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Current knowledge of obesity's effects in the pre- and periconceptional periods, and avenues for future research

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Abstract

The prevalence of obesity is growing among reproductive age women. This is concerning as obesity has significant health related consequences. Aside from long term risks of diabetes, heart disease, and some types of cancer, obesity poses immediate threats for young women including subfertility and adverse early and late pregnancy outcomes. Epidemiologic and experimental studies demonstrate associations between pre-pregnancy obesity and poor reproductive outcomes, however, the mechanisms involved are poorly understood. We discuss current knowledge of the pathophysiology of obesity in early reproductive events and how these events may affect reproductive outcomes including fertility, and miscarriage risk. We also discuss avenues for future research and interventions to improve reproductive outcomes for obese women.

Key words/phrases

embryo; fertility; obesity; oocyte; ovulation

I. Introduction

Almost a quarter of reproductive age women in the United States are obese with a body mass index of 30 kg/m^2 or greater[1]. This figure is worrisome as obesity may jeopardize long term health with increased risks of type II diabetes, cardiovascular disease, and some types of cancer[2]. Of more immediate concern for reproductive age women, obesity is associated with increased risks of subfertility[3–5].For those who do conceive, obesity has been associated with increased risks of miscarriage[6], preeclampsia[7, 8], and congenital anomalies in the offspring[9]. Of further concern, emerging evidence suggests that children born to obese mothers are at increased risk for obesity[10–12], type II diabetes[13], and cardiovascular disease later in life[14], perhaps the result of epigenetic modification of the embryonic genome in response to the alterations of the in utero environment in the setting of maternal obesity[14] (Table 1).

Interventions aimed at improving reproductive outcomes for obese pregnant women often focus on limiting weight gain during pregnancy[15], however, many of the risks of obesity in pregnancy may be linked to abnormalities in reproductive events occurring pre-conceptionally and early in pregnancy including abnormalities in events of oocyte

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recruitment and development, ovulation, pre-implantation embryonic development, and implantation[16–18]. While managing weight gain during pregnancy may be helpful in preventing some adverse outcomes in obese pregnancy[19], such intervention does not address abnormalities in events which have already occurred. Accordingly, increased intervention for weight loss and increased efforts in counseling of the risks of obesity to reproductive potential and outcome should also be undertaken by clinicians working with reproductive age women. For obese women who do conceive, research elucidating the pathophysiology of obesity in early reproductive events may help shed light on effective interventions for preventing the adverse pregnancy outcomes that weight management in pregnancy has not been able to address.

II. Obesity and ovulation

Increased incidence of subfertility among obese women may be attributed in part to the frequent co-occurrence of obesity with polycystic ovary syndrome (PCOS)[20]—a relatively common condition characterized by hyperandrogenism and anovulation, and associated with insulin resistance[21, 22]. PCOS is not uncommon in women of normal weight, however, in obese women insulin resistance may lead to clinical features consistent with PCOS[23, 24]. Insulin resistance and hyperinsulinemia consequent of obesity hamper hepatic production of steroid hormone binding globulin (SHBG) with subsequent hyperandrogenemia. Lower SHBG levels and increased peripheral aromatization of androgens to estrogens in obese women also result in higher free circulating estrogen levels which may lead to increased negative feedback on the hypothalamic-pituitary axis. This increased negative feedback adversely affects the gonadotropin secretion needed for adequate ovarian follicular recruitment and subsequent ovulation[24–27]. Weight loss among obese women with PCOS often helps in restoring ovulation and improving chances of conception[28, 29].

Independent of PCOS, obesity is associated with abnormalities of the hypothalamic-pituitary-ovarian (HPO) axis that may affect the quality of follicular development and ovulation[26, 30, 31]. As a consequence, fertility is decreased even among obese women with regular menses[3, 32]. In a large study of women participating in the Study of Women's Health Across the Nation (SWAN) study, a body mass index increasing over 25 kg/m^2 was associated with a longer follicular phase and a shortened luteal phase[26]. Further detailed study conducted by some of the same researchers demonstrated decreased LH amplitude and mean serum LH levels in cycling obese women compared to women of normal weight possibly leading to a shortened luteal phase[30, 31]. While the concept and definition of the luteal phase deficiency and its role in fertility have long been debated, shorter luteal phases theoretically could affect endometrial development and subsequent embryo implantation[33]. If this problem did exist in obese women, it could explain in part findings demonstrating that obesity may be associated with increased risk of miscarriage in spontaneous conceptions[6] and decreased embryonic implantation rates in obese women receiving donor oocytes after in vitro fertilization (IVF)[34].

