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REVIEW

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Maternal obesity: A potential disruptor of female fertility and current interventions to reduce associated risks

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Summary

Currently, obesity has achieved epidemic levels in reproductive-aged women with a myriad of consequences. Obesity is susceptible to several reproductive complications that eventually affect fertility rates. These complications originate from the deteriorated quality of oocytes from mothers with obesity, which increases the probability of chromosomal aneuploidy, elevated reactive oxygen species production, compromised embryonic developmental competency, and eventually reduced fertility. Maternal obesity is linked to pregnancy complications such as implantation error, abortion, miscarriage, and early pregnancy loss. This review highlights the adverse effects of maternal obesity on female fertility, with a focus on the mechanistic link between maternal obesity and oocyte quality and discusses possible measures to reduce its associated risks.

KEYWORDS
infertility, obesity, oocyte quality, oxidative stress

1 | INTRODUCTION

Female fertility is one of the most important physiological phenomena for establishing clinical pregnancy.[1] Several risk factors negatively affect the fertility spectrum of females, including maternal obesity, advanced maternal age, stress, environmental conditions, drinking, and smoking. Maternal obesity is a principal risk factor that adversely affects the reproductive health of adult females, which eventually reduces pregnancy outcomes. Obesity is a multifactorial chronic disorder defined as an imbalance between energy consumption and energy ingestion. Obesity has become a major health concern, with a dramatic increase in the prevalence of overweight adults worldwide; in the last three decades, the prevalence of obesity has nearly doubled globally.[2] A recent report by the World Obesity Federation indicated a dramatic increase in the prevalence of maternal obesity in developed countries, which is estimated to be 45%–50% by the end of 2030 (Table 1).

Maternal obesity is accompanied by reproductive abnormalities such as congenital defects, early pregnancy losses, and neonatal conditions.[3,4] Obesity-associated errors in female fertility originate from the oocytes of a mother with obesity.[5,6] Several meiotic defects related to oocytes have been observed in mothers with obesity, including chromosomal errors, impaired spindle morphology, and mitochondrial dysfunction.[6,7] In addition, several pregnancy complications, including implantation error, abortion, and early pregnancy loss, are highly associated with maternal obesity.[8,9] Scientists have adopted measures to reduce obesity-associated fertility risk; however, maternal obesity remains a challenge for clinicians and embryologists to achieve a successful pregnancy. Here, we review the current scientific evidence regarding the adverse impact of maternal obesity on female fertility, with a focus on the mechanistic link between maternal obesity and oocyte development, and the possible measures being adopted to reduce its associated fertility risks.

TABLE 1 Estimated prevalence of mothers with obesity (BMI ≥ 35 kg/m^2) by 2030.

Country	Prevalence %
USA	47
China	10
India	8
Brazil	33
Mexico	41
Egypt	52
Russian Federation	30
Turkey	50
Indonesia	14
Iran	42
Pakistan	17
Nigeria	20
South Africa	50
United Kingdom	37
Germany	25
Algeria	46
France	26
Columbia	34
Argentina	36
Iraq	45

2 | MATERNAL OBESITY AND SIGNALING PATHWAYS

Over the past few decades, extensive investigation regarding the pathophysiology of obesity and the implication of several signaling pathways have been adopted to prevent obesity in a more precise way. Mitogen-activated protein kinases (MAPKs) are considered essential mediators in mammalian cell signal transduction. Upon phosphorylation by MAPK, downstream transcription factors are activated, which increases the gene expressions for different cellular activities such as proliferation, differentiation, and apoptosis.[10] MAPK composed of its different signaling members, including extracellular signaling-regulated kinase (ERK1/2), c-Jun N-terminal kinase (JNK), and p38MAPK, play important roles in several metabolic processes such as adipogenesis, glucose homeostasis, regulation of appetite, and thermogenesis.[11] MAPK-mediated appetite regulation, as well as other MAPK functions in the central nervous system (CNS), indicating its contribution to the pathogenesis of obesity. ERK1/2 increases the expressions of genes associated with glucose stimulation in hypothalamic neurons and is involved in anorexigenic action and even ERK1$^{-/-}$ mice are resistant to developing obesity with high-fat diet (HFD).[12,13] JNK is highly involved in leptin-associated activities that directly impact AgRP neurons in mice fed with HFD.[14] Moreover, JNK1 knockout reduces food intake and enhances the energy expenditure by blocking the negative feedback of the hypothalamic–pituitary-thyroid axis.[15] The role of p38 in the suppression of adipogenesis by increasing the expressions of PPARγ was also demonstrated in the previous study.[16]

