

An update of impact of obesity on female infertility and its management

Abstract

With the increase in worldwide incidence of obesity the incidence of obese infertile couples has significantly increased. Obesity has a significant effect on the outcomes of in vitro fertilization with clinical impact on oocytes, endometrium as well as preimplantation embryos. Also it takes longer time for stimulation with higher doses of gonadotropins, greater time for stimulation along with higher cancellation cycles raising the cost factor. Further obesity is associated with higher incidence of PCOS along with its metabolic sequelae. Pregnancy in obesity is further confounded with multiple complications like PIH, higher incidence of preterm labour, still birth incidence along with greater chances of caesarean delivery. Yet there is no certainty whether prior weight reduction therapies help in achieving better incidence of live birth rates with poor efficacy of currently available antiobesity therapies and even the most effective bariatric surgery. More studies are needed to develop better antiobesity drugs and study bariatric surgery with prospective trials for improving the understanding of effectiveness of obesity treatment prior to pregnancy.

Keywords: female infertility, obesity, HPO

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Introduction

Obesity is increasing worldwide having reached epidemic proportions globally with the increasing incidence one encounters more obese women in infertile clinics worldwide.¹⁻³ We have reviewed the aetiopathogenesis in our early reviews and how it impacts management. Here we further emphasize and update its effects on infertility treatment and further on management.⁴⁻⁷

Obesity has a negative effect on reproductive potential due to functional changes in the Hypothalamo-Pituitary-Ovarian (HPO) axis. Obesity is often associated with hyperinsulinemia, a known stimulus for increased androgen production.⁸ Androgens get converted to oestrogen (Og) in periphery namely in Adipose tissue (AT) present in excess=> negative feedback on the HPO axis and thus affecting gonadotropin production.⁹ This presents with menstrual abnormalities along with ovulatory dysfunction. Hyperinsulinemia is commonly found to be an aetiopathological factor of PCOS. Obesity contributes to insulin resistance (IR) and exacerbates the symptoms of PCOS with obese women often showing a more severe phenotype.^{10,11} Increased androgen levels in PCOS=> further accumulation of visceral fat accelerating IR and hyperinsulinemia and thus stimulating more ovarian as well as adrenal androgen production in a perceptual cycle.¹² Prevalence of PCOS in some obese populations approaches 30% although causative role of obesity in PCOS development has not been established.¹³⁻¹⁵ Various studies have shown that obese women take a longer time to conceive. In a Danish cohort of women planning pregnancies showed decrease in fecundity ratios with increasing BMI's.^{16,17} Obese women do not conceive despite not having ovulatory dysfunction. On examining a large American cohort of >7000 ladies, Law et al showed reduced fecundity in eumenorrhic obese women [18]. Further data given from a huge Danish cohort by van den Steer in 3000 ladies with normal cycles, probability of spontaneous conception reduced linearly with each BMI point >29kg/m².¹⁹ Obesity also affects ART results providing a direct scenario that the pathologies lie beyond the ovulatory disorder. Obese women who undergo IVF have smaller oocytes which are less likely to fertilize normally.^{20,21} Various studies have shown a negative impact on live

birth rates (LBR's) and this appears to correlate with increasing BMI.²¹⁻²⁴ In a review of ART in both overweight and obese women showed a modest impact on LBRs with a pooled odds ratio of 0.90 but in a large study of women with class III obesity (BMI >40KG/m²) there was a 50% reduced probability of live birth.^{21,25}

Effect on HPO axis

Animal models along with human studies show that obesity has an impact on the HPO axis. In mice model with DIO it was shown by Tortorello et al.²⁶ that there was a 60% reduction in natural pregnancy rates but that the defect could be overcome with the use of exogenous gonadotropins implicating a central mechanism.²⁶ The same group also engineered a mouse model with genetic mutations=> an obese and infertile phenotype independently from the diet. They found mice who were resistant to developing the phenotype had >levels of leptin receptors in the hypothalamus.²⁷ Obese women have greater levels of leptin, a cell signaling protein as compared to normal matched controls which might=> down regulation of its receptor in the brain. It is seen that women who have >leptin concentrations and increased leptin-BMI ratios have lower rates of pregnancy with IVF.²⁸ Jain et al.²⁹ studied eumenorrhic obese women and found that amplitude of LH pulsatility was significantly reduced which also supports that there is a significant central defect in obesity.²⁹