The mechanism responsible for the observed decreased LH pulse amplitude in obese women is unknown. Several theories exist including interference of adipokine hormones, or hormones made by adipose tissue, including leptin, TNF-alpha, or interleukin-1beta, with the pituitary response to GnRH[23, 30, 31, 35, 36]. While some work has been done to look at the effects of obesity on the HPO axis and infertility in animal models, further work examining these relationships in women are needed[37].

III. Obesity and the oocyte

Insight into the importance of maternal physiology on oocyte quality can be demonstrated in experimental animal models of maternal diabetes where there is an increase in granulosa cell

apoptosis of the ovarian follicle and impaired oocyte maturation[15, 16, 38]. Similar to diabetes, obesity is a condition marked by aberrations in circulating levels of substrates for energy production and it too appears to have effects on oocyte quality. Visually these effects appear to be primarily on oocyte maturation[39–41] although there is data suggesting that even subjectively normal oocytes are altered at the molecular level by conditions like PCOS[42]. These alterations are in genes associated with chromosome alignment and segregation during mitosis and/or meiosis and in genes associated with peroxisome proliferator-activated receptors—receptors important to cellular growth and development in the fetus[43] and known to be activated by thiazolidinedione drugs. Thiazolidinedione drugs have been shown to improve oocyte competence as measured by embryonic development in mouse models of maternal obesity[44] and to induce ovulation in women with PCOS[45].

There are a variety of factors that may impair oocyte maturation in obese women including abnormalities in ovarian follicular recruitment and development due to blunted LH amplitude as discussed above[26, 31]. On the other hand, there is evidence that the follicular environment in which the oocyte develops and matures is altered in obese women compared to non-obese women. Because these differences are noted in women undergoing IVF where exogenous gonadotropins are used to achieve follicular recruitment and development, it is unlikely that the abnormalities are the result of obesity-related HPO-axis dysfunction. Instead, it may be that some component of obesity alters composition of the follicular fluid directly which could influence oocyte metabolism or metabolism of the cells that support the developing oocyte and follicle including granulosa cells, cumulus cells and theca cells[46]. Changes in metabolism of these cells could further alter the composition of follicular fluid. Alterations noted in follicular fluid from obese women include increased insulin, glucose and lactate, increased androgen activity, increased C-reactive protein, and decreased hCG levels[47, 48]. There is also evidence that follicular leptin levels correlate with BMI[49]. In vitro studies have shown that leptin impairs steroidogenesis in granulosa cells[50, 51], and such an impairment could also impact follicular development, oocyte quality and ovulation in obese women[52].

Further work is needed to determine how oocyte quality specifically influences pregnancy outcome for obese women, however as mentioned, data from animal models of obesity and type I diabetes mellitus demonstrate that poor maternal physiology affects oocyte quality. In the case of type I diabetes, these affected oocytes predispose to increased risks of fetal abnormalities including congenital anomalies and fetal growthrestriction[15, 17] perhaps via adverse effects on the meiotic spindle of the oocyte or on mitochondrial structure and function[53]. Like diabetes, obesity is also a condition of abnormal maternal physiology. While laboratory evidence supports a role for poor oocyte quality as a factor in adverse reproductive outcomes in the setting of obesity[41], clinical evidence is lacking.

One avenue to consider exploring for additional information regarding relationships between oocytes and pregnancy outcome is data from donor oocyte cycles in clinical in vitro fertilization (IVF) practice. One published abstract suggests donor oocytes taken from obese women do not affect live birth rates in recipient women of normal weight, however, the numbers of patients included in the study were too small (64 IVF cycles using oocytes from normal weight women vs. 8 IVF cycles using oocytes from donors who were obese) to adequately control for potential confounding factors[54]. On the other hand, some IVF centers may restrict oocyte donation to women of normal weight[55] as overweight and obese women are known to require additional gonadotropin stimulation in their IVF cycles and they often produce fewer oocytes which can increase the cost of an IVF cycle[56]. Because of this exclusion it may be difficult to find existing data to explore this question further. National IVF databases such as those compiled by the Society for Assisted Reproductive Technology may provide adequate numbers for future study and are worth pursuing.