Phosphatidylinositol 3-kinase phosphatase (PI3K)/AKT signaling pathway is critical for cell proliferation and differentiation; however, aberrant stimulation of that pathway promotes the risk of developing obesity.[17,18] It regulates the appetite via CNS and peripheral tissues. The mammalian target of rapamycin (mTOR) is a key downstream target of the PI3K/AKT pathway, and hypothalamic stimulation of mTOR reduces food intake and ameliorates age-dependent obesity by activating POMC neurons in several animal-based models.[19,20] However, the PI3K/AKT is indispensable to the insulin signaling pathway and disruption of this signaling is highly associated with developing obesity and insulin resistance.[21,22] The Janus kinase (JAK) signal transducer and activator of transcription (STAT) is also a major signaling pathway associated with obesity as it is a downstream mediator of hormones, cytokines, and various growth factors. The energy homeostasis regulated by leptin is mediated via JAK/STAT, and dysregulation of this pathway directly or in association with MAPK and PI3K promotes

obesity.[23] The JAK/STAT signaling in CNS increases the leptin sensitivity in POMC neurons and plays a pivotal role to control food intake.[24]

3 | IMPACT OF MATERNAL OBESITY ON OOCYTES AND EMBRYOS DEVELOPMENTAL COMPETENCY

Oocyte quality is a major indicator of early embryonic developmental competency and pregnancy outcomes, which collectively affect overall female fertility. In sexually producing animals, germ cells are produced from primordial stem cells via mitotic proliferation.[25] These germ cells produce excess numbers of oogonia after mitotic divisions with incomplete cytokinesis. After mitotic division, cells enter meiosis I and progress before being arrested at prophase I. After meiosis resumption, the cluster of cells start to break down, and several oocytes are lost due to apoptosis at that stage and the remaining oocytes become surrounded by the layers of pre-granulosa cells, eventually forming primordial follicles. After puberty, mature follicles are active in response to LH surge, which results in germinal vesicle breakdown, nuclear maturation, and completion of first meiotic division. These oocytes are again arrested at metaphase II and resume meiosis with fertilization in response to sperm penetration. Several studies have shown that oocytes from mothers with obesity exhibit compromised quality that adversely impacts oocyte meiotic maturation, consequently impairing embryonic developmental competency.[6,26,27] Emerging evidence has shown that reproductive defects, including implantation errors and miscarriages, originate from the oocytes of mothers with obesity.[26] A previous report has demonstrated the compromised quality of the resultant oocytes and embryos from mothers with obesity.[28] The impaired ovarian structure of mothers with obesity provides deteriorated oocytes with the least developmental potential.[26] Disrupted ovarian structure associated with a high level of free radicles enhances the index of oxidative stress that is directly involved in a number of reproductive complications such as miscarriage, abortion, and preeclampsia, which directly impair oocyte meiotic maturation and early embryonic developmental competency.[29] This claim was further justified by a report that a high percentage of miscarriage in women associated with obesity is highly associated with compromised oocyte quality,[30] suggesting an impact of maternal obesity on the quality of oocytes, which directly affects female fertility. Abnormalities in the ovarian structure of mothers with obesity reduce oocyte quantity, as evidenced by the decreased number of Graafian follicles, which leads to the formation of few mature oocytes.[31] Obesity adversely affects the oocyte quality in multiple ways, including lipotoxicity, mitochondrial dysfunction, changes in DNA methylation, and increased apoptotic index.[27,32–34]

Mitochondrial dysfunction is the leading factor that primarily enhances the level of oxidative stress in oocytes, which impairs their meiotic structure.[6] Obesity disrupts the mitochondrial ultrastructure of oocytes by increasing apoptosis. It was observed that quality-related abnormalities of oocytes in mothers with obesity can be partially reversed by shifting from a high-fat to a normal diet; however, cytoplasmic and meiotic measurement errors still exist, suggesting that obesity has a detrimental effect on female fertility.[35] Collectively, these findings suggest an adverse impact of obesity on oocyte quality, which eventually causes meiotic structure complications (Table 2).

