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Long-term consequences of obesity on female fertility and the health of the offspring

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Abstract

Purpose of review—Obesity has reached near epidemic levels among reproductive age women with a myriad of consequences. Obesity adversely affects the maternal milieu by creating conditions that decrease fertility and increase the risk of gestational diabetes, hypertensive disease in pregnancy, fetal growth abnormalities and congenital anomalies. The effects of obesity are not limited to pregnancy. Indeed, beyond the immediate postpartum period, obese women maintain a higher prevalence of insulin resistance and cardiovascular disease. In this article, we will review the pathophysiology underlying the effects of obesity on fertility, pregnancy outcome and health status of offspring. The purpose of this review is to outline proposed models responsible for the short-term and long-term consequences of obesity on fertility and offspring development, and identify knowledge gaps where additional research is needed.

Recent findings—Maternal over or under nutrition adversely affect maternal reproductive capacity and pregnancy success. Separate from effects on maternal reproductive function, maternal over or under nutrition may also ‘program’ fetal pathophysiology through inheritance mechanisms that suggest epigenetic modification of DNA, differential RNA translation and protein expression, or modification of the fetal hypothalamic–pituitary axis function through programmed adverse effects on the developing hypothalamic circuitry. The concept of maternal health modifying the risk of developing noncommunicable diseases in the offspring is based on Developmental Origins of Health and Disease hypothesis.

Summary—Of importance, the long-term effects of obesity are not limited to maternal health, but also programs pathophysiology in their offspring. Children of obese gravida are at increased risk for the development of cardiometabolic disease in childhood and throughout adulthood. Future studies directly interrogating mechanisms underlying the risks associated with obesity will allow us to develop interventions and therapies to decrease short-term and long-term morbidities associated with maternal obesity.

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Conflicts of interest

There are no conflicts of interest.

Keywords

fetus; infertility; obesity; outcomes; pregnancy

INTRODUCTION

Obesity, defined as having a BMI at least 30 kg/m², affects more than one-third of reproductive age women in the United States [1,2]. The overall prevalence of obesity has doubled among reproductive aged women from 1976 to 2004 [2]. Furthermore, the rate of severe obesity (BMI ≥ 40 kg/m²) in the reproductive aged population has increased three-fold during this time [2,3]. A burgeoning number of studies report robust relationships between maternal obesity, and adverse maternal and fetal outcomes. Adverse outcomes include, but are not limited to maternal thromboembolic and hypertensive disease and insulin resistance, labor dystocia, fetal macrosomia, intrauterine growth restriction, congenital anomalies and increased risk of fetal stillbirth [1,3]. Equally important, epidemiological studies also suggest that maternal obesity may program cardiovascular disease, diabetes and asthma in adult offspring. The mechanisms by which maternal obesity influences these outcomes are not yet clearly elucidated [2,4].

Current theories support the concept of fetal origins of disease based on the Barker Hypothesis. In 1990, Sir David Barker formalized the concept that the origins of certain noncommunicable diseases may trace back to the in-utero period, and is currently referred to as Developmental Origins of Health and Disease [5]. Maternal over or under nutrition and environmental exposures may irrevocably 'program' fetal pathophysiology and increase risk of certain adult onset diseases such as cardiovascular disease, diabetes, malignancies and so on [6–8]. Moreover, disease may be programmed across multiple generations through maternal or paternal inheritance mechanisms that reflect epigenetic modification of DNA, and differential RNA translation and protein expression [4,9]. Another hypothesized mechanism includes modification of the fetal hypothalamic–pituitary axis (HPA) through effects on the developing hypothalamic circuitry and by causing downstream dysregulation in the expression of key neuropeptides involved in the HPA axis function and their cognate receptors [10]. Below, we first address the effects of maternal obesity on fertility. We then focus on the relationship between maternal obesity and adverse fetal and neonatal outcomes, specifically addressing potential mechanisms by which in-utero fetal programming may result in adult disease. The goals of this review are to provide an update on our current knowledge regarding the impact of obesity on maternal reproductive function and offspring outcomes as well as to identify where knowledge gaps exist.

Pathophysiology of obesity and the reproductive axis

Energy metabolism and female fertility are intimately connected and reciprocally regulated. Although lipids are critical for granulosa steroidogenesis [11], human and rodent studies suggest hyperlipidemia imposes deleterious effects on reproduction. Specifically, overweight and obese women exhibit metabolic dysfunction that is characterized by hypercholesterolemia and increased nonesterified fatty acid concentrations, hyperglycemia and insulin resistance [12]. This in turn creates a chronic low-grade metabolic inflammatory

state [13,14], and endocrine dysfunction that affect age of menarche and the development of polycystic ovarian syndrome and subfertility. Human and rodent studies also suggest that over nutrition results in follicular fluid hypertriglyceridemia which causes oxidative stress, lipid-induced oocyte toxicity, mitochondrial dysfunction and apoptosis of granulosa cells [15,16] resulting in reduced fecundity and infertility [17–19]. Indeed, among subfertile women, the chance of conception is decreased by 5% for each unit increase in BMI greater than 29kg/m² [20,21]. Moreover, among obese women undergoing in-vitro fertilization, obesity adversely affects oocyte quality and uterine receptivity [20,21]. Finally, obesity may adversely affect ovarian reserve [22], a surrogate marker of fertility, and may give rise to luteinizing hormone (LH) surge and corpus luteum dysfunction [23,24,25,26]. Hence, overweight and obese women should be encouraged to lose weight to optimize fertility and pregnancy outcome [11].