IV. Obesity and the embryo

Embryo quality is affected by poor oocyte quality and this may be an issue for obese women. This has been documented clinically in obese women undergoing IVF where embryos derived from oocytes fertilized in vitro are of poorer quality than of those derived from normal weight women[48, 57]. On the other hand, IVF studies investigating embryo quality in obese women are conflicting and their findings on embryo quality may not reflect what truly happens in spontaneous conceptions[58]. Another issue to consider is the contribution of sperm to embryo quality. Obesity is known to affect sperm quality, however, there is very little evidence to illustrate how sperm quality in obese men relates embryo quality or pregnancy outcome[59].

Aside from the contributions gametes may make to embryo quality after fertilization occurs, the pre-implantation embryo itself is particularly vulnerable to metabolic insult. Study of human embryos from spontaneous conception is obviously difficult; however, experimental animal models provide an alternate mechanism for studying the effects of maternal obesity on early conception and pregnancy outcomes. In one such example, pre-implantation embryos subjected to conditions of maternal insulin resistance demonstrated decreased insulin-stimulated glucose uptake and increased apoptosis[60]. When these embryos were transferred into normal surrogates, resulting pregnancies were associated with increased miscarriage rates and growth abnormalities in resulting offspring suggesting lasting developmental programming at the pre-implantation stage of development[17, 61].

Recent work suggests abnormalities in offspring stemming from metabolic insults at the pre-implantation embryonic stage of development may occur as a result of alterations in embryonic mitochondrial physiology[62], or in epigenetic modifications like embryonic allelic expression of imprinted genes associated with growth like Igf2[63, 64]. Epigenetic modifications of the genome at this stage of development are generally stable for a lifetime providing an explanation for the long-term influence of such insults on health of the offspring later in life[65].

V. Obesity and early pregnancy

In addition to increased risks of congenital anomalies, preeclampsia, gestational diabetes, and stillbirth among obese pregnant women[8, 9, 66–68], there is also data to suggest risk of miscarriage is increased among obese women[69]. This association is difficult to study though as many spontaneously pregnant women are not followed closely in early pregnancy and may not ever present for care if they experience a miscarriage. Women undergoing infertility treatment may offer more information regarding adverse pregnancy outcomes like miscarriage as they tend to be followed very closely in early pregnancy. Overall, it appears that miscarriage risk is increased among obese women undergoing fertility treatment, however, data regarding the risk of miscarriage among women undergoing specific types of fertility treatment are not entirely clear yet[6].

When considering mechanisms that could influence early pregnancy among obese women, it is conceivable that obesity's effects on the oocyte or embryo could affect the embryo's potential for development. Additionally, it is possible that obesity imparts a negative influence on the endometrium influencing the risk of miscarriage. Supporting this concept, it appears that the endometrium is responsive to hormones influenced by obesity including insulin and adipokines such as leptin and adiponectin[70–73]. Furthermore, data from obese women receiving oocytes for IVF from healthy women shows obese women experience increased risks of miscarriage compared to normal weight recipients[6] although data demonstrating increased miscarriage rates after IVF in obese women using their own oocytes are insufficient in that most are retrospective, underpowered, and fail to include

information to adequately account for potentially confounding factors[6, 56, 74]. If the endometrium and subsequent implantation are affected by obesity, it is possible this could also influence the development of other pathologies related to implantation including preeclampsia.

VI. Limitations of current evidence and future avenues for research

The bulk of the current data available investigating relationships between obesity and oocytes and early reproduction in spontaneous conception are restricted to work in animal models and a small amount of clinical data from obese women undergoing in vitro fertilization (Table 2). Unfortunately, the available clinical data is limited in that most women undergoing IVF are treated with gonadotropins. Drug regimens and protocols, and response to drugs may vary from patient to patient with many obese women requiring larger amounts of gonadotropin stimulation to achieve mature ovarian follicles prior to undergoing ultrasound-guided follicular aspiration[56]. These variations in stimulation protocols could potentially affect ovarian follicles and their content, and the resulting oocytes independent of one's BMI[75].

Another limitation of data derived from women undergoing IVF is that complete investigation of the oocyte would require destruction of the oocyte making it difficult to justify studies of oocytes from women undergoing IVF for procreative management. Instead we are often left using surrogate markers of oocyte quality including subjective measures like direct visualization of nuclear maturation, grading of embryo quality after fertilization, and more objective measures like fertilization rate and pregnancy rates after IVF. The problem with the latter measure is that it relies on other factors including competence of the sperm to fertilize the oocytes, quality of the embryo culture, and endometrial receptivity.