Emerging evidence has shown that poor oocyte quality in women with obesity is linked to impaired early embryonic developmental competency.[67,68] A recent clinical study has shown reduced fertilization and blastocyst formation in Chinese women with increased BMI.[69] Multiple reports have shown a reduced embryonic developmental percentage in 4-cell- and blastocyst-stage embryos obtained from obesity-induced oocytes.[70,71] An extremely sophisticated report in an animal model of obesity provides evidence that the reduced embryonic developmental competency based on blastocyst percentage originates from the oocytes of the mothers with obesity.[26] Reduced levels of various proteins within oocytes from mothers with obesity are responsible for generating meiotic errors and reducing embryo developmental competency. In vitro trials have also provided evidence that abnormalities in embryonic development can be attributed to multiple factors within oocytes.[27,72,73] The higher index of reactive oxygen species (ROS) might be a possible reason for the poor quality of oocytes that impairs their meiotic structure, consequently reducing embryonic development. Collectively, these findings suggest

TABLE 2 Adverse impact of maternal obesity on female fertility.

Fertility parameters	Adverse impact	Reference
Oocytes attributes	↓ Oocytes number	36, 37
	↓ Maturation rate	27, 38
	↓ Oocytes quality	39
	↑ Meiotic defects	7, 40
	↑ Aneuploidy	41, 42
	↑ ROS level	43, 44
	↑ Mitochondrial dysfunction	45, 46
Embryonic features	↑ Fertilization failure	47, 48
	↓ Blastocyst percentage	26, 49
	↓ Embryo quality	50, 51
Implantation success	↓ Implantation rate	52
	↓ Endometrial receptivity	53
Hormonal profile	↓ E2 level	54
	↓ FSH level	55
	↓ LH level	56
	↓ P4 level	57
Pregnancy complications	↑ Miscarriage	8, 58
	↑ Abortion	59, 60
	↑ Still birth	61, 62
	↑ Pregnancy loses	63, 64
	↓ Clinical pregnancy rate	65, 66

Abbreviation: ROS, reactive oxygen species.

that maternal obesity impairs the developmental competency of oocytes and embryos, which is a hallmark of reduced pregnancy outcomes (Figure 1, Table 2).

4 | MATERNAL OBESITY CAUSES ANEUPLOIDY IN OOCYTES

Aneuploidy in oocytes and embryos is considered a major cause of miscarriage, congenital diseases, and infertility in women.[74,75] In humans, aneuploidy is mostly observed during chromosomal segregation in the maternal germline and its probability increases with maternal obesity. It was also observed that environmental toxins and obesity are considered predominant factors causing oocyte segregation errors.[76,77] Errors in chromosomal alignment and spindle morphology were observed in the oocytes of women with obesity with BMI (35 kg/m^2) relative to those of women with normal BMI (18.5–24.5 kg/m^2).[5] The oocytes of such women showed misaligned chromosomes with two abnormal spindles compared with single spindles in women with normal BMI. A recent study showed the adverse impact of obesity on oocyte chromosomal segregation and also manifested weakened sister chromosome cohesion in oocytes derived from mice with obesity.[41] Elevated chromosomal abnormalities were observed in oocytes from mice with obesity in both the MI and MII stages, which further impact the developmental competency of oocytes,[77] and meiotic aneuploidy is the major reason for the early embryonic loss. Oocytes from mice with obesity revealed abnormal morphology of chromosomes in the form of a clustered shape and spindles appearing in fragmented form rather than showing barrel-shaped symmetry. Quantitative analyses revealed a higher percentage of abnormalities (approximately 45% vs. 13% in the spindles and 35.8% vs. 17.5% in chromosomal defects) in HFD versus control mice.

Multiple reports have provided evidence of obvious abnormalities in the spindles and chromosomal structures of oocytes from mothers