Oocytes and obesity

Women who are obese and undergoing IVF have altered follicular environment with >insulin, triglyceride levels along with inflammation markers like lactate and CRP in follicular fluid (FF).³⁰ Also there is >need of gonadotropin doses and longer treatment courses required for follicular development.^{31,32} Oocyte yield also is lower in obese women with >number of cycle cancellations.^{32,33} In DIO mouse models the ovaries show higher apoptotic follicles and oocytes smaller and <likely to mature.³⁴ Higher rates of meiotic aneuploidy and fragmented disorganized meiotic spindles and chromosomes which are not aligned on the metaphase plate.³⁵ Similarly Machlinger et al.³⁶ examined oocytes which failed to fertilize in IVF cycles of morbidly obese

women. They Similarly showed disarrayed spindles with misaligned metaphase chromosomes.³⁶ Besides aneuploidy obesity also alters mitochondrial function in oocytes. It has been seen that mitochondrion in DIO mice have disrupted architecture with fewer cristae, more vacuoles and evidence of swelling.³⁵ There is also a change in distribution of mitochondrion with clumping throughout the ooplasm compared with uniform perinuclear localization in control subjects.³⁷ There is evidence of metabolic stress in these mitochondria with lower levels of citrate, which is a tricarboxylic acid cycle end product. Due to this stress there may be a compensatory higher mitochondrial production as evidenced by higher mitochondrial DNA copy number in oocytes of obese mice.^{35,37,38} Also there is higher Endoplasmic reticulum (ER) stress in obese state (as reviewed in ref 4). Cumulus oocyte complex of mice fed a high fat diet show increased expression of ATF4 and GPR78 and increased granulosa cell apoptosis.³⁹ This has a correlation with increasing activating transcription factor levels in follicular fluid of obese women undergoing IVF.³⁹ Similarly impaired oocyte competence is seen in obese PCOS women which is associated with lower pregnancy rates along with ovulation induction and altered FF biomarkers but these studies have to be taken with a pinch of salt as there are lot of metabolic disturbances along with obesity in women with PCOS.⁴⁰

One reason for oocyte organelle damage in obesity is lipotoxicity. Excess FA's obtained from the diet get stored as triglycerides in adipocytes and they do not appear to cause cellular damage in this storage compartment. Once storage capacity is overachieved secondary to over eating FA's accumulate in other tissues like muscle, liver and heart causing lipotoxicity.⁴¹ Higher circulating FA's cause damage to non adipose cells due to increase in ROS which causes mitochondrial and ER stress=>apoptosis.⁴² Those having IVF, have increased FFA in FF correlates with abnormal morphology of cumulus-oocyte complex.⁴³ Oocytes in obese mice have two fold increased production of ROS along with depleted glutathione which is an important cellular defense against ROS damage.³⁷ Lipotoxicity plays a role in development of IR and an increased inflammatory state in obese women.⁴⁴

Also obesity is a state of chronic low grade inflammation (reviewed in ref 4). Inflammatory pathways are important in reproductive pathways like follicular rupture during ovulation and also for invasion of trophoblast into receptive sites. Developing blastocyst produces adiponectin, IL1 & IL6.⁴⁵ Hence altered inflammatory milieu in obese women exerts an influence on these processes.

Also greater leptin is also correlated with increased leptin in follicular fluid.⁴⁶ In vitro studies showed that leptin affects steroid production in a dose dependent manner.⁴⁷⁻⁵⁰ Effects of obesity at level of oocyte may have downstream effects on endometrial receptivity and embryo implantation.

Embryos and obesity

Human IVF cycle with autologous oocytes show that obese women have greater chance of making poor quality embryos.^{51,52} Dams having DIO where mouse embryos are created have lower expression of IGF1R, which negatively affects insulin sensitivity and glucose transport at a critical stage in development.³⁴ Embryos in women with BMI>25KG/m² were less likely to develop after fertilization as found by Leary et al.⁵³ and that those that actually reach morula stage developed more quickly. Also the ones which developed to blastocyst stage had lesser cells in the trophectoderm and showed poor glucose

uptake and increased levels of triglycerides.⁵³ Similar to oocytes embryos were also more susceptible to lipotoxicity. Murine embryos were cultured in the media having high palmitic acid had lower nuclei and altered IGF1R expression. On trying to transfer these embryos in dams, pups born had lower birth weights but normal catch up growth just like in DIO models.⁵⁴ Also murine trophoblastic stem cells which were exposed to palmitic acid in vitro proliferated less and undergo increased apoptosis in a dose dependent fashion.⁵⁴ Raised levels of omega 3 fatty acids like α linoleic acid in women who were having IVF done had lower pregnancy rates.⁵⁵ Greater ratio of linoleic acid and omega 6 fatty acid:linoleic acid showed higher pregnancy rates in that population.⁵⁶

Besides acting centrally raised leptin has a direct negative impact on the developing embryo. Leptin has a stimulating effect on human trophoblastic stem cells growth, and its inhibition reduces proliferation and dramatically increases apoptosis.⁵⁷ Raised levels of leptin in obesity may decrease the sensitivity of the trophoblast to its effect.