One final limitation of data derived from women undergoing IVF is that pregnancy rates in IVF pregnancy may be improved over those in spontaneous conception because multiple embryos are often transferred (single embryo transfer is not common in the United States[9]), and these embryos are chosen for their superior morphological characteristics compared to others in the cohort. Because of laboratory intervention, it is conceivable that early pregnancy outcomes among obese women conceiving via IVF are improved over those conceiving spontaneously as only one embryo is typically "available" in spontaneous conception[6], although the effects of obesity on later pregnancy outcomes may be more difficult to tease out in this population. Data from obese women receiving donor oocytes from normal weight women may allow for further elucidation of the effects of obesity at later, post-implantation events in the reproductive process. Potential questions to explore in these patients include whether or not pregnancy rates among these women are the same as they are in obese women receiving embryos created from their own oocytes when controlling for other factors. Also, are rates of miscarriage, preeclampsia and other adverse pregnancy outcomes the same among these women? Studies of this nature are difficult to perform at one center because numbers of patients may be limited, however, collaboration among multiple participating centers and disciplines would allow such work to take place.

While IVF data is limited, as discussed, it does provide unique opportunity for further investigation of adverse effects of obesity on reproduction and interventions that have not been fully explored. Unlike spontaneous conception, IVF allows the opportunity to follow a woman from the pre-conceptional period to the peri-conceptional period. Tissue specimens and laboratory data are available at these time points that are not available in spontaneous conception. With cooperation and organization, collaboration between reproductive endocrinologists and obstetricians following these women in pregnancy allows for continued monitoring and data and specimen collection throughout pregnancy and delivery. The

opportunity to follow offspring of these pregnancies also exists. In the past most studies of IVF offspring has focused on IVF's affects on offspring health, however, future studies may take advantage of the availability of maternal specimens and data available in the pre- and peri-conceptional periods to focus on the affects of maternal physiology on reproductive outcomes and the health of offspring.

Obese women undergoing IVF also provide opportunity to see the influence of different pharmacologic interventions on oocyte quality, embryo health, and pregnancy outcomes. Some possible interventions to explore further in this population include IVF pretreatment with insulin-sensitizing agents such as metformin or PPAR agonists like rosiglitazone investigating not just IVF and obstetrical outcomes, but also looking into changes in composition of follicular fluid and function of retrieved granulosa cells as there are animal studies showing improvements in oocyte quality, embryo quality and pregnancy outcomes with such treatment[44, 76]. Not only would this type of work provide improved insight on the effects of obesity on early reproduction and subsequent pregnancy outcomes, but it would also provide mechanistic information to address debate in clinical literature regarding use of these agents in populations of anovulatory obese women with PCOS to optimize outcomes for these women[77, 78].

In considering obesity and its effects on reproduction, it is important to recognize that most obese women experience normal fertility and favorable reproductive outcomes. Further investigations into the underlying mechanisms responsible for poor reproductive outcomes in obese women will help to identify which obese women are particularly at risk for poor reproductive outcomes whether it be women who have developed other obesity related health issues like insulin resistance, PCOS, or metabolic syndrome, or whether it be women with some other underlying process that has yet to be discovered. Such investigations will also bring us closer to improving reproductive outcomes women who are at risk.

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References

1. Vahratian A. Prevalence of overweight and obesity among women of childbearing age: results from the 2002 National Survey of Family Growth. Matern Child Health J. 2009; 13:268–273. [PubMed: 18415671]
2. Flegal KM, Graubard BI, Williamson DF, Gail MH. Cause-specific excess deaths associated with underweight, overweight, and obesity. JAMA. 2007; 298:2028–2037. [PubMed: 17986696]
3. Gesink Law DC, Maclehose RF, Longnecker MP. Obesity and time to pregnancy. Hum Reprod. 2007; 22:414–420. [PubMed: 17095518]
4. Ramlau-Hansen CH, Thulstrup AM, Nohr EA, Bonde JP, Sorensen TI, Olsen J. Subfecundity in overweight and obese couples. Hum Reprod. 2007; 22:1634–1637. [PubMed: 17344224]
5. Wise LA, Rothman KJ, Mikkelsen EM, Sorensen HT, Riis A, Hatch EE. An internet-based prospective study of body size and time-to-pregnancy. Hum Reprod. 25:253–264. [PubMed: 19828554]
6. Metwally M, Ong KJ, Ledger WL, Li TC. Does high body mass index increase the risk of miscarriage after spontaneous and assisted conception? A meta-analysis of the evidence. Fertil Steril. 2008; 90:714–726. [PubMed: 18068166]
7. O'Brien TE, Ray JG, Chan WS. Maternal body mass index and the risk of preeclampsia: a systematic overview. Epidemiology. 2003; 14:368–374. [PubMed: 12859040]

8. Dokras A, Baredziak L, Blaine J, Syrop C, VanVoorhis BJ, Sparks A. Obstetric outcomes after in vitro fertilization in obese and morbidly obese women. Obstet Gynecol. 2006; 108:61–69. [PubMed: 16816057]
9. 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]
10. Chang GQ, Gaysinskaya V, Karatayev O, Leibowitz SF. Maternal high-fat diet and fetal programming: increased proliferation of hypothalamic peptide-producing neurons that increase risk for overeating and obesity. J Neurosci. 2008; 28:12107–12119. [PubMed: 19005075]
11. 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]
12. Nohr EA, Timpson NJ, Andersen CS, Davey Smith G, Olsen J, Sorensen TI. Severe obesity in young women and reproductive health: the Danish National Birth Cohort. PLoS One. 2009; 4:e8444. [PubMed: 20041193]
13. 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]
14. Symonds ME, Sebert SP, Hyatt MA, Budge H. Nutritional programming of the metabolic syndrome. Nat Rev Endocrinol. 2009; 5:604–610. [PubMed: 19786987]
15. Chang AS, Dale AN, Moley KH. Maternal diabetes adversely affects preovulatory oocyte maturation, development, and granulosa cell apoptosis. Endocrinology. 2005; 146:2445–2453. [PubMed: 15718275]
16. Jungheim ES, Moley KH. The impact of type 1 and type 2 diabetes mellitus on the oocyte and the preimplantation embryo. Semin Reprod Med. 2008; 26:186–195. [PubMed: 18302110]
17. Wyman A, Pinto AB, Sheridan R, Moley KH. One-cell zygote transfer from diabetic to nondiabetic mouse results in congenital malformations and growth retardation in offspring. Endocrinology. 2008; 149:466–469. [PubMed: 18039778]
18. Norman RJ, Chura LR, Robker RL. Effects of obesity on assisted reproductive technology outcomes. Fertil Steril. 2008; 89:1611–1612. [PubMed: 17548073]
19. Artal R, Lockwood CJ, Brown HL. Weight gain recommendations in pregnancy and the obesity epidemic. Obstet Gynecol. 115:152–155. [PubMed: 20027048]
20. Alvarez-Blasco F, Botella-Carretero JI, San Millan JL, EscobarMorreale HF. Prevalence and characteristics of the polycystic ovary syndrome in overweight and obese women. Arch Intern Med. 2006; 166:2081–2086. [PubMed: 17060537]
21. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. Fertil Steril. 2004; 81:19–25.
22. Azziz R, Carmina E, Dewailly D, et al. The Androgen Excess and PCOS Society criteria for the polycystic ovary syndrome: the complete task force report. Fertil Steril. 2009; 91:456–488. [PubMed: 18950759]
23. Yildiz BO, Azziz R. Ovarian and adipose tissue dysfunction in polycystic ovary syndrome: report of the 4th special scientific meeting of the Androgen Excess and PCOS Society. Fertil Steril. 2009
24. Chang, RJ. Polycystic Ovary Syndrome and Hyperandtrogenic States. In: Strauss; Barbieri, editors. Yen and Jaffe's Reproductive Endocrinology. Philadelphia: Saunders; 2009.
25. Nestler JE. Obesity, insulin, sex steroids and ovulation. Int J Obes Relat Metab Disord. 2000; 24(Suppl 2):S71–S73. [PubMed: 10997613]
26. Santoro N, Lasley B, McConnell D, et al. Body size and ethnicity are associated with menstrual cycle alterations in women in the early menopausal transition: The Study of Women's Health across the Nation (SWAN) Daily Hormone Study. J Clin Endocrinol Metab. 2004; 89:2622–2631. [PubMed: 15181033]
27. Rachon D, Teede H. Ovarian function and obesity--interrelationship, impact on women's reproductive lifespan and treatment options. Mol Cell Endocrinol. 316:172–179. [PubMed: 19818376]
28. Norman RJ, Dewailly D, Legro RS, Hickey TE. Polycystic ovary syndrome. Lancet. 2007; 370:685–697. [PubMed: 17720020]

29. Teitelman M, Grotegut CA, Williams NN, Lewis JD. The impact of bariatric surgery on menstrual patterns. Obes Surg. 2006; 16:1457–1463. [PubMed: 17132411]
30. Helm, KD.; Ness, RM.; Evans, WS. Physiologic and Pathophysiologic Alternations of the Neuroendocrine Components of the Reproductive Axis. In: Strauss; Barbieri, editors. Yen and Jaffe's Reproductive Endocrinology. Philadelphia: Saunders; 2009.
31. 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]
32. 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]
33. Speroff; Fritz. Clinical Gynecologic Endocrinoology and Infertility. Philadelphia: Lippincott Williams & Wilkins; 2005.
34. Dessolle L, Darai E, Cornet D, et al. Determinants of pregnancy rate in the donor oocyte model: a multivariate analysis of 450 frozen-thawed embryo transfers. Hum Reprod. 2009; 24:3082–3089. [PubMed: 19726449]
35. Fenichel RM, Dominguez JE, Mayer L, Walsh BT, Boozer C, Warren MP. Leptin levels and luteinizing hormone pulsatility in normal cycling women and their relationship to daily changes in metabolic rate. Fertil Steril. 2008; 90:1161–1168. [PubMed: 18304548]
36. Moschos S, Chan JL, Mantzoros CS. Leptin and reproduction: a review. Fertil Steril. 2002; 77:433–444. [PubMed: 11872190]
37. Tortoriello DV, McMinn J, Chua SC. Dietary-induced obesity and hypothalamic infertility in female DBA/2J mice. Endocrinology. 2004; 145:1238–1247. [PubMed: 14670988]
38. Ratchford AM, Chang AS, Chi MM, Sheridan R, Moley KH. Maternal diabetes adversely affects AMP-activated protein kinase activity and cellular metabolism in murine oocytes. Am J Physiol Endocrinol Metab. 2007; 293:E1198–E1206. [PubMed: 17684106]
39. Wittemer C, Ohl J, Bailly M, Bettahar-Lebugle K, Nisand I. Does body mass index of infertile women have an impact on IVF procedure and outcome? J Assist Reprod Genet. 2000; 17:547–552. [PubMed: 11209534]
40. Robker RL. Evidence that obesity alters the quality of oocytes and embryos. Pathophysiology. 2008; 15:115–121. [PubMed: 18599275]
41. Jungheim ES, Schoeller EL, Marquard KL, Louden ED, Schaffer JE, Moley KH. Diet induced obesity model: Abnormal oocytes and persistent growth abnormalities in the offspring. Endocrinology. 2010 Accepted for publication.
42. Wood JR, Dumesic DA, Abbott DH, Strauss JF 3rd. Molecular abnormalities in oocytes from women with polycystic ovary syndrome revealed by microarray analysis. J Clin Endocrinol Metab. 2007; 92:705–713. [PubMed: 17148555]
43. Rees WD, McNeil CJ, Maloney CA. The Roles of PPARs in the Fetal Origins of Metabolic Health and Disease. PPAR Res. 2008; 2008:459030. [PubMed: 18288289]
44. Minge CE, Bennett BD, Norman RJ, Robker RL. Peroxisome proliferatoractivated receptor-gamma agonist rosiglitazone reverses the adverse effects of diet-induced obesity on oocyte quality. Endocrinology. 2008; 149:2646–2656. [PubMed: 18276752]
45. Azziz R, Ehrmann D, Legro RS, et al. Troglitazone improves ovulation and hirsutism in the polycystic ovary syndrome: a multicenter, double blind, placebo-controlled trial. J Clin Endocrinol Metab. 2001; 86:1626–1632. [PubMed: 11297595]
46. Sutton-McDowall ML, Gilchrist RB, Thompson JG. The pivotal role of glucose metabolism in determining oocyte developmental competence. Reproduction. 139:685–695. [PubMed: 20089664]
47. 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]
48. Carrell DT, Jones KP, Peterson CM, Aoki V, Emery BR, Campbell BR. Body mass index is inversely related to intrafollicular HCG concentrations, embryo quality and IVF outcome. Reprod Biomed Online. 2001; 3:109–111. [PubMed: 12513872]