Adipose tissue is a key endocrine organ that regulates glucose and fat metabolism, energy expenditure, inflammation and reproduction [27]. Adiponectin increases fatty acid oxidation in fat and imposes insulin-sensitizing and anti-inflammatory effects. Adiponectin receptors are noted in mammalian pituitary, ovaries, uterus and placenta [28,29]. It stimulates granulosa cell steroidogenesis, and is hypothesized to assist developing preimplantation embryos and uterine receptivity. Leptin, a byproduct of adipose tissue, is significantly higher among obese individuals [30]. High concentrations of leptin are associated with dysfunctional steroidogenesis in human granulosa and theca cells and abnormal follicular development, resulting in oligoovulation and anovulation [31–34]. However, what remains unclear is whether all phenotypes of obesity (metabolic vs. nonmetabolic) confer similar effects on steroidogenesis, or whether adipose tissue type (brown vs. white) modifies the association between obesity and subfertility. Mechanistic studies unraveling the association between adipokine levels, body composition and dysfunctional steroidogenesis are much needed.

Insulin, a peripheral regulator of energy homeostasis, acts through its cognate receptor to activate one of two second messenger systems, the phosphatidyl-inositol 3 kinase pathway or the mitogen-activated protein kinase pathway, to mediate metabolic and proliferative effects. Insulin is hypothesized to coregulate gonadal steroidogenesis with LH, and to inhibit hepatic synthesis of sex hormone-binding globulin (SHBG) [35]. Insulin resistance and hyperinsulinemia are common features of obesity. In the setting of insulin resistance, hyperinsulinemia potentiates gonadotropin-stimulated ovarian androgen synthesis [36], inhibits SHBG synthesis resulting in increased free testosterone levels and increased selective ovarian tissue insulin resistance [37]. Although human studies designed to investigate the effect of insulin on the reproductive neuroendocrine axis are less clear [36,38–40], transgenic mice with selective deletion of insulin receptors in the pituitary [41] and gonadotropin releasing hormone (GnRH) neurons [42] exhibit LH hypersecretion and increased GnRH pulse frequency. As a group, these data suggest that abnormal insulin signaling in the hypothalamic–pituitary–gonadal axis contributes to obesity-related subfertility.

At the level of the ovary, 5' AMP-activated protein kinase, a sensor of energy status, affects the regulation of oocyte maturation, steroidogenesis, proliferation and survival of theca and

granulosa cells [43,44]. For this reason, it is hypothesized that metformin may provide reproductive benefit in obese women with ovulatory dysfunction through direct effects on granulosa survival and theca cell function. High levels of saturated free fatty acids, such as palmitic acid and stearic acid, suppress granulosa cell survival due to increased apoptosis, as evidenced by DNA ladder formation and annexin V/propidium iodide staining. Furthermore, women with elevated free fatty levels in their follicular fluid have poor morphology of the cumulus oocyte complex.

Maternal obesity and effects on fetal birthweight

Obese women are at increased risk for fetal over-growth and undergrowth in utero. Effectively studying the underlying pathophysiology contributing to abnormal fetal growth has been challenged by contrasting fetal outcomes. The inability to completely control for social and behavioral confounding factors poses the greatest hurdle to defining the relationship between obesity and fetal growth abnormalities. For example, maternal nutrition, physical activity, stress levels and sleep quality each has the potential to modify the risk for maternal weight gain, gestational diabetes mellitus and hypertensive disease in pregnancy [1,3]. Hence, it is our duty as counseling practitioners to make obese women aware of these concerns and continue to encourage healthy lifestyle practices and limit gestational weight gain in accordance with the Institute of Medicine guidelines during pregnancy.

Fetal macrosomia and large for gestational age infants

Preconceptional maternal obesity significantly increases the risk of having fetal macrosomia or a large for gestational age (LGA) infant (>90% in weight for gestational age). Fetal macrosomia is 2–3 times higher and affects up to 20% of births to obese women. The risk of having fetal macrosomia or an LGA infant correspondingly increases with higher obesity classes [1,45,46].

The precise mechanism underlying the cause of fetal overgrowth among obese gravida and the extent to which social and behavioral factors confound and contribute to the problem are not clearly elucidated. It is well documented that maternal obesity is highly correlated with gestational diabetes, and gestational diabetes positively correlates with fetal overgrowth. The prevailing mechanistic theory explaining this phenomenon suggests upregulation of placental transporters for glucose (GLUT 1 and 2), amino acids and fatty acids [47,10]. However, the risk of fetal overgrowth persists among nondiabetic obese gravida too. Specifically, fetuses of obese gravida may be exposed to metabolic changes such as maternal hypertriglyceridemia, and lower levels of high density lipoprotein (HDL) cholesterol; all of which are associated with increased birth weight in observational studies. Consistent with this theory, rodent models suggest that excessive maternal dietary lipids, independent of an upregulation in glucose transporters, affect fetal birth weight by increased uptake of the chylomicron remnant core lipids by the placenta [48]. Tyrrell *et al.* [49] used maternal/neonate dyads and single nucleotide polymorphism (SNP) data from 30487 women in Europe, North America and Australia to determine if a genetic basis explained the association between maternal BMI and birth-weight. SNPs robustly associated with BMI and obesity-related traits (hyperglycemia, hypertriglyceridemia and hyperlipidemia) were

selected. Even in women without clinical gestational diabetes Tyrrell *et al.* found genetic evidence through the calculation of a weighted genetic score that there is a causal association between maternal hyperglycemia and birth weight. However, they did not find a significant causal association between triglyceride or HDL and increased birthweight. Nonetheless, this study suggests that even among obese women without a diagnosis of overt gestational diabetes, there are changes that affect the risk for fetal overgrowth. Additional studies are needed to investigate potential mechanisms by which maternal metabolic status, independent of diabetes, might contribute fetal growth abnormalities.