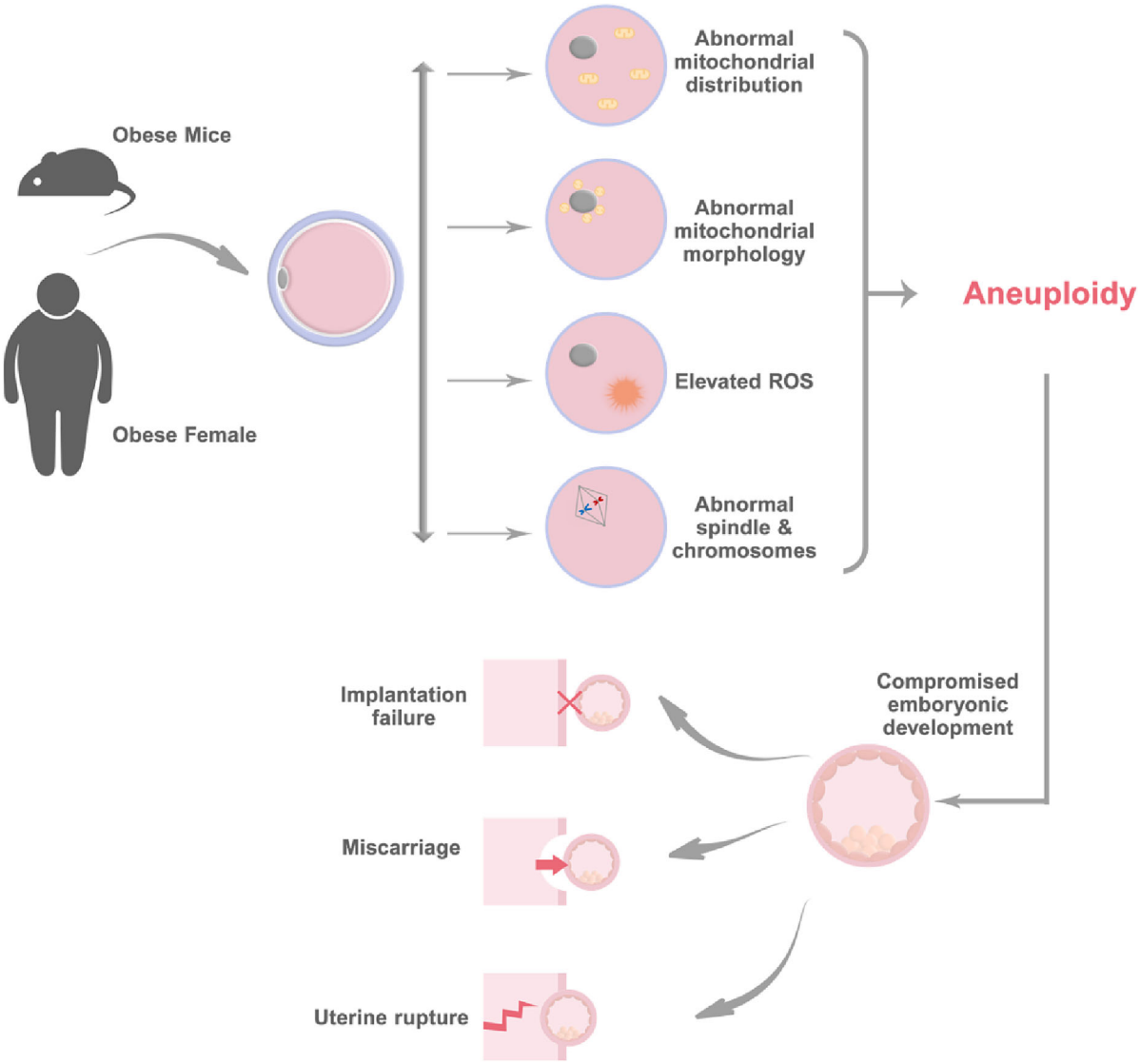

FIGURE 1 Meiotic defects in oocytes from mothers with obesity leads to reproductive complications.

with obesity.[70,78] Both in vivo and in vitro studies have revealed prominent spindle disorganization and chromosomal misalignment in oocytes associated with obesity. Another study showed the adverse impact of maternal obesity on oocyte telomerase morphology, which was confirmed by the reduced expression of telomerase reverse transcriptase and reduced activity of telomerase.[79] Shortening of telomerase in oocytes and embryos due to obesity leads to senescence and increases the apoptotic index. To elevate aneuploidy in the oocytes of mothers with obesity, different antioxidants were used in the culture medium. For example, melatonin was administered orally to mice and supplemented with the culture medium, which provides promising outcomes regarding the reduction in the percentage of spindle and chromosomal abnormalities.[70] Phycocyanin (PC) was observed to reduce spindle-chromosome morphology defects generated in oocytes due to maternal obesity.[43] Another well-known antioxidant, coenzyme Q10, provides evidence of reduced spindles and chromosomal defects when added to the culture medium.[78] Collectively, these findings suggest that oocytes from mice with obesity exhibited abnormal spindle and chromosome morphology, which might be the major cause of miscarriage and pregnancy loss in females (Figure 1).