49. Hill MJ, Uyehara CF, Hashiro GM, Frattarelli JL. The utility of serum leptin and follicular fluid leptin, estradiol, and progesterone levels during an in vitro fertilization cycle. J Assist Reprod Genet. 2007; 24:183–188. [PubMed: 17333366]
50. Lin Q, Poon SL, Chen J, Cheng L, HoYuen B, Leung PC. Leptin interferes with 3',5'-cyclic adenosine monophosphate (cAMP) signaling to inhibit steroidogenesis in human granulosa cells. Reprod Biol Endocrinol. 2009; 7:115. [PubMed: 19849856]
51. Mantzoros CS. Role of leptin in reproduction. Ann N Y Acad Sci. 2000; 900:174–183. [PubMed: 10818404]
52. Brannian JD, Hansen KA. Leptin and ovarian folliculogenesis: implications for ovulation induction and ART outcomes. Semin Reprod Med. 2002; 20:103–112. [PubMed: 12087495]
53. Wang Q, Ratchford AM, Chi MM, et al. Maternal diabetes causes mitochondrial dysfunction and meiotic defects in murine oocytes. Mol Endocrinol. 2009; 23:1603–1612. [PubMed: 19574447]
54. Wu DHGD, Eckert J, Aubuchon M, Williams DB, Thomas MA. Oocyte donors' body mass index (BMI) confers no adverse effect on recipients' pregnancy outcomes. Fertil Steril. 2009; 92:A15–A77.
55. Obeso ISR, Galache P, Sepulveda J, Diaz P, Patrizi P. The impact of body mass index (BMI) on ovarian stimulation in young oocyte donors. Fertil Steril. 2009; 92:S103.
56. Jungheim ES, Lanzendorf SE, Odem RR, Moley KH, Chang AS, Ratts VS. Morbid obesity is associated with lower clinical pregnancy rates after in vitro fertilization in women with polycystic ovary syndrome. Fertil Steril. 2009; 92:256–261. [PubMed: 18692801]
57. Metwally M, Cutting R, Tipton A, Skull J, Ledger WL, Li TC. Effect of increased body mass index on oocyte and embryo quality in IVF patients. Reprod Biomed Online. 2007; 15:532–538. [PubMed: 18044034]
58. Bellver J, Ayllon Y, Ferrando M, et al. Female obesity impairs in vitro fertilization outcome without affecting embryo quality. Fertil Steril. 93:447–454. [PubMed: 19171335]
59. Hammoud AO, Gibson M, Peterson CM, Meikle AW, Carrell DT. Impact of male obesity on infertility: a critical review of the current literature. Fertil Steril. 2008; 90:897–904. [PubMed: 18929048]
60. Chi MM, Schlein AL, Moley KH. High insulin-like growth factor 1 (IGF-1) and insulin concentrations trigger apoptosis in the mouse blastocyst via down-regulation of the IGF-1 receptor. Endocrinology. 2000; 141:4784–4792. [PubMed: 11108294]
61. Pinto AB, Schlein AL, Moley KH. Preimplantation exposure to high insulin-like growth factor I concentrations results in increased resorption rates in vivo. Hum Reprod. 2002; 17:457–462. [PubMed: 11821295]
62. Chi MM, Hoehn A, Moley KH. Metabolic changes in the glucose-induced apoptotic blastocyst suggest alterations in mitochondrial physiology. Am J Physiol Endocrinol Metab. 2002; 283:E226–E232. [PubMed: 12110526]
63. Shao WJ, Tao LY, Gao C, Xie JY, Zhao RQ. Alterations in methylation and expression levels of imprinted genes H19 and Igf2 in the fetuses of diabetic mice. Comp Med. 2008; 58:341–346. [PubMed: 18724775]
64. Rivera RM, Stein P, Weaver JR, Mager J, Schultz RM, Bartolomei MS. Manipulations of mouse embryos prior to implantation result in aberrant expression of imprinted genes on day 9.5 of development. Hum Mol Genet. 2008; 17:1–14. [PubMed: 17901045]
65. Gluckman PD, Hanson MA, Cooper C, Thornburg KL. Effect of in utero and early-life conditions on adult health and disease. N Engl J Med. 2008; 359:61–73. [PubMed: 18596274]
66. Cedergren MI. Maternal morbid obesity and the risk of adverse pregnancy outcome. Obstet Gynecol. 2004; 103:219–224. [PubMed: 14754687]
67. ACOG Committee Opinion number 315, September 2005. Obesity in pregnancy. Obstet Gynecol. 2005; 106:671–675. [PubMed: 16135613]
68. Weiss JL, Malone FD, Emig D, et al. Obesity, obstetric complications and cesarean delivery rate--a population-based screening study. Am J Obstet Gynecol. 2004; 190:1091–1097. [PubMed: 15118648]

69. Lashen H, Fear K, Sturdee DW. Obesity is associated with increased risk of first trimester and recurrent miscarriage: matched case-control study. Hum Reprod. 2004; 19:1644–1646. [PubMed: 15142995]