Intrauterine growth restriction and small for gestational age infants

Preconception maternal obesity is a risk factor for intrauterine growth restriction and small for gestational age (SGA) infant (<10% in weight for gestational age). Women with classes I and II obesity are two times more likely, whereas those with class III obesity are three times more likely to deliver an SGA infant [3■■,50,51]. The increased risk for an SGA or low birth weight infant is directly related to preterm birth complicated by medical conditions including maternal hypertensive disease, cardiac disease and so on. Although there is some suggestion that SGA may reflect abnormal placental development and suboptimal perfusion that results in compromised nutrient transfer to the fetus, the causal nature of this relationship is not definitively established in conditions of obesity [52].

Maternal obesity and congenital fetal anomalies

As compared to normal weight gravida, the risk for neural tube, cardiac and limb defects is increased by 50, 30–40 and 30%, respectively, in obese gravida [53]. Other anomalies including facial clefts and anorectal atresia are also increased among infants of obese women (Table 1) [54]. Waller *et al.* [55] performed a multisite case–control study of mothers enrolled in the National Birth Defects Prevention Study and found the odds of experiencing spina bifida, cardiac defects, anorectal atresia, hypospadias, diaphragmatic hernia or omphalocele were 1.3–2.1 times higher among obese mothers than normal weight controls. Blomberg *et al.* [56] found similar results from studies of women in the Swedish Medical Health Registries. In contrast, multiple observational studies have found a correspondingly decreased risk of fetal gastroschisis among obese women [55,57].

The mechanisms by which maternal obesity results in congenital fetal anomalies are not understood. [53,58]. After controlling for dietary folic acid intake, serum folic acid levels are significantly reduced in obese gravida suggesting that abnormal folic acid metabolism may be an underlying cause for increased prevalence of neural tube defect (NTD)[59]. Maternal diabetes is also associated with an increased risk of fetal cardiac defects and NTDs [60]. Mouse models suggest that hyperglycemic environments disrupt the expression of regulatory genes responsible for embryonic development such as the Pax-3 gene encoding neural tube formation [61]. Importantly, obese gravida without diabetes maintain a similar risk for congenital anomalies possibly due to subclinical maternal insulin resistance creating a hyperglycemic environment for the fetus. Finally, obesity represents a state of chronic oxidative stress and increased inflammation, both of which may alter developmental gene expression and promote abnormal patterns of cellular apoptosis [62].

Although the correlation between obesity and fetal birth defects is well established, social and behavioral factors often confound observational studies querying this relationship. These limitations may be overcome with longitudinal human studies analyzing multiple pregnancies in the same woman or by performing sibling studies. In the meantime, clinical providers should, when possible, encourage women to optimize their health preconceptionally and to adopt healthy lifestyle practices during pregnancy.

Long-term consequences of maternal obesity on exposed offspring

Glucose metabolism—Glucose is the most important fetal energy substrate, and the usual insulin resistance state in pregnancy optimizes glucose supply and utilization by the fetus and the placenta [63,64]. Interestingly, after assessing umbilical cord glucose and insulin concentrations, Catalano *et al.* [65] noted that fetuses of obese women may develop insulin resistance in utero. It is possible that exposure to in-utero insulin resistance may predispose offspring of obese gravida to increased risk of type 2 diabetes during adolescence and adulthood.

Several animal models have revealed multiple potential mechanisms by which the fetal in-utero environment programs adult metabolic disease [66,67]. For example, studies in sheep suggest that posttranscriptional changes in microRNA levels result in the downregulation of insulin receptor substrate (IRS-1) genes involved in hepatic and adipocyte insulin receptor signaling in the fetus [66]. In addition, studies by Stecclorum and Bouret [68] found that maternal hyperglycemia disrupted hypothalamic function in offspring by creating a state of leptin resistance and by disrupting the ability of leptin to activate intracellular signaling pathways in key hypothalamic areas involved in metabolism. In addition, offspring born to hyperglycemic females exhibited abnormal neural projections of proopiomelanocortin and Agouti-related peptide neurons, neurons involved in appetite regulation.

Cardiovascular effects—Multiple epidemiologic studies demonstrate a direct relationship between prepregnancy obesity and the development of childhood obesity, higher total body fat mass and waist circumference in childhood, increased rates of adolescent obesity, and ultimately long-term adult cardiovascular disease in the offspring [69]. In rodent models, maternal obesity is associated with increased leptin and C-peptide levels in umbilical cord blood [70], suggesting the in-utero environment creates the foundation for development of adult onset cardiovascular disease and metabolic syndrome. Although the data are variable, observational studies in childhood demonstrate that offspring from obese gravida tend to have elevated blood pressure, hyperlipidemia, insulin resistance and elevated inflammatory markers [71–73]. Modification of maternal diet and exposure to breastmilk may modify this risk in childhood and adulthood; however, large clinical trials are needed to confirm the benefits of these interventions [74,75].