5 | OXIDATIVE STRESS AND MITOCHONDRIAL FUNCTION IN FEMALES ASSOCIATED WITH OBESITY

Oxidative stress induced by excessive ROS production in oocytes may have a detrimental effect on female fertility. ROS are produced routinely within mitochondria during the metabolic process, and their increased production damages the mitochondrial structure. Previous reports have shown an association between oocyte deterioration and oxidative stress levels.[80,81] The oocyte quality is highly impaired by ROS production, which further disrupts mitochondrial functional activity. Wang et al reported that maternal obesity enhances the production of ROS in oocytes, which increases the frequency of meiotic defects.[40] Elevated levels of ROS induce DNA damage, apoptosis, lipid oxidation, and ultimately cell death.[82] A study based on the proteomic analysis of oocytes from mice with obesity revealed that depletion of the TP53-induced glycolysis and apoptosis regulator (TIGAR) in oocytes significantly increases the level of oxidative stress, which is further associated with failure in meiotic apparatus assembly.[7] Overexpression of TIGAR in oocytes reduces the level of ROS, spindle assembly, and chromosomal alignment defects, suggesting that maternal obesity has an adverse impact on oocyte proteomics. The association among obesity, the sirtuin protein family, and oxidative stress levels have been thoroughly studied in previous reports. SIRT3, an active member of the sirtuin family, regulates ROS homeostasis at the level of electron transport, and the lack of SIRT3 enhances the ROS index in oocytes of mice with obesity.[83,84] However, overexpression of SIRT3 in oocytes of mothers with obesity partially reversed the meiotic defects by decreasing the ROS index.

There is a strong association between maternal obesity and mitochondrial dysfunction. A study based on clinical data revealed abnormalities in placental mitochondria, a feature of mothers with obesity during pregnancy.[85] The number of mitochondria was highly reduced in the placenta of mothers with obesity, and the ultrastructure of syncytiotrophoblast mitochondria of mothers with obesity displayed several abnormalities, including a low-density matrix and disrupted cristae structure with an irregular pattern. A recent report in a murine with obesity revealed that mitochondrial dysfunction is linked to elevated redox index in oocytes.[86] Mitochondria play an important role in providing energy during oocyte meiotic maturation, fertilization, and the progression of embryonic development; however, errors in mitochondrial function hinder the developmental pathway in oocytes. Prior to conception, altered mitochondrial metabolism adversely affects oocyte development, which is highly associated with poor pregnancy outcomes.

A recent report indicated that mitochondrial dysfunction associated with obesity causes ROS production, which impairs oocyte quality and ultimately disrupts overall female fertility.[87] Mitochondrial abnormalities linked to obesity disturb cellular homeostasis and play a role in the progression of polycystic ovary syndrome (a hormonal disorder that enlarged the ovaries with the formation of cysts on the ovarian edges), which is a common cause of female infertility.[88] Maternal obesity impairs mitochondrial morphology and cellular activity, such as reduced mitochondrial size, reduced levels of autophagy, and problems with biogenesis.[89] Collectively, these results suggest that maternal obesity impairs cellular redox homeostasis, which causes mitochondrial dysfunction and influences overall pregnancy outcomes.

6 | OBESITY-INDUCED APOPTOSIS IN OOCYTES AND EMBRYOS

Homeostasis between cell proliferation and cell death is necessary for successful embryonic development. Any pathological condition that disturbs homeostasis leads to cell death. There is a strong association between mitochondrial dysfunction and the apoptotic index in the oocytes of mothers with obesity.[34] The higher apoptotic index in the oocytes of mice with obesity may be due to the accumulation of excessive calcium in the membrane of the endoplasmic reticulum (ER). However, reduced calcium levels may be useful in decreasing apoptosis, suggesting a novel therapeutic approach for obesity-induced oocytes.

As noted previously, several meiotic defects in oocytes are associated with maternal obesity, which eventually increases apoptosis.[79] Blastocysts obtained from HFD mice were treated using the TUNEL assay, and the resultant higher fluorescent intensity was observed, indicating an elevated apoptotic index in embryos.[50] Increased apoptosis in embryos with reduced total cell numbers is highly associated with implantation errors. A previous study reported the role of obesity-induced apoptosis in oocytes, which consequently reduced pregnancy outcomes.[68] An increased level of oxidative stress causes mitochondrial dysfunction, which increases apoptosis in the oocytes of mice with obesity. A recent report showed elevated levels of

apoptosis in obesity-associated ovarian structures.[90] Granulosa cells, which have paracrine effects and play an important role in germ cell development, are highly affected by the excessive apoptotic index, which eventually reduces the quality of the resultant oocytes. Collectively, these findings suggest that obesity induces apoptosis in oocytes and embryos, which directly affects overall pregnancy outcomes.

7 | MATERNAL OBESITY LEADS TO IMPLANTATION FAILURE

Implantation is a highly organized reproductive phenomenon that involves a strong interaction of the receptive uterine structure with the blastocyst-stage embryo. Implantation is considered a hallmark of a successful pregnancy. Defective implantation adversely affects female pregnancy outcomes, including spontaneous abortion, miscarriage, preeclampsia, intrauterine growth retardation, and ultimately, infertility. A study on the Chinese population showed a lower implantation percentage in mothers with obesity undergoing in vitro fertilization (IVF) and embryo transfer than in women with normal weight. The implantation percentage was 24.5% in women with obesity compared to 35% in normal-weight women. Reduced implantation negatively affects the overall pregnancy rate and the live birth rate.

Previously, obesity was shown to disrupt the endometrial structure of the uterus, leading to implantation failure.[91] In contrast, few clinical reports have demonstrated no association between obesity and implantation success, as a similar implantation rate was observed in mothers with obesity relative to normal-weight women.[92,93] Additionally, it has been suggested that the pregnancy rate, miscarriage percentage, and live birth rate are dispensable for maternal obesity. However, a recent report highlighted the detrimental effect of obesity on endometrial receptivity by displaying the window of implantation.[94] Overall, the above reports demonstrated the direct interaction of obesity with implantation percentage and endometrial receptivity, which are the pillars of a successful pregnancy.

8 | OBESITY-ASSOCIATED PREGNANCY COMPLICATIONS

Maternal obesity has short- and long-term adverse consequences in pregnant mothers and children. Early pregnancy loss and congenital anomalies are strongly associated with maternal obesity. A report described the adverse impact of obesity on pregnancy duration, such as insulin resistance in mothers with obesity, prolonged gestational duration, and enhanced production of oxidative stress that may cause early pregnancy losses.[95] Several reports have shown that mothers with obesity have an increased risk of spontaneous abortion and miscarriage.[8,9] Women with BMI ≥ 25 have a higher risk of miscarriage than women with a decreased BMI.[96] A cohort study in females associated with recurrent pregnancy loss revealed that mothers with obesity had a 52% greater chance of euploid miscarriage than 37% of women with normal body weight.[97] These findings suggest a higher risk of miscarriage in women with obesity.

A systemic review and meta-analysis indicated several obesity-related anomalies, including neural tube defects, spina bifida, limb reduction anomalies, and cardiovascular anomalies in the offspring of mothers with obesity.[98] In addition, serious life-threatening pregnancy complications such as preeclampsia, induced labor, and thromboembolism are also associated with maternal obesity.[99] The chances of preeclampsia, rectovaginal *Streptococcus* colonization, labor induction, and cesarean section were higher in mothers with obesity than that in mothers without obesity.[100] Another clinical finding provides evidence that mothers with obesity have an increased risk of cesarean section and are likely to have a higher miscarriage percentage than women with normal BMI.[101] A recent meta-analysis and UK-based cohort studies have also found a doubled percentage of stillbirths in mothers with obesity compared to healthy women.[102,103]

Obesity-related pregnancy complications are not only limited to the mother, but may also directly influence offspring health status, including cardiovascular abnormalities, and the inflammatory response by increasing the level of cytokines and fetal adiposity. Lifelong cardiometabolic risks have been observed in the offspring of mothers with obesity.[104] Accumulating evidence suggests that obesity-related pregnancy complications involve several factors, such as compromised quality of oocytes and embryos, endometrial receptivity and developmental issues, and implantation errors.[105,106]

Pregnancy-related complications in mothers with obesity were also observed in in vitro trials using assisted reproductive technologies (ARTs). Recently published clinical data on Saudi women showed several pregnancy-related complications, including preeclampsia, perineal tears, and episiotomy after ART.[107] Notably, mothers with obesity have fewer chances of achieving clinical pregnancy after IVF compared to normal-weight women, and there may be a higher chance of miscarriage even after getting pregnant,[108–110] as demonstrated by a lower pregnancy rate in mothers with obesity after ART.[111] A recent cohort study was conducted on Chinese women who underwent frozen–thawed embryo transfer, and pregnancy outcomes were measured.[65] Mothers with obesity showed a lower percentage of successful clinical pregnancies, reduced implantation percentage, and significantly decreased live births by this method. Additionally, a higher rate of pregnancy loss was noted in both first- and second-trimester pregnancies of mothers with obesity. Notably, underweight females showed an increased pregnancy rate with overall reduced pregnancy losses. Collectively, these findings suggest that maternal obesity leads to several pregnancy complications that affect fertility.

9 | POSSIBLE MEASURES TO REDUCE MATERNAL OBESITY DURING PREGNANCY

Previously, it was noted that a higher BMI during pregnancy leads to pregnancy complications that ultimately affect pregnancy outcomes. Scientists are focusing on developing new interventions and measures to reduce the burden of obesity on female fertility during the

antenatal period of life; however, extending these interventions to the postpartum period may also be valuable for pregnancy outcomes.

