obesity are limited, although there is some evidence for disrupted markers of reproductive capacity in adult offspring (see Table 3). Importantly, there are also challenges for modeling maternal obesity itself, which occurs slowly and chronically in humans, but (typically) quickly and acutely in rodent models. Most models for studying some aspects of human reproduction, in which HFD is most appropriate [9, 11], which presents a challenge for interpretation and translation of the hormonally driven events in mice that do not occur, or simply have not yet been identified, in humans [111]. Importantly, there are also challenges for modeling maternal obesity itself, which occurs slowly and chronically in humans, but (typically) quickly and acutely in rodent models. Most previous studies induce obesity in dams via an HFD because obesity is a chronic condition and laboratory rodents have a short lifespan that does not allow for the slow development of obesity. Additionally, there are no strict criteria in animals distinguishing overweight vs obesity [50] or consensus on which HFD is most appropriate [112], which presents an obstacle for interpretation and translation of findings. The use of a HFD also does not quite accurately represent the human Western diet, which is low in fiber and high in sugar, salt, and fat [112]. Additionally, women with obesity do not necessarily always consume Western/HF diets in pregnancy,
thus HFD feeding in rodent models could mask the diet-independent effect of obesity on reproductive development. To address concerns around modeling of reproductive development, nonhuman primate models may be needed to address some of the more physiological aspects of reproductive development, both short and long term. In any chosen experimental model, more focus will be needed on maternal obesity rather than the dietary intervention. This may require longer preconception HFD or Western diet treatment, or again, the use of nonhuman primates, which have been shown to spontaneously develop obesity and experience similar physiologic changes to humans, especially in pregnancy [113–115].

Conclusion
Maternal obesity has known deleterious consequences for offspring cardiometabolic development, but recent experimental studies suggest that maternal obesity could also impair offspring fertility and health by disrupting gonadal development and damaging sperm production and programming ovarian dysfunction. In human epidemiologic studies, maternal obesity has been associated with altered AGD, genital malformations in boys, early menarche, precocious puberty in boys and girls, PCOS, and cancer. However, epidemiologic studies directly linking maternal obesity exposure in utero to long-term fertility/reproductive health in offspring are limited. Given the limitations of current experimental models and the paucity of human epidemiologic research, it is critical that future studies evaluating the effects of maternal obesity go beyond the long-term metabolic outcomes to also consider the reproductive health and capacity of offspring.

Acknowledgments
We are grateful to Dr Humphrey Yao from the National Institute of Environmental Health Sciences for his generous discussion and review of this manuscript.

Financial Support
This work was supported by the National Institute for Environmental Health Sciences (NIH/NIEHS grant Nos. R00 ES024795 and T32 ES007255), and the National Institute of Child Health and Human Development (grant No. R03 HD100775). Its contents are solely the responsibility of the grantee and do not necessarily represent the official views of the NIH. This project was also supported by the US Department of Agriculture National Institute of Food and Agriculture and Michigan AgBioResearch.

Disclosures
The authors have nothing to disclose.

Data Availability
Data sharing is not applicable to this article as no data sets were generated or analyzed during the present study.

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