In adulthood, offspring of obese gravida have higher BMI, waist circumference, blood pressure, insulin and triglyceride levels and lower HDL cholesterol levels [69]. However, these studies are limited by their observational design and the implicit confounds of genetic diversity, sociodemographic, life-time nutritional and lifestyle choices. To control for the previous list of confounding factors, Kral *et al.* [76] performed a sibling comparison study

among siblings of mothers with high prepregnancy weight loss due to maternal bariatric surgery. They found that the risk of being overweight, obese and dysregulation of cardio-metabolic factors was higher in siblings born to the same mothers before bariatric surgery, supporting the hypothesis that maternal weight loss directly benefits fetal and neonatal health [76]. A study by Patro *et al.* [77] compared maternal and paternal BMI and childhood anthropometric measures including fat mass and waist hip ratio, implying that a higher paternal association with anthropometric measurements may be because of shared lifestyle characteristics. However, these studies demonstrated that maternal rather than paternal BMI negatively influenced childhood anthropometric measures.

Studies utilizing rabbit and rat models of disease suggest that in-utero hyperleptinemia increases central sympathetic drive through effects on the hypothalamic nucleus of the solitary tract. Aberrant central sympathetic tone alters renal sympathetic nerve activity, resulting in vascular dysregulation and hypertension [78,79]. This early insult then continues through childhood and adolescence, increasing the propensity for cardiometabolic disease in adulthood.

Maternal obesity is also hypothesized to alter in-utero adipocyte morphology in the offspring and increases ectopic liver and pancreas lipid deposition [80,81]. Abnormal lipid deposition in affected offspring creates a chronic inflammatory state, increases oxidative stress, alters hepatic protein expression and lipid profiles and increases sympathetic nervous system tone; all pathophysiological events that define and increase the risk of cardiometabolic disease. The pathophysiology underpinning abnormal adipocyte deposition and function in offspring of obese gravida may reflect aberrant circadian biology. Circadian rhythms in all mammals are predominantly driven by light exposure regulating the central *Clock* genes in the suprachiasmatic nucleus of the hypothalamus [82]. Transgenic mouse models demonstrate that *Clock* null mice become obese and develop hepatic steatosis. In addition rodent maternal/fetal dyad studies suggest that maternal obesity (feeding through high-fat diet) shifts the circadian rhythm of offspring and is associated with increased risk for nonalcoholic fatty liver disease among the offspring, increasing the risk of intraabdominal adipose tissue deposition, possibly due to disruption in the *Clock* gene expression [10[■], 81,82].

Long-term Neuropsychiatric effects—Maternal prepregnancy obesity may also be associated with impairments in offspring neuropsychiatric development. A study by Casas *et al.* [83] of two birth cohorts in Europe noted reduced infant cognitive development scores among offspring of women with prepregnancy obesity. Interestingly, paternal overweight/obesity was not associated with infant cognitive development. In rodent models, leptin induces excitatory synaptogenesis and promotes dendritic spine formation in the hippocampus, which mediates learning and task functions [84]. In rodent models, leptin induces excitatory synaptogenesis and promotes dendritic spine formation in the hippocampus, which mediates learning and task functions [85]. Interestingly, hypoleptinemia and hyperleptinemia both seem to impair the formation of synapses and dendritic spines affecting hippocampal maturation [84,86]. Future studies in rodent and nonhuman primate models investigating the nuances of leptin equilibrium and its role in hippocampal development are needed to clarify this association.

CONCLUSION

Obesity adversely affects female reproductive function, pregnancy outcome and exposed offspring. Given the rising rates of obesity worldwide, especially among reproductive age women, the clinical and financial implications that obesity poses in healthcare are significant. Additional studies focused on how maternal metabolic dysfunction programs adult disease and adversely affects fetal outcomes are warranted. In particular, there is a gap in our understanding of how maternal adipose phenotype, deposition and distribution affect fetal and adult offspring health. A more in-depth understanding of how maternal obesity phenotypes affects the fetal unit may provide insight into opposing fetal outcomes (i.e. fetal macrosomia vs. intrauterine growth restriction). This in turn may allow us to develop targeted intervention and therapeutic approaches to decrease the short-term and long-term consequences of maternal obesity on adult offspring outcomes.

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REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

■ of special interest

■■ of outstanding interest

1. ACOG. Practice Bulletin No 156: obesity in pregnancy. *Obstetr Gynecol.* 2015; 126:e112–e126.
2. Ogden CL, Carroll MD, Kit BK, Flegal KM. Prevalence of childhood and adult obesity in the United States, 2011–2012. *JAMA.* 2014; 311:806–814. [PubMed: 24570244]
- 3■■. Stang J, Huffman LG. Position of the Academy of Nutrition and Dietetics: obesity, reproduction, and pregnancy outcomes. *J Acad Nutr Diet.* 2016; 116:677–691. Comprehensive review of reproductive risks associated with obesity, and suggests behavioral counseling methods and approaches to lifestyle modification. [PubMed: 27017177]
4. Zambrano E, Ibanez C, Martinez-Samayoa PM, et al. Maternal obesity: lifelong metabolic outcomes for offspring from poor developmental trajectories during the perinatal period. *Arch Med Res.* 2016; 47:1–12. [PubMed: 26827819]
5. Barker DJ. The fetal and infant origins of adult disease. *BMJ.* 1990; 301:1111. [PubMed: 2252919]
6. Daniels SR. The Barker hypothesis revisited. *J Pediatr.* 2016; 173:1–3.
7. de Boo HA, Harding JE. The developmental origins of adult disease (Barker) hypothesis. *Aust New Zealand. J Obstetr Gynaecol.* 2006; 46:4–14.
8. Geary M, Crowley D. The Barker hypothesis. *Irish Med J.* 1999; 92:390–391.
9. Zambrano E, Nathanielsz PW. Mechanisms by which maternal obesity programs offspring for obesity: evidence from animal studies. *Nutr Rev.* 2013; 71(Suppl 1):S42–S54. [PubMed: 24147924]