Obesity and endometrium

Despite investigators showing no effect on implantation rates,^{58,59} in a retrospective review by Desolle et al.⁶⁰ of a 450 donor oocyte frozen embryo transfer cycles there was an impact of BMI on success.⁶⁰

Both mice studies as well as human studies show endometrial decidualization is impaired in obesity.^{46,61} In the same study the authors looked for decidualization in primary cells from obesity vs control women and found a decrease in obese women. Both the mice and human studies showed a relationship between decidualization and the process of autophagy, a self eating, which is triggered by starvation. Many factors contribute to poor reproductive outcomes and the studies by Broughton et al suggested that the importance of decidualization defects. These defects may add to compromised endometrial receptivity and poor implantation. Placentation process might get affected by these defects and associated with pregnancy complication like still birth, PIH. Role of obesity and first trimester abortions is again debatable. In an Italian study 700 women undergoing donor oocytes cycles found significantly >spontaneous abortions in obese women 38.1 vs 13.3% in normal control women but a follow up study from same group of a large cohort of donor oocytes >2600 did not show any significant differences in implantation, pregnancy and miscarriage rates between BMI groups. Although a composite measure of ongoing pregnancy/cycle was calculated and shown to be significantly lower in the obese cohort.⁶² Metwaily et al.⁶³ conducted a metaanalysis in 2008 & showed the risk of miscarriage at <20wks gestation was higher in both spontaneous as well as ART conceptions with an odds ratio of 1.67. In the study group analysis it was confirmed in donor oocyte cycles but not in general cohort undergoing ICSI.⁶³ Lasher also showed a higher risk of recurrent abortions in a big obese cohort with an odds ratio of 3.5.⁶⁴ Also obesity is a known risk factor for recurrent pregnancy loss (RPL).⁶⁵ In a study where chromosome analysis of 115 miscarriage specimens was done on women having RPL it was shown that obese group had euploid miscarriages which suggests obesity has an independent effect on endometrium.⁶⁶

Also leptin is known to affect endometrium. Leptin receptors are known to be expressed in the endometrial endothelial cells in culture.⁶⁷ Leptin causes a remodeling of human endometrial epithelium which stimulates proliferation and apoptotic cell pathways *in vitro*.⁶⁸ There is upregulation of markers of receptivity with leptin exposure both in epithelial and stromal cells.⁶⁷

Transgenerational effect

Increasing evidence suggests that metabolic obesity confers a risk of metabolic dysfunction through multiple generations. Obesity affects intergenerational risk, meaning risk to offspring of developing disease later in life. Children of obese mothers have more chance of developing obesity, type II diabetes and cardiovascular diseases as adults.⁶⁹ This maybe due to epigenetic modifications in utero. In the DIO mouse models, pups are smaller at birth but they should catch up over growth and development of metabolic syndrome.⁷⁰ Gene expression in the placentas of dams with DIO shows alterations in imprinted genes and genes regulating lipid metabolism.⁷¹ Nomura et al.⁷² examined the placentas of obese mothers and found increased levels of global methylation.⁷² A recent study in a DIO mouse model showed that the metabolic dysfunction mediated through impaired mitochondrial dynamics can be passed through the maternal germline to 2nd and 3rd generation offspring.⁷³ The authors showed that maternal diet induced MS in an inbred mouse models results in transgenerational inheritance of aberrant mitochondrion. An expression of mitochondrial chain complex and dynamic proteins was seen in 1st through 3rd generation offspring (F1-F3) despite the fact that they were eating a regular diet immediately after weaning. The transmission appeared to be germline and through aberrant oocytes. In humans with diets of children closely paralleling those of their parents, the effect of maternal metabolic syndrome may be > than in the mouse model.

Management of obesity

Weight loss effects

In 170 women having IVF short term weight loss was associated with a greater yield of metaphase II oocytes in obese women but clinical pregnancy rates and LBR's were not affected.²⁰ Kort et al.⁷⁴ studied 52 overweight/obese women with infertility who were referred for weight loss counseling with a goal of 10% weight loss. 32% patients achieved this goal and these patients had significantly high pregnancy rates and LBR's.⁷⁴ Similarly in a RCT of 49 obese women having fertility treatment those who received intensive 12wk life style intervention had 6.6kg weight loss and significantly greater live birth rates as compared to control 44% vs 14% and needed lower treatment cycles [2 vs 4].⁷⁵

A large RCT was carried out by Mutsaerts in 600 obese infertile women who received 18mths life style intervention before infertility treatment vs prompt treatment for 24mths. Marked discontinuation rates was found in intervention group (21.8%). Only 43% reached a target discontinuation of 5% weight loss. Significantly higher primary outcomes of a live vaginal delivery was seen in immediate treatment group [35.2% vs 27.1%]. There was no difference in LBR when carried upto 24mths of treatment for both grps.⁷⁶ Still it remain unanswered whether delaying infertility treatment helps or not but one advantage of obtaining weight loss is pregnancy risks get decreased by weight loss like PIH etc.⁷⁷

Lifestyle Intervention/exercise and newer antiobesity therapies

Role of exercise

A lot of work has been done to see the effect of physical activity in obese infertile patients independently from weight loss. In a

retrospective group of obese infertile women who underwent IVF/ICSI, outcomes of patients who engaged in regular physical activity were compared with those who were sedentary as assessed by the validated Global Physical Activity Questionnaire. Significantly higher pregnancy rates and LBR's were found in the active group (41 cycles with a 3.71 relative risk of live birth).⁷⁸ Wise et al.⁷⁹ explored the effect of exercise on time to pregnancy in a big Danish group comprising of 3628 patients. They followed an inverse relationship between fecundity and vigorous physical activity when comparing women who completed >5hrs/week to those who did not. However the relationship did not exist for overweight or obese women who performed vigorous physical activity. Moderate physical activity was associated with small rise in fecundity across the cohort.⁷⁹ Physical activity has been associated with reduced systemic inflammatory mediators which may contribute to the improvement in fertility suggested by the sum of evidence.⁸⁰

Dietary factors

There is no effect on fertility just by increased caloric intake but by distribution of those calories across food groups. In a study comparing dietary factors in women with PCOS in USA and Italy it was noted that the American women had > average body mass and higher CVS risk (impaired GTT, caloric intake was similar for both cohorts, but American ladies ingested more saturated fats.⁸¹ A follow up study sought to find the prevalence of MS in Italian PCOS group which approaches 50% in American women with PCOS. It was much lesser in Italian women (8-16%) depending on the diagnostic criteria used.⁸² These studies and others on prevalence including obesity and type II diabetes across populations led to interest in the main therapeutic benefit of Mediterranean diet" characterized by > intake of unsaturated fats, and lower intake of animal fats and lower intake of omega 6 to omega 3 fatty acids.⁸³ Sticking to Mediterranean diet" for 2yrs in patients with metabolic syndrome significantly decreased IR and serum concentration of inflammatory markers including CRP and IL-6.⁸⁴ Dietary patterns of 161 couples who underwent IVF/ICSI was compared by Vujkovic et al.⁸⁴ and compared 2 categories a health conscious low processed diet vs a Mediterranean diet compared to an increased chance of pregnancy.⁸⁴ Spanish nested case control study compared the dietary patterns of fertile and infertile women categorized as western or primary Mediterranean diet". A lower risk of infertility was seen in women in the highest quartile of adherence to the Mediterranean diet.⁸⁵ Work has been done by Chavarrone et al.⁸⁶ on fertility diet, a pattern of diet intake which has been associated with lower risk of ovulatory infertility and characterized by < consumption of low glycaemic carbohydrates, high fat dairy and multivitamin.⁸⁶⁻⁸⁹ They followed a cohort of 17,000 women in the Nurses Health Study for 8y ears when they attempted pregnancy. They were given dietary scores based on their adherence to the fertility diet. Women in the highest quartile of adherence has an adjusted relative risk of 0.34 for ovulatory infertility, suggesting a significant impact of diet.⁹⁰ Since understanding of mechanisms of underlying obesity's impact on fertility has provoked investigation of targeted dietary supplementation. Given that ROS have been implicated in oocyte mitochondrial dysfunction, antioxidants may moderate obesity's impact on the ovary. An important antioxidant in the electron transport chain is coenzyme Q10, which has been shown to decrease with aging.⁹¹ In an aged murine model, mice supplemented with CoQ-10 had higher rates of ovulatory and larger litter size. This correlated with lower mitochondrion DNA copy number indicating < mitochondrial

stress.⁹¹ A small randomized trial in older women undergoing IVF showed potential benefit with lower rates of aneuploidy and higher pregnancy rates.⁹² Results of Q10 supplementation in the DIO mouse model have had varying results. CoQ 10 did not decrease the levels of ROS in obese mice, but it did appear to improve oocyte mitochondrial distribution and spindle and chromosome alignment.⁹³ CoQ10 has been studied in PCOS population-in a RCT of 100 patients undergoing ovulation induction had previously been resistant to clomiphene showed that CoQ10 supplementation improved ovulation and pregnancy rates.⁹⁴ These studies have still got to be tried in the obese infertile populations.

Bariatric surgery

There is limited literature available on the effect of bariatric surgery on reproductive health outcomes. Pregnancy outcomes following bariatric surgery was examined in a retrospective study which showed there was lower risk of gestational DM and large for gestational age infants but it also showed a concerning increase in risk of small for gestational age infants towards higher risk of still births and neonatal deaths with no improvement in preterm births.⁹⁵ In a survey study of 195 female patients in bariatric surgery 71% of women who were anovulatory before surgery had regained normal menses and this correlated with a higher degree of weight loss.⁹⁶ In a prospective group of 29 morbidly obese women who underwent Roux-en Y bypass-90% were ovulatory before surgery, which came as a surprise. The only significant change seen after surgery was a shortening of the follicular phase but the impact of this is unclear in the absence of fertility outcomes.⁹⁷ Bariatric Surgery does appear to improve the PCOS phenotype. In a small study of 17 women who underwent biliopancreatic diversion or laparoscopic bypass, 16 did not sustain the diagnosis because of lowering of androgen levels by return of regular periods. Metabolic parameters including insulin sensitivity and BP were also improved.⁹⁸ Again this showed that obesity had a marked impact on the pathophysiology of PCOS. Still many studies are required to see the effects of bariatric surgery on obesity related infertility.

Role of weight loss medications

Reviewed in ref 15 and further Legro R reviewed how few prospective studies have examined preconceptual weight loss interventions.⁹⁹ Although some effective medications like liraglutide (GLP1R agonist), Qsymia (topiramate/phentermine), contrive (naltrexone/bupropion) are available in USA, we do not have either liraglutide/Qsymia available. We have reported our experience of topiramate alone in ovulation induction [100] in morbidly obese women and since tolerance develops to the effects of topiramate and although no teratogenic effects have been reported in those women receiving topiramate as an anticonvulsant except for occasional cleft lip there is need to develop more effective weight loss therapies which cause significant weight loss and most importantly report the effects in preconceptual intervention on important perinatal outcomes like live birth and the health of the infant and mother. The current data from RCT which come closest to meeting these criteria have not documented improved LBR after the interventions compared with control groups. There is a tendency for equating results from most successful treatments of morbid obesity like bariatric surgery with an average 40% weight loss suggest a mixed risk benefit ratio on perinatal outcomes. Though interventions to control gestational weight gain have been more completely studied than preconception ones and have documented successful interventions to achieve

appropriate weight gain there is no clear evidence regarding controlling gestational weight gain actually improves any important perinatal outcomes. Future studies are needed for more successful and effective interventions, capture perinatal outcomes instead of weight changes as the primary outcome use at least at preconception, develop newer antiobesity drugs and study bariatric surgery in prospective trials to improve understanding of effectiveness of obesity treatment before pregnancy.⁹⁹

Conclusion

There is an indication that obesity impacts on risks of sub fertility. It is not only by causing decreased fecundity but also it causes suboptimal responses to ART. Laboratory work has shown varied mechanisms which affect the oocyte, endometrium and pre implantation embryo by inducing weight loss, physical activity, dietary changes and bariatric surgery there is some promise for obese patients wanting to conceive. Yet still more work is needed to understand the interplay between obesity and reproduction, with the aim of building healthy families.

Unsaturated fats, lower intake of animal fats and lower intake of omega 6 to omega 3 fatty acids,⁸³ Sticking to Mediterranean diet for 2yrs in pts with MS.

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Conflict of interest

There is no conflict to publish the article in this Journal.

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