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Impact of obesity on medically assisted reproductive treatments

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Review Article

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Summary

Increasing evidence has demonstrated that obesity impairs female fertility and negatively affects human reproductive outcome following medically assisted reproduction (MAR) treatment. In the United States, 36.5% of women of reproductive age are obese. Obesity results not only in metabolic disorders including type II diabetes and cardiovascular disease, but might also be responsible for chronic inflammation and oxidative stress. Several studies have demonstrated that inflammation and reactive oxygen species (ROS) in the ovary modify steroidogenesis and might induce anovulation, as well as affecting oocyte meiotic maturation, leading to impaired oocyte quality and embryo developmental competence. Although the adverse effect of female obesity on human reproduction has been an object of debate in the past, there is growing evidence showing a link between female obesity and increased risk of infertility. However, further studies need to clarify some gaps in knowledge. We reviewed the recent evidence on the association between female obesity and infertility. In particular, we highlight the association between fat distribution and reproductive outcome, and how the inflammation and oxidative stress mechanisms might reduce ovarian function and oocyte quality. Finally, we evaluate the connection between female obesity and endometrial receptivity.

Introduction

Obesity affects over 600 million adults worldwide. Its prevalence is rising steadily in developing and developed nations, inducing higher morbidity and mortality rates (Wang YC *et al*., 2011; Flegal *et al*., 2013; Meng *et al*., 2021). In some countries, such as in the United States, obesity has evolved from a health problem to an epidemic. Recent data have shown that 68% of the United States adult population is overweight, and 39.6% is obese. In females of reproductive age (20–39 years), the prevalence of obesity is comparable with the general population (36.5%), but it is higher in the African American (55%) and Hispanic (51%) communities (Hales *et al*., 2017).

Obesity is defined as a body mass index (BMI) greater than 30 kg/m^2 and overweight when the BMI is more than 25 kg/m^2. Considerable attention has been given to research on the mechanisms underlining obesity and its consequences. The raising of lipid storage in adipose tissue and other metabolic organs leads to cellular lipid toxicity, inflammation and ROS formation that induces oxidative stress. At the end of the last century, the adverse effect of obesity on reproduction was always considered the object of discussion and mainly controversy (Bellver *et al*., 2006).

At this time, there is enough evidence suggesting that obese women report an increased risk of ovulatory and anovulatory infertility compared with the age-matched lean women (Maheshwari *et al*., 2007; Ramlau-Hansen *et al*., 2007; Kumbak *et al*., 2012). Furthermore, obese women have reduced receptiveness to gonadotropins and show a decreased oocyte number and quality. In addition, reduced implantation rates and pregnancy outcomes following MAR treatments have been reported, as well as higher risk for miscarriage rates compared with their lean counterparts (Boots and Stephenson, 2011; Kumbak *et al*., 2012; Broughton and Moley, 2017). However, the mechanisms by which high BMI impairs almost each reproductive system component, from oocyte to embryo development and the uterus, have not been completed elucidated (Bellver, 2008; Jungheim *et al*., 2010; Wu *et al*., 2010). Therefore, the primary goal of this review was to summarize current evidence assessing the reproductive outcome in obese patients: analyzing how lipid toxicity impairs ovarian function and oocyte competency.

A preliminary investigation showed that gene expression during the window of implantation revealed endometrial dysregulation in obese women correlated to normal-weight controls (Bellver *et al*., 2011). Finally, we highlight recent studies investigating the relationship between female obesity and endometrial receptivity, which might reduce pregnancy outcomes in MAR

cycles (Bellver *et al.*, 2008; Boots and Stephenson, 2011; Kumbak *et al.*, 2012; Broughton and Moley, 2017).

Sign of oogenesis

The precursors of oocytes are the proliferating primordial germ cells (PGCs). They develop in fetal life and start the meiosis process that had been arrested in the diplotene stage of prophase I. The germinal vesicle (GV) stage lasts for several years in humans. The GV-arrested oocytes are surrounded by a single layer of flattened granulosa cells (GC) and compose the primordial follicles, usually formed during fetal life in primates (Hunt and Hassold, 2008). Subsequently, GC proliferation and oocyte growth promote preantral follicle development, under the control of intraovarian factors, either activating or inhibitory. At this stage, GC express follicle-stimulating hormone (FSH) receptors that stimulate follicular growth and oestradiol (E2) production and control GC proliferation.