- 10■■■. Penfold NC, Ozanne SE. Developmental programming by maternal obesity in 2015: outcomes, mechanisms, and potential interventions. *Horm Behav.* 2015; 76:143–152. Provides possible mechanisms by which obesity may mediate developmental programming. [PubMed: 26145566]
11. Grummer RR, Carroll DJ. A review of lipoprotein cholesterol metabolism: importance to ovarian function. *J Anim Sci.* 1988; 66:3160–3173. [PubMed: 3068221]
12. Lebovitz HE. Insulin resistance: a common link between type 2 diabetes and cardiovascular disease. *Diabetes Obes Metab.* 2006; 8:237–249. [PubMed: 16634983]
13. Marra F, Valente AJ, Pinzani M, Abboud HE. Cultured human liver fat-storing cells produce monocyte chemotactic protein-1. Regulation by proinflammatory cytokines. *J Clin Invest.* 1993; 92:1674–1680. [PubMed: 8408620]
14. Suganami T, Nishida J, Ogawa Y. A paracrine loop between adipocytes and macrophages aggravates inflammatory changes: role of free fatty acids and tumor necrosis factor alpha. *Arterioscler Thromb Vasc Biol.* 2005; 25:2062–2068. [PubMed: 16123319]
15. Jungheim ES, Macones GA, Odem RR, et al. Associations between free fatty acids, cumulus oocyte complex morphology and ovarian function during in vitro fertilization. *Fertil Steril.* 2011; 95:1970–1974. [PubMed: 21353671]
16. Robker RL, Akison LK, Bennett BD, et al. Obese women exhibit differences in ovarian metabolites, hormones, and gene expression compared with moderate-weight women. *J Clin Endocrinol Metab.* 2009; 94:1533–1540. [PubMed: 19223519]
17. Fujimoto VY, Kane JP, Ishida BY, et al. High-density lipoprotein metabolism and the human embryo. *Hum Reprod Update.* 2010; 16:20–38. [PubMed: 19700490]
18. Schisterman EF, Mumford SL, Browne RW, et al. Lipid concentrations and couple fecundity: the LIFE study. *J Clin Endocrinol Metab.* 2014; 99:2786–2794. [PubMed: 24846535]
19. Valckx SD, De Pauw I, De Neubourg D, et al. BMI-related metabolic composition of the follicular fluid of women undergoing assisted reproductive treatment and the consequences for oocyte and embryo quality. *Hum Reprod.* 2012; 27:3531–3539. [PubMed: 23019302]
20. Hassan MA, Killick SR. Negative lifestyle is associated with a significant reduction in fecundity. *Fertil Steril.* 2004; 81:384–392. [PubMed: 14967378]
21. van der Steeg JW, Steures P, Eijkemans MJ, et al. Obesity affects spontaneous pregnancy chances in subfertile, ovulatory women. *Hum Reprod.* 2008; 23:324–328. [PubMed: 18077317]
22. Bernardi LA, Carnethon MR, de Chavez PJ, et al. Relationship between obesity and anti-Mullerian hormone in reproductive-aged African American women. *Obesity (Silver Spring).* 2017; 25:229–235. [PubMed: 27925445]
- 23■■■. Chosich J, Bradford AP, Allshouse AA, et al. Acute recapitulation of the hyperinsulinemia and hyperlipidemia characteristic of metabolic syndrome suppresses gonadotropins. *Obesity (Silver Spring).* 2017; 25:553–560. Novel experimental study design analyzing direct effects of hyperinsulinemia and hyperlipidemia as mechanisms underlying obesity-related hypogonadotropic hypogonadism. [PubMed: 28158916]
24. Jain A, Polotsky AJ, Rochester D, et al. Pulsatile luteinizing hormone amplitude and progesterone metabolite excretion are reduced in obese women. *J Clin Endocrinol Metab.* 2007; 92:2468–2473. [PubMed: 17440019]
- 25■■■. Kuokkanen S, Polotsky AJ, Chosich J, et al. Corpus luteum as a novel target of weight changes that contribute to impaired female reproductive physiology and function. *Syst Biol Reprod Med.* 2016; 62:227–242. Interesting study analyzing the effects of weight gain and weight loss on menstrual cycle and corpus luteum transcriptome utilizing a nonhuman primate model. [PubMed: 27187064]
26. Roth LW, Allshouse AA, Bradshaw-Pierce EL, et al. Luteal phase dynamics of follicle stimulating and luteinizing hormones in obese and normal weight women. *Clin Endocrinol (Oxf).* 2014; 81:418–425. [PubMed: 24576183]
27. Wozniak SE, Gee LL, Wachtel MS, Frezza EE. Adipose tissue: the new endocrine organ? A review article. *Dig Dis Sci.* 2009; 54:1847–1856. [PubMed: 19052866]
28. Chabrolle C, Tosca L, Rame C, et al. Adiponectin increases insulin-like growth factor I-induced progesterone and estradiol secretion in human granulosa cells. *Fertil Steril.* 2009; 92:1988–1996. [PubMed: 19081562]