Lifestyle interventions, including restricted diet control, physical activities, and a combination of both, are crucial for reducing the weight of mothers with obesity. The National Institute for Health and Care Excellence in the United Kingdom advised that the use of a healthy diet while performing a minimum of 30 min of physical activity may be useful to prevent additional weight gain during gestation. Physical activity in combination with dietary therapy is effective in managing weight.[112] Another key point is nutritional intervention such as restricted timing of eating, which beneficially impacts pregnancy outcomes of mothers with obesity. Reducing the duration of eating from >14 to <10–12 h/d may decrease weight gain by up to 3.3 kg. Recently, it was shown that time-restricted eating behavior of <10 h/d improves insulin sensitivity with β-cell responsiveness and lowers glucose concentration, which is essential for weight reduction.[113,114] Most extensively studied nutritional supplement omega-3 polyunsaturated fatty acids (n-3, PUFAs) adequacy in diet may also lead to obesity.[115] They observed an increased n-6/n-3 ratio in women with obesity compared to normal pregnant women. Another report indicated lower levels of n-3 PUFA and higher levels of n-6 PUFA during the second trimester of pregnancy with more abdominal and body fat in childhood.[116] Using these strategies, a significant reduction in weight gain was observed in a report by the National Institute for Health Research, United Kingdom.[117] Randomized trials on mothers with obesity based on lifestyle interventions proved useful in reducing weight gain during pregnancy.[118,119] A study on lifestyle in pregnancy and treatment of pregnant women with obesity reported significant outcomes of gestational weight reduction by using lifestyle interventions.[120,121] Lifestyle interventions reduce gestational weight in pregnant women; however, physical inconvenience, limitations of being pregnant, and lack of exercise due to time limitations are major factors that hinder mothers with obesity and need to be addressed. High-intensity intermittent exercise beneficially enhances the adherence of 80%–90% of reproductive-aged women with obesity, and a 20% improvement in insulin sensitivity was detected.[122,123]

Mothers with obesity encounter issues with insulin resistance during pregnancy, and different drugs such as metformin are used to increase insulin sensitivity. The use of these drugs during pregnancy generates several complications, such as fetal and neonatal outcomes of stillbirth, miscarriage, cessation of pregnancy, and neonatal death. However, the use of some pharmacological drugs beneficially reduces the weight of mothers with obesity without increasing insulin resistance. A recent report has shown that the administration of human recombinant leptin in leptin-deficient patient at a dose of 0.03 mg/kg per day reduces the food intake and cause reduction in adipose mass and body weight.[124] At one point, leptin was considered a big hope for the treatment of obesity; however, exogenous administration shows limited efficacy in clinical studies.[125] It was shown that the leptin substitute FDA approved an orphan drug metroleptin that provides metabolic improvements in patients associated with lipodystrophy and also treated the condition of anorexia nervosa.[126] Another drug setmelanotide, a Mc4R agonist exerted beneficial impact in reducing obesity by changing eating behavior without any cardiovascular effect.[127] Previous reports have shown that the use of probiotics results in the modification of lipopolysaccharides and insulin sensitivity, which eventually aids in the reduction of gestational weight and risk of gestational diabetes.[121,128,129] Other possible measures are preconception and postpartum interventions that promote fertility and reduce the percentage of miscarriage by adopting a balanced diet with lifestyle interventions.[130,131] Few effective interventions, such as smoking cessation and folic acid supplementation prior to conception, are directed measures to target the weight of pregnant women.[132] Smoking during pregnancy increases the risk of miscarriage, placental abruption, and reduced birth weight.[132] In some reports, frequent or exclusive breastfeeding increases the probability of reversing weight