70. Tanaka T, Umesaki N. Leptin regulates the proliferation and apoptosis of human endometrial epithelial cells. Int J Mol Med. 2008; 22:683–689. [PubMed: 18949391]

71. Gonzalez RR, Leavis P. Leptin upregulates beta3-integrin expression and interleukin-1beta, upregulates leptin and leptin receptor expression in human endometrial epithelial cell cultures. Endocrine. 2001; 16:21–28. [PubMed: 11822823]

72. Mozzanega B, Mioni R, Granzotto M, et al. Obesity reduces the expression of GLUT4 in the endometrium of normoinsulinemic women affected by the polycystic ovary syndrome. Ann N Y Acad Sci. 2004; 1034:364–374. [PubMed: 15731326]

73. von Wolff M, Ursel S, Hahn U, Steldinger R, Strowitzki T. Glucose transporter proteins (GLUT) in human endometrium: expression, regulation, and function throughout the menstrual cycle and in early pregnancy. J Clin Endocrinol Metab. 2003; 88:3885–3892. [PubMed: 12915684]

74. Obesity and reproduction: an educational bulletin. Fertil Steril. 2008; 90:S21–S29. [PubMed: 19007633]

75. Tamer Erel C, Senturk LM. The impact of body mass index on assisted reproduction. Curr Opin Obstet Gynecol. 2009; 21:228–235. [PubMed: 19395966]

76. Eng GS, Sheridan RA, Wyman A, et al. AMP kinase activation increases glucose uptake, decreases apoptosis, and improves pregnancy outcome in embryos exposed to high IGF-I concentrations. Diabetes. 2007; 56:2228–2234. [PubMed: 17575082]

77. Palomba S, Pasquali R, Orio F Jr, Nestler JE. Clomiphene citrate, metformin or both as first-step approach in treating anovulatory infertility in patients with polycystic ovary syndrome (PCOS): a systematic review of head-to-head randomized controlled studies and meta-analysis. Clin Endocrinol (Oxf). 2009; 70:311–321. [PubMed: 18691273]

78. Tang T, Lord JM, Norman RJ, Yasmin E, Balen AH. Insulin-sensitising drugs (metformin, rosiglitazone, pioglitazone, D-chiro-inositol) for women with polycystic ovary syndrome, oligo amenorrhoea and subfertility. Cochrane Database Syst. Rev:CD003053.

Table 1

Epidemiologic studies of adverse reproductive outcomes in obese women

Outcome	Odds Ratio	Reference	Type of study	Patients (n)
Subfertility	2.2 (95% CI: 1.8–2.6)	Nohr et al (12)	Prospective cohort	4901
Miscarriage	1.67 (95% CI: 1.25–2.25)	Metwally et al (6)	Meta-analysis	2257
Various fetal anomalies	1.2 (95% CI: 1.03–1.4, cleft lip and palate); 2.24 (95% CI: 1.86–2.69, spina bifida)	Stothard et al (9)	Meta-analysis	863; 1188
Large-for-gestational-age	2.3 (95% CI: 1.9–2.7)	Nohr et al (12)	Prospective cohort	4901
Preeclamspia	1.6 (95% CI: 1.1–2.25, obese vs. non-obese); 3.3 (95% CI: 2.4–4.5, morbidly obese vs. non-obese)	Weiss et al (68)	Prospective cohort	15,225; 14,629
Obesity in the offspring at age 1 (BMI ≥ 95th percentile)	1.9 (1.3–2.6)	Nohr et al (12)	Prospective cohort	4901

Table 2

Proposed mechanisms by which obesity may affect early stages of reproductive development

Stage of development	Proposed mechanism	Possible effects on reproduction	Evidence	References
Oocyte	Abnormal hypothalamic GnRH pulsatility; abnormal follicular environment	Poor oocyte quality; impaired ovulation	Human serum samples; human IVF specimens; animal specimens	Jain et al (31); Robker et al (40, 47); Jungheim et al (41)
Pre-implantation embryo	Poor oocyte quality; impaired embryonic metabolism and quality; epigenetic modification	Impaired implantation; miscarriage; fetal anomalies and growth abnormalities	Animal specimens; human IVF specimens	Jungheim et al (41); Carrell et al (48); Metwally et al (57); Eng et al (76)
Implantation	Abnormal endometrium	Impaired implantation; miscarriage; fetal growth abnormalities	Human endometrial biopsies	Mozzanega et al (72)