29. Kim ST, Marquard K, Stephens S, et al. Adiponectin and adiponectin receptors in the mouse preimplantation embryo and uterus. *Hum Reprod.* 2011; 26:82–95. [PubMed: 21106494]
30. Fontana R, Della Torre S. The deep correlation between energy metabolism and reproduction: a view on the effects of nutrition for women fertility. *Nutrients.* 2016; 8:87. Recent comprehensive review on energy metabolism and fertility. [PubMed: 26875986]
31. Perez-Perez A, Sanchez-Jimenez F, Maymo J, et al. Role of leptin in female reproduction. *Clin Chem Lab Med.* 2015; 53:15–28. [PubMed: 25014521]
32. Spicer LJ, Francisco CC. The adipose obese gene product, leptin: evidence of a direct inhibitory role in ovarian function. *Endocrinology.* 1997; 138:3374–3379. [PubMed: 9231790]
33. Merhi Z, Buyuk E, Berger DS, et al. Leptin suppresses anti-Mullerian hormone gene expression through the JAK2/STAT3 pathway in luteinized granulosa cells of women undergoing IVF. *Hum Reprod.* 2013; 28:1661–1669. [PubMed: 23503941]
34. Sheffer-Babila S, Sun Y, Israel DD, et al. Agouti-related peptide plays a critical role in leptin's effects on female puberty and reproduction. *Am J Physiol Endocrinol Metab.* 2013; 305:E1512–E1520. [PubMed: 24169048]
35. Diamanti-Kandarakis E, Dunaif A. Insulin resistance and the polycystic ovary syndrome revisited: an update on mechanisms and implications. *Endocr Rev.* 2012; 33:981–1030. [PubMed: 23065822]
36. Dunaif A, Graf M. Insulin administration alters gonadal steroid metabolism independent of changes in gonadotropin secretion in insulin-resistant women with the polycystic ovary syndrome. *J Clin Invest.* 1989; 83:23–29. [PubMed: 2642919]
37. Pasquali R, Cantobelli S, Vicennati V, et al. Nitrendipine treatment in women with polycystic ovarian syndrome: evidence for a lack of effects of calcium channel blockers on insulin, androgens, and sex hormone-binding globulin. *J Clin Endocrinol Metab.* 1995; 80:3346–3350. [PubMed: 7593449]
38. Lawson EA, Buchbinder BR, Daniels GH. Hypopituitarism associated with a giant aneurysm of the internal carotid artery. *J Clin Endocrinol Metab.* 2008; 93:4616. [PubMed: 19056841]
39. Poretsky L, Piper B. Insulin resistance, hypersecretion of LH, and a dual-defect hypothesis for the pathogenesis of polycystic ovary syndrome. *Obstet Gynecol.* 1994; 84:613–621.
40. Tosi F, Negri C, Perrone F, et al. Hyperinsulinemia amplifies GnRH agonist stimulated ovarian steroid secretion in women with polycystic ovary syndrome. *J Clin Endocrinol Metab.* 2012; 97:1712–1719. [PubMed: 22419715]
41. Brothers KJ, Wu S, DiVall SA, et al. Rescue of obesity-induced infertility in female mice due to a pituitary-specific knockout of the insulin receptor. *Cell Metab.* 2010; 12:295–305. [PubMed: 20816095]
42. DiVall SA, Herrera D, Sklar B, et al. Insulin receptor signaling in the GnRH neuron plays a role in the abnormal GnRH pulsatility of obese female mice. *PLoS One.* 2015; 10:e0119995. [PubMed: 25780937]
43. Bertoldo MJ, Faure M, Dupont J, Froment P. AMPK: a master energy regulator for gonadal function. *Front Neurosci.* 2015; 9:235. [PubMed: 26236179]
44. Tosca L, Rame C, Chabrolle C, et al. Metformin decreases IGF1-induced cell proliferation and protein synthesis through AMP-activated protein kinase in cultured bovine granulosa cells. *Reproduction.* 2010; 139:409–418. [PubMed: 19906888]
45. Athukorala C, Rumbold AR, Willson KJ, Crowther CA. The risk of adverse pregnancy outcomes in women who are overweight or obese. *BMC Pregnancy Childbirth.* 2010; 10:56. [PubMed: 20849609]
46. Schummers L, Hutcheon JA, Bodnar LM, et al. Risk of adverse pregnancy outcomes by prepregnancy body mass index: a population-based study to inform prepregnancy weight loss counseling. *Obstet Gynecol.* 2015; 125:133–143.
47. Gaccioli F, Lager S, Powell TL, Jansson T. Placental transport in response to altered maternal nutrition. *J Dev Orig Health Dis.* 2013; 4:101–115. [PubMed: 25054676]
48. Rebholz SL, Burke KT, Yang Q, et al. Dietary fat impacts fetal growth and metabolism: uptake of chylomicron remnant core lipids by the placenta. *Am J Physiol Endocrinol Metab.* 2011; 301:E416–E425. [PubMed: 21586694]