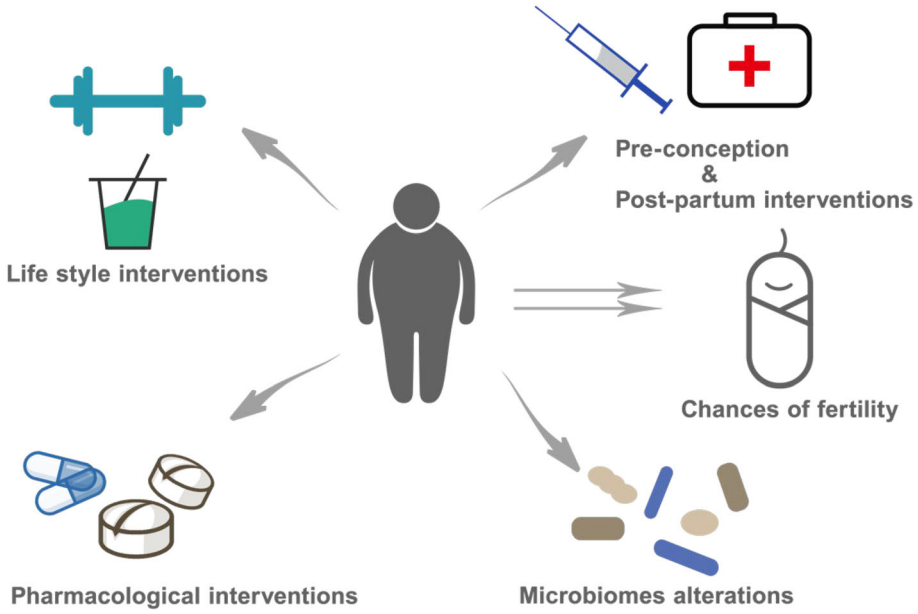

FIGURE 2 Possible interventions to reduce the maternal obesity during pregnancy.

gain and BMI after the postpartum period; however, it is based on the behavior of the mother during exclusive breastfeeding.[133,134]

Another alternative way of achieving pregnancy in women with obesity is ART; however, high doses of gonadotropin for stimulation, fewer retrieved oocytes with compromised quality, and early pregnancy losses are the major challenges to face.[135] It was shown that loss of weight through lifestyle interventions and then progress to the IVF procedure is a preferred approach that may improve pregnancy outcomes in women with obesity.[135] Recent reports demonstrated that weight loss reaching up to 10% prior to IVF can significantly reduce the concentration of gonadotropin and improve the clinical pregnancy and live birth rate.[136,137] Collectively, high-quality healthy diets and exclusive breastfeeding in combination with lifestyle interventions may reduce the gestational weight of mothers with obesity and increase the chances of a successful pregnancy (Figure 2). Moreover, reduction in weight loss and then progress to ART also put a beneficial impact on overall pregnancy outcomes.

10 | CONCLUSION

The dramatic increase in the prevalence of obesity and overweight among women has become a serious health challenge worldwide. The ratio of obesity-associated infertile couples is increasing daily, which directly affects the status of females in society. Mothers with obesity have a higher incidence of reproductive dysfunction with developmental abnormalities originating from oocytes, including defects in their meiotic structure (spindle and chromosomal abnormalities, mitochondrial dysfunction, elevated ROS index, and increased level of apoptosis), leading to impaired developmental competency of oocytes and embryos, implantation errors, abortion, miscarriage, and early pregnancy loss.

Currently, clinicians and research scientists are focusing on strategies to improve the fertility of mothers with obesity. Accumulating evidence has shown that obesity-related abnormalities originate from oocytes, which requires us to focus on solutions that improve the oocyte quality, which may be beneficial for overall pregnancy outcomes. Currently, the use of selective growth factors and antioxidants in the culture medium provides beneficial outcomes regarding the oocyte quality in animal models and might be useful in human ART. Alternatively, weight loss is the primary focus to prevent infertility in women. Different interventions, including lifestyle interventions, pharmacological drug-exclusive breastfeeding, and pre- and post-conception interventions have proven useful in reducing the weight of mothers with obesity. Additionally, various awareness programs should be introduced to inform women regarding the adverse effects of obesity on female reproductive health. With the increasing prevalence of obesity worldwide, experimental, clinical, and genetic research will continue to elucidate its mechanism and design possible preventive measures. There is an urgent need to search for a "magic bullet" to treat infertile couples affected by obesity; however, the importance of exercise, diet, and lifestyle modification must continue to be the cornerstone of obesity management.

Although considerable progress has been made to understand the etiology of obesity and its adverse consequences on female reproduction, however; the personalized therapies against that anomaly are not satisfactory yet. The prescription of more exercise with less eating and lifestyle interventions are effective; however; in combination with different strategies such as decoding of cellular signaling network enables us to find a precise medicine, enriching our arsenal in the fight against obesity. In addition, we should focus on energy-consuming drugs based on the importance of balancing energy intake and energy expenditure. Finally, in-depth learning of known signals and development, efficient tools such as artificial intelligence may play an important role in achieving precise treatment of obesity in the future that eventually will reduce the reproductive defects associated with obesity.

AUTHOR CONTRIBUTIONS

Hongbin Liu, Zi-Jiang Chen and Gang Lu conceived the review. Tahir Muhammad wrote the original draft. Yanling Wan edited the draft. Hanzhen Li drew the pattern diagram. Yue Lv and Wai-Yee Chan critically reviewed the paper. All authors have read and agreed to the published version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

No conflict of interest statement.

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