Preantral follicles are also reactive to the transforming growth factor (TGF) family and the androgens, insulin and insulin-like growth factor-1. A critical component is the formation of theca cell (TC) layers from the ovarian stroma, which provide follicles with luteinizing hormone receptors. Starting from cholesterol, LH coordinates the production of androgen that is converted to E2 in GC. Oestrogens also regulate FSH receptor activation and LH receptor expression in GC (Canipari *et al.*, 2012). During this growth phase, the oocyte secretes the zona pellucida (ZP) glycoproteic shell around the ooplasm, responsible for the interaction with sperm cells at the time of fertilization and critical for avoiding polyspermy and abnormal fertilization.

The pulsatile secretion of FSH stimulates the transition to the antral phase, identified by the presence of the antral cavity filled with follicular fluid (FF) and by the differentiation of the cells around the oocyte, the cumulus cells (CC), and mural GC lining the antrum. FSH is produced from a cohort of antral follicles, the follicle with the higher mitotic rate of GC and elevated E2 production becomes the dominant follicle, while the less mature follicles proceed to atresia. The preovulatory follicle containing the GV-arrested oocyte at this point is ready to respond to the LH surge that triggers meiotic maturation and ovulation (Rajkovic and Pangas, 2017).

The process of meiotic resumption is a delicate and intricate one, which involve the cooperation between hormones and signalling pathways (Canipari *et al.*, 2012; Liu *et al.*, 2019). The LH signal induces the activation of mitosis promoting factor (MPF) and mitogen-activated protein kinase (MAPK) signalling leading to the formation of the first meiotic spindle together with the extrusion of the first polar body (PBI), and the oocyte arrested at metaphase II (MII). At ovulation, the oocyte is released into the fallopian tube. After fertilization, the second meiosis will be completed by the extrusion of the second polar body and male and female pronuclei formation. The release of progesterone is essential to prepare the endometrium for implantation (Edson *et al.*, 2009).

Obesity and inflammation

Adipose tissue is not only involved in energy storage but it is an endocrine organ that secretes numerous bioactive and chemical signals (Berg and Scherer, 2005). Accumulating evidence suggests that obesity is linked to a chronic low-grade inflammation state (Hotamisligil, 2006). Increased lipid storage in adipose tissue and metabolic organs leads to cellular lipid toxicity, inflammation and oxidative stress (Snider and Wood, 2019), which induces metabolic dysfunctions like type II diabetes and cardiovascular diseases (Wang YC *et al.*, 2011; Finkelstein *et al.*, 2012). Chronic inflammation is associated with persistent and irregular chemokine and cytokine production (Snider and Wood, 2019).

Chemokines are molecules with chemotactic activity directed at specific leukocytes populations. These compounds are released by stromal cells and endothelial cells, whereas their receptors are located on the leukocytes' surface, allowing a specific targeting during immune responses (Shimizu *et al.*, 2011). Persistent inflammation induces changes in cell metabolism and microbiome modifications that can induce a *de novo* inflammatory response (Garn *et al.*, 2016; Kuroda and Sakaue, 2017). Low-grade chronic inflammation in adipose tissue has a pivotal role in obesity-related complications
as insulin resistance, metabolic syndrome and type 2 diabetes (Kuroda and Sakaue, 2017). In the context of obesity, adipocyte hypertrophy results from the storage of increased circulating triglycerides (Engin, 2017).

Macrophages are recognized as a centre of inflammatory response in obesity, producing cytokines and chemokines (Cinti *et al.*, 2005). Furthermore, macrophage infiltration into adipose tissue is enhanced by obesity (Xu *et al.*, 2003; Ouchi *et al.*, 2011; Kuroda and Sakaue, 2017). Notably, cytokines and adipokines released into the bloodstream might promote an inflammatory response in other organs, including the ovary (Ouchi *et al.*, 2011; Wang and Huang, 2015; Xie *et al.*, 2016). Due to the interdependence of inflammation and oxidative stress, it is not surprising that obesity is a state of chronic oxidative stress, producing ROS and overcoming the antioxidant system (Piya *et al.*, 2013; Rimessi *et al.*, 2016).

Investigators have identified a symbiotic relationship between different anatomical sites, including skin, colon and vagina, with local bacteria changes (Cho and Blaser, 2012; Belizário *et al.*, 2015). In the gut, there is a symbiotic relationship between its microbiome, the intestinal epithelia, immune system and inflammatory responses. Gut dysbiosis can be identified in obese patients, with an increased ratio of two bacteria families: Firmicutes and Bacteroidetes (Ley *et al.*, 2005; Turnbaugh *et al.*, 2006; Riva *et al.*, 2017).