49. Tyrrell J, Richmond RC, Palmer TM, et al. Genetic evidence for causal relationships between maternal obesity-related traits and birth weight. *JAMA*. 2016; 315:1129–1140. [PubMed: 26978208]
50. Li N, Liu E, Guo J, et al. Maternal prepregnancy body mass index and gestational weight gain on offspring overweight in early infancy. *PLoS One*. 2013; 8:e77809. [PubMed: 24204979]
51. Shin D, Song WO. Prepregnancy body mass index is an independent risk factor for gestational hypertension, gestational diabetes, preterm labor, and small- and large-for-gestational-age infants. *J Matern Fetal Neonatal Med*. 2015; 28:1679–1686. [PubMed: 25211384]
52. Higgins L, Greenwood SL, Wareing M, et al. Obesity and the placenta: a consideration of nutrient exchange mechanisms in relation to aberrant fetal growth. *Placenta*. 2011; 32:1–7. [PubMed: 21030077]
53. Carmichael SL, Rasmussen SA, Shaw GM. Prepregnancy obesity: a complex risk factor for selected birth defects. *Birth Defects Res. A Clin Mol Teratol*. 2010; 88:804–810.
54. Stothard KJ, Tennant PW, Bell R, Rankin J. Maternal overweight and obesity and the risk of congenital anomalies: a systematic review and meta-analysis. *JAMA*. 2009; 301:636–650. [PubMed: 19211471]
55. Waller DK, Shaw GM, Rasmussen SA, et al. Prepregnancy obesity as a risk factor for structural birth defects. *Arch Pediatr Adolesc Med*. 2007; 161:745–750. [PubMed: 17679655]
56. Blomberg MI, Kallen B. Maternal obesity and morbid obesity: the risk for birth defects in the offspring. *Birth Defects Res A Clin Mol Teratol*. 2010; 88:35–40. [PubMed: 19711433]
57. Waller DK, Tita AT, Werler MM, Mitchell AA. Association between prepregnancy maternal body mass index and the risk of having an infant with a congenital diaphragmatic hernia. *Birth Defects Res A Clin Mol Teratol*. 2003; 67:73–76. [PubMed: 12749387]
58. Kimmons JE, Blanck HM, Tohill BC, et al. Associations between body mass index and the prevalence of low micronutrient levels among US adults. *MedGenMed*. 2006; 8:59.
59. Mojtabai R. Body mass index and serum folate in childbearing age women. *Eur J Epidemiol*. 2004; 19:1029–1036. [PubMed: 15648596]
60. Becerra JE, Khoury MJ, Cordero JF, Erickson JD. Diabetes mellitus during pregnancy and the risks for specific birth defects: a population-based case-control study. *Pediatrics*. 1990; 85:1–9. [PubMed: 2404255]
61. Fine EL, Horal M, Chang TI, et al. Evidence that elevated glucose causes altered gene expression, apoptosis, and neural tube defects in a mouse model of diabetic pregnancy. *Diabetes*. 1999; 48:2454–2462. [PubMed: 10580436]
62. Loeken MR. Free radicals and birth defects. *J Matern Fetal Neonatal Med*. 2004; 15:6–14. [PubMed: 15101606]
63. Herrera E. Metabolic adaptations in pregnancy and their implications for the availability of substrates to the fetus. *Eur J Clin Nutr*. 2000; 54(Suppl 1):S47–S51. [PubMed: 10805038]
64. Metzger BE, Persson B, Lowe LP, et al. Hyperglycemia and adverse pregnancy outcome study: neonatal glycemia. *Pediatrics*. 2010; 126:e1545–e1552. [PubMed: 21078733]
65. Catalano PM, Presley L, Minium J, Hauguel-de Mouzon S. Fetuses of obese mothers develop insulin resistance in utero. *Diabetes Care*. 2009; 32:1076–1080. [PubMed: 19460915]
66. Nicholas LM, Morrison JL, Rattanatrak L, et al. Differential effects of exposure to maternal obesity or maternal weight loss during the periconceptional period in the sheep on insulin signalling molecules in skeletal muscle of the offspring at 4 months of age. *PLoS One*. 2013; 8:e84594. [PubMed: 24386400]
67. Rattanatrak L, MacLaughlin SM, Kleemann DO, et al. Impact of maternal periconceptional overnutrition on fat mass and expression of adipogenic and lipogenic genes in visceral and subcutaneous fat depots in the postnatal lamb. *Endocrinology*. 2010; 151:5195–5205. [PubMed: 20861234]
68. Steculorum SM, Bouret SG. Maternal diabetes compromises the organization of hypothalamic feeding circuits and impairs leptin sensitivity in offspring. *Endocrinology*. 2011; 152:4171–4179. [PubMed: 21862611]

- 69■■■. Gaillard R. Maternal obesity during pregnancy and cardiovascular development and disease in the offspring. *Eur J Epidemiol.* 2015; 30:1141–1152. Recent review addressing the relationship between maternal obesity and offspring cardiovascular development. [PubMed: 26377700]
70. Ferretti G, Cester AM, Bacchetti T, et al. Leptin and paraoxonase activity in cord blood from obese mothers. *J Matern Fetal Neonatal Med.* 2014; 27:1353–1356. [PubMed: 24147648]
71. Catalano PM, Farrell K, Thomas A, et al. Perinatal risk factors for childhood obesity and metabolic dysregulation. *Am J Clin Nutr.* 2009; 90:1303–1313. [PubMed: 19759171]
72. Gaillard R, Steegers EA, Duijts L, et al. Childhood cardiometabolic outcomes of maternal obesity during pregnancy: the Generation R Study. *Hypertension.* 2014; 63:683–691. [PubMed: 24379180]
73. Yu Z, Han S, Zhu J, et al. Prepregnancy body mass index in relation to infant birth weight and offspring overweight/obesity: a systematic review and meta-analysis. *PLoS One.* 2013; 8:e61627. [PubMed: 23613888]
74. Wen LM, Rissel C, Baur LA, et al. A 3-Arm randomised controlled trial of Communicating Healthy Beginnings Advice by Telephone (CHAT) to mothers with infants to prevent childhood obesity. *BMC Public Health.* 2017; 17:79. [PubMed: 28088203]
75. Yang Z, Huffman SL. Nutrition in pregnancy and early childhood and associations with obesity in developing countries. *Matern Child Nutr.* 2013; 9(Suppl 1):105–119. [PubMed: 23167588]
76. Kral JG, Biron S, Simard S, et al. Large maternal weight loss from obesity surgery prevents transmission of obesity to children who were followed for 2 to 18 years. *Pediatrics.* 2006; 118:e1644–1649. [PubMed: 17142494]
77. Patro B, Liber A, Zalewski B, et al. Maternal and paternal body mass index and offspring obesity: a systematic review. *Ann Nutr Metab.* 2013; 63:32–41. [PubMed: 23887153]
78. Prior LJ, Davern PJ, Burke SL, et al. Exposure to a high-fat diet during development alters leptin and ghrelin sensitivity and elevates renal sympathetic nerve activity and arterial pressure in rabbits. *Hypertension.* 2014; 63:338–345. [PubMed: 24191287]
79. Samuelsson AM, Matthews PA, Argenton M, et al. Diet-induced obesity in female mice leads to offspring hyperphagia, adiposity, hypertension, and insulin resistance: a novel murine model of developmental programming. *Hypertension.* 2008; 51:383–392. [PubMed: 18086952]
80. Alfaradhi MZ, Fernandez-Twinn DS, Martin-Gronert MS, et al. Oxidative stress and altered lipid homeostasis in the programming of offspring fatty liver by maternal obesity. *Am J Physiol Regul Integr Comp Physiol.* 2014; 307:R26–R34. [PubMed: 24789994]
81. Martin-Gronert MS, Fernandez-Twinn DS, Poston L, Ozanne SE. Altered hepatic insulin signalling in male offspring of obese mice. *J Dev Orig Health Dis.* 2010; 1:184–191. [PubMed: 25141786]
82. Carter R, Mouralidarane A, Soeda J, et al. Nonalcoholic fatty pancreas disease pathogenesis: a role for developmental programming and altered circadian rhythms. *PLoS One.* 2014; 9:e89505. [PubMed: 24657938]
83. Casas M, Chatzi L, Carsin AE, et al. Maternal prepregnancy overweight and obesity, and child neuropsychological development: two Southern European birth cohort studies. *Int J Epidemiol.* 2013; 42:506–517. [PubMed: 23569191]
84. Grissom NM, Herdt CT, Desilets J, et al. Dissociable deficits of executive function caused by gestational adversity are linked to specific transcriptional changes in the prefrontal cortex. *Neuropsychopharmacology.* 2015; 40:1353–1363. [PubMed: 25418810]
85. Dhar M, Zhu M, Impey S, et al. Leptin induces hippocampal synaptogenesis via CREB-regulated microRNA-132 suppression of p250GAP. *Mol Endocrinol.* 2014; 28:1073–1087. [PubMed: 24877561]
86. Walker CD, Naef L, d'Asti E, et al. Perinatal maternal fat intake affects metabolism and hippocampal function in the offspring: a potential role for leptin. *Ann N Y Acad Sci.* 2008; 1144:189–202. [PubMed: 19076377]

KEY POINTS

- Obesity affects more than one-third of reproductive age women in the United States, and the prevalence of obesity has doubled among reproductive aged women from 1976 to 2004.
- Overweight and obese women exhibit metabolic dysfunction that is characterized by hypercholesterolemia hyperglycemia and insulin resistance, in turn creating a chronic low-grade metabolic inflammatory state, leading to endocrine dysfunction and subfertility.
- Maternal over or under nutrition and environmental exposures may irrevocably 'program' fetal pathophysiology and increase risk of certain adult onset diseases such as cardiovascular disease, diabetes and malignancies.

Table 1

Risk of congenital anomalies among obese gravida

Congenital anomaly	Odds ratio	95% Confidence interval
Neural tube defects	1.87	1.62–2.15
Cardiovascular anomalies	1.30	1.12–1.51
Cleft lip and palate	1.20	1.03–1.40
Anorectal atresia	1.48	1.12–1.97
Esophageal atresia	1.27	0.6–2.67
Hydrocephaly	1.68	1.19–2.36
Limb reduction anomalies	1.34	1.03–1.73
Diaphragmatic hernia	1.28	0.95–1.71
Gastroschisis	0.17	0.10–0.30

Data from [54].