This change induces a loss of tight junctions among cells with increased epithelial permeability (Saad *et al.*, 2006) and leakage of lipopolysaccharides (LPS), resulting in low-level endotoxemia and induction of systemic inflammation (Figure 1). Increased fatty acid and LPS in the blood circulation, associated with gut microbiome changes and high caloric diet, have been described by several authors (Ley *et al.*, 2005; Saad *et al.*, 2006; Turnbaugh *et al.*, 2006; Cani *et al.*, 2007; Cox and Blaser, 2013). Together, these studies have established the now well accepted paradigm that obesity is a chronic condition characterized by low-grade inflammation, oxidative stress and increased gut permeability.

Cytokine and chemokine signalling in the ovary

As previously discussed, the process of folliculogenesis starts with the recruitment of primordial follicles, progressing through the proliferation of granulosa and thecal cells, oocyte maturation, steroidogenesis and ovulation (Richards *et al.*, 1988; McLaughlin and McIver, 2009). Each stage involves paracrine and endocrine environmental dialogue between the oocyte and somatic cell layers, mediated mainly by a vast ensemble of hormones and cytokines

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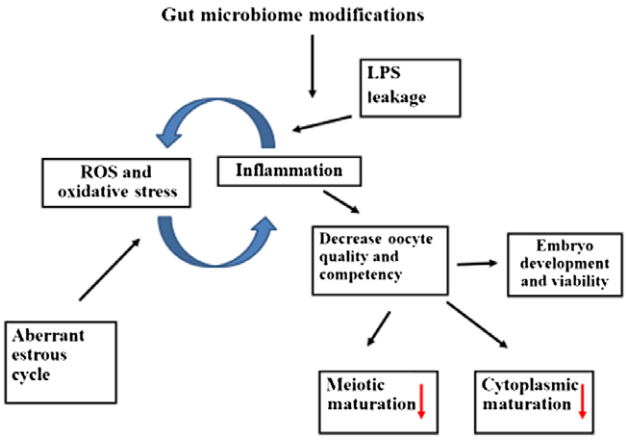

Figure 1. Illustrates how changes in the gut microbiota following oxidative stress and inflammation impair oocyte competency. LPS, lipopolysaccharide; ROS, reactive oxygen species.

(Pasquali and Gambineri, 2006), critical for producing a mature, competent oocyte (Eppig, 1985; Richards and Hedin, 1988; Buccione *et al.*, 1990; Oktay *et al.*, 2000).

Cytokines are key regulators of ovarian physiology, contributing to creating an appropriate environment for follicle selection and growth (Field *et al.*, 2014). They support resident and infiltrating leukocytes to process a complex spectrum of signals resulting from direct-cell contact with their environment (Połeć *et al.*, 2011). Therefore, leukocytes are the most relevant cytokine producers in the ovary, although ovarian somatic cells, including stromal, luteal, granulosa and thecal cells, are also an important source of those compounds (Gilchrist *et al.*, 2000).

Evidence suggests that primordial-to-primary follicle transition is mediated by pre-GC, surrounding oocyte in primordial follicles. Pre-GC action in animal models is mediated by a range of cytokines, such as stem cell factor, fibroblast growth factor (FGF-2) and leukaemia-inhibitor factor (LIF) (Nilsson and Skinner, 2004; Wang and Roy, 2004). During the follicular phase, activated T-lymphocytes, macrophages, monocytes and neutrophils can be found in the theca layer (Wu *et al.*, 2006). Granulocyte–macrophage colony-stimulating factors (GM-CSF) increase preantral follicle progression, and decrease granulosa cell proliferation and oestradiol (E2) and progesterone (P4) synthesis (Wang and Roy, 2004; Zhang *et al.*, 2008). Interleukin-8 (IL-8) stimulates follicular progression from preantral to preovulatory stage, inhibits E2 synthesis by GC and increases P4 production by theca and GC (Shimizu *et al.*, 2013).

These mechanisms regulate cumulus expansion and ovulation as well as participate in the luteinization process following the LH surge (Brännström and Enskog, 2002; Jang *et al.*, 2015). As cytokines mediate folliculogenesis, it is reasonable to investigate their potential role as biomarkers and assess their diagnostic and prognostic value in MAR treatments, considering that morphological evaluation is still the main method of assessment for oocyte maturity, despite evidence of a highly subjective intraoperator variation (Rienzi *et al.*, 2011). As an example, Jasper and collaborators (2000) identified a specific role for GM-CSF in the development of the corpus luteum.

This biochemical finding correlated well with clinical evidence of women undergoing ovarian hyperstimulation, who presented significantly increased plasma and follicular GM-CSF levels compared with non-stimulated patients (Jasper *et al.*, 2000). Yanagi and co-workers showed a positive correlation between FF granulocyte colony-stimulating factor (G-CSF) concentration and oocyte quality and maturity, and used by others to predict live birth (Yanagi *et al.*, 2002). Similar results have been reported by others investigating macrophage-stimulating factor (M-CSF) (Salmassi *et al.*, 2010). Finally, analyzing the cytokine profiles of the FF at the time of oocyte retrieval might offer a useful and non-invasive analytical strategy for assessing the development potential of the oocyte and the embryo (Field *et al.*, 2014).

Obesity ovarian function and oocyte competency

It has been established that high lipid content negatively impacts ovarian function and oocyte competence (Douchi *et al.*, 2002). In this vein, obesity is associated with irregular menses, anovulatory cycles and polycystic ovarian syndrome (Rich-Edwards *et al.*, 1994). It has been reported that women with a high BMI are three times more likely to be infertile compared with women with a normal weight (Rich-Edwards *et al.*, 1994; Douchi *et al.*, 2002; Metwally *et al.*, 2007).

A linear association between BMI and increased need for gonadotropin stimulation, lower serum oestradiol concentration on the day of HCG administration, lower cumulus–oocyte complexes retrieved, and poorer quality blastocysts describe the average profile of obese women facing MAR treatment (Metwally *et al.*, 2007; Minge *et al.*, 2008). Obesity compromises follicle growth and development mostly due to a depletion of the primordial follicle pool, advancement of follicles to antral stage, and an increase in atretic follicles number (Minge *et al.*, 2008; Wu *et al.*, 2015; De Araújo *et al.*, 2018). The adverse effects of maternal obesity on fertilization and preimplantation embryo development are probably multifactorial and initiate in the ovary at the follicular phase of the developing oocyte. However, mechanisms by which obesity interferes with the reproductive system are still debated.

Robker and colleagues found a higher level of triglycerides in FF in obese women. They noted that a high concentration of fatty acids within the bloodstream increases the ovary's insulin levels at the follicular level and the oocyte surrounding the CC, compromising ovarian function (Robker *et al.*, 2009). Moreover, insulin-like growth factor-1, transforming growth factor-beta, insulin and LH are involved in higher leptin levels in the follicles, which may inhibit ovarian granulosa and thecal cell steroidogenesis. Therefore, data have suggested that the obesity-dependent reduction in the number of primordial follicles and augmentation in the number of antral and atretic follicles leads to a reduction in the ovarian reserve, contributing to subfertility (Valckx *et al.*, 2014; Wang N *et al.*, 2014).

O'Gorman and collaborators used the FF lipid profile as a predictor of oocyte quality. They compared the fatty acid composition from FFs to which oocytes were fertilized and developed to embryos with those fluids in which oocytes after fertilization could not cleave, and were arrested at the zygote stage. Nine fatty acids were significantly different between FF from the cleaved and the non-cleaved sample (O'Gorman *et al.*, 2013). When the oocyte reaches the end of the growth phase in the follicle, it acquires the ability to resume meiosis (Canipari *et al.*, 2012). It is also important that the oocyte achieves cytoplasmic maturation with the right amount of mitochondria supporting the energy requirement at the early stage of embryo development.

Together with nuclear maturation, this condition makes the oocyte competent for fertilization and embryo development,

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Table 1. Obesity negatively impacts both meiotic and cytoplasmic maturation of the oocyte

Events	References
Reduced germinal vesicle (GV) breakdown	Mao *et al.*, 2014; Wang H *et al.*, 2018
Polar body (PB) extrusion	Chaffin *et al.*, 2014; Mao *et al.*, 2014; Hou *et al.*, 2016; Wang H *et al.*, 2018
Spindle damage	Mao *et al.*, 2014; Zhang *et al.*, 2015; Hou *et al.*, 2016; Wang H *et al.*, 2018
Chromosome segregation abnormalities	Minge *et al.*, 2008; Hunter, 2015; Luzzo *et al.*, 2012; Pohlmeier *et al.*, 2014; Zhang *et al.*, 2015; Hou *et al.*, 2016; Wang H *et al.*, 2018, Wang S *et al.*, 2019, Wang S *et al.*, 2021
Embryo aneuploidy	Minge *et al.*, 2008; Hunter, 2011; Luzzo *et al.*, 2012; Mao *et al.*, 2014; Pohlmeier *et al.*, 2014; Zhang *et al.*, 2015; Wang H *et al.*, 2018, Wang S *et al.*, 2019, Wang S *et al.*, 2021
Mitochondria dysfunction and energy depletion	Igosheva *et al.*, 2010; Van Blerkom, 2011; Luzzo *et al.*, 2012; Turner and Robker, 2015; Babayev and Seli, 2015

implantation and the resulting in pregnancy to term (Mao *et al.*, 2014). Moreover, meiotic maturation necessitates the resumption of meiosis, spindle formation and correct chromosomes migration, which relies on the GV breakdown, progression from prophase I to metaphase II and extrusion of the first polar body. Errors at this stage of maturation might lead to spindle alteration and abnormalities in chromosome segregation, resulting in embryo aneuploidies, implantation failure and miscarriage (Turner and Robker, 2015). Several animal studies have reported that maternal obesity negatively affects oocyte function leading to defective mitochondria heritage.

For instance, diet-induced maternal obesity mice have revealed a decrease in oocyte quantity and quality, as indicated by disrupted meiotic spindle morphology and oxidative stress, leading to poor oocyte fertilization and embryo aneuploidy (Zhang *et al.*, 2015; Hou *et al.*, 2016; Wang H *et al.*, 2018). Therefore, it is essential to improve weight loss through a periconceptional lifestyle, with a low energy diet and exercise in obese women. It has been demonstrated that even a modest weight loss of 10% in obese women might be effective in improving hormonal profiles, menstrual regulatory, ovulation and pregnancy rates following IVF/ICSI cycles (Norman *et al.*, 2004; Rondanelli *et al.*, 2014).

Mitochondrial dysfunction: potential implication of gut microbiome in infertility

As pointed out earlier, obesity is characterized by the accumulation of intracellular lipid, including LPS, triglycerides, cholesterol and free fatty acids in the blood circulation and ovarian cells. Elevated lipid content might modify the functionality of several cellular organelles, including the endoplasmic reticulum (ER) and mitochondria (Borradaile *et al.*, 2006). Abnormal ER function or oxidative stress might lead to a change in protein secretion pathways (Ozcan and Tabas, 2012). At the same time, calcium released from the ER modifies mitochondrial membrane potential inducing uncoupling of oxidative phosphorylation, producing ROS and reactive lipid peroxides.

All these mechanisms that generate oxidative stress and apoptosis are not only cytotoxic but might cause damage to mitochondrial function (Malhotra and Kaufman, 2007; Vannuvel *et al.*, 2013). Mitochondria are fundamental for oocyte maturation and embryo development to the blastocyst stage (Igosheva *et al.*, 2010; Van Blerkom, 2011; Babayev and Seli, 2015). In oocytes, their crucial role involves the process of oxidative phosphorylation and energy production (ATP), vital for the meiotic completion and spindle formation. This represents a compelling concern; therefore, a high level of embryos generated by MAR treatments display several abnormal chromosomes, most of them are due to a high frequency of chromosome mis-segregation in oocytes that generate aneuploid in oocytes and embryos (Wang S *et al.*, 2019; Wang S *et al.*, 2021).

Although maternal age is considered one of the main factors responsible for human embryo aneuploidy, it needs to be considered that this question also involves young women. During meiosis maturation, a necessary process occurs, i.e. crossover (CO) recombination, which is imperative to assure genetic variety in the future generation. Faulty or atypical CO arrangements due to several elements, including the kinetochore, spindle formation, checkpoints, energy affluence, oxidative stress, BMI and age might play a crucial role in the correct process of chromosome segregation. Therefore, abnormal CO configuration might lead to mis-segregation, which is the primary cause of embryo aneuploidy, implantation failure and miscarriage (Hunter, 2015; Wang S *et al.*, 2019; Wang S *et al.*, 2021).

Those findings are reinforced by animal studies demonstrating that oocytes collected from diet-induced obese mice have weakened quality and decreased embryo development (Minge *et al.*, 2008; Pohlmeier *et al.*, 2014). Table 1 illustrates the major effects that obesity might have on oocyte maturation. Recent studies have suggested the important role of the gut microbiome in influencing female subfertility and infertility. Several authors have illustrated the association of PCOS with decreased diversity of the gut microbiome (Lindheim *et al.*, 2017; Liu *et al.*, 2017; Insenser *et al.*, 2018). Furthermore, Elgaart and colleagues reported in *Drosophila melanogaster* that the loss of gut microbes repressed oogenesis (Elgart *et al.*, 2016). Figure 1 shows the mechanism by which changes in the gut microbiome might affect infertility.

Although future investigations need to evaluate these preliminary results further, it however seems that inflammation and oxidative stress processes might impair ovary function and oocyte competency, through which the change in gut permeability increased the leakage of LPS. The increased concentration of LPS in the blood circulation once reaching the FF might arrest the meiotic resumption, damage the spindle structure and mitochondrial membrane potential, compromising oocyte competency (Magata and Shimizu, 2017). However, studies showing a causative effect of gut microbiome changes on obesity-dependent changes in the ovary are still required.

Therefore, it might be common that obese women might experience abnormalities in folliculogenesis and ovulation, which can be overcome by controlled ovarian stimulation (Pohlmeier *et al.*, 2014). Oocyte quality and embryo development, implantation

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and pregnancy outcomes are deeply influenced by endocrine and metabolic environment (Pasquali and Gambineri, 2006). Evidence has suggested that obese women are three times more likely to be infertile compared with women with a normal weight (Rich-Edwards *et al.*, 1994). Finally, multiple studies have reported that obese women undergoing MAR treatments have decreased pregnancy and implantation rates and show higher miscarriage rates compares with their lean counterparts (Rich-Edwards *et al.*, 1994; Douchi *et al.*, 2002; Kumbak *et al.*, 2012; Kawwass *et al.*, 2016).

Obese women: miscarriage and endometrial receptivity

Several authors have investigated the relationship between obesity and impaired endometrium receptivity in humans. Boots and Stephenson (2011), in a systematic review and meta-analysis, investigated this aspect in natural conception. Data were analyzed and compared in three groups: normal-weight, overweight and obese patients. The authors found a higher miscarriage rate of 13.6% in 3800 obese versus 10.7% in 17,146 normal-weight patients, concluding that high BMI is linked with a higher miscarriage rate in women who conceive naturally (Boots and Stephenson, 2011). However, many studies have used the oocyte-donation model to clinically investigate this concern with generally contradictory results (Bellver *et al.*, 2003, 2007, 2013; Wattanakumtornkul *et al.*, 2003; Styne-Gross *et al.*, 2005; DeUgarte *et al.*, 2010).

A 2003 study investigated ~700 oocyte-donation cycles and found no differences in implantation or pregnancy rates in obese recipients. However, results revealed a significant difference in abortion rates between the obese (38.1%), the normal (13.3%) and overweight (15.5%) groups, even if the sample included only 50 patients in the obese group (Bellver *et al.*, 2003). In a subsequent analysis, the authors investigated more than 2600 patients who were undergoing a first egg-donation cycle, including 122 obese recipients. They reported a trend towards lower pregnancy rate when BMI increased (38.3% versus 45.5%) (Bellver *et al.*, 2007). In 2013, in a subsequent analysis including more than 9000 first egg-donation cycles with oocytes donated by normoweight donors, the same group reported a significant reduction in implantation, pregnancy and clinical pregnancy according to the increased BMI (Bellver *et al.*, 2013).

A study by Desolle and collaborators observed a statistically significant decrease in pregnancy rates when obese recipients received frozen embryos from donated oocytes (Dessolle *et al.*, 2009). Although this study was relatively small, with 450 cycles and only 33 obese patients, the authors speculated that obesity could be considered an independent risk factor for pregnancy failure. Another systematic review and meta-analysis including almost 48,000 cycles noted that obese women resulted in significantly lower clinical pregnancy and live birth rates than patients with normal BMI (Rittenberg *et al.*, 2011). A recent study also investigated the effect of BMI and increase risk of miscarriage following the transfer of euploid blastocysts in almost 3500 cycles of *in vitro* fertilization with preimplantation genetic testing for aneuploidy (PGT-A).

The authors found that miscarriage rates were significantly higher in obese women compared with women with normal weight. Live birth rates were also reduced in obese patients, indicating that endometrial receptivity, rather than aneuploidy, is responsible for these results (Cozzolino *et al.*, 2021). Therefore, according to these reports, there is agreement between BMI and adverse pregnancy outcome and excess weight induces an extra ovarian detrimental effect that decreased uterine receptivity and live birth rates (Wang JX *et al.*, 2002; Bellver *et al.*, 2007; DeUgarte *et al.*, 2010; Sobaleva and El-Toukhy, 2011; Aydogan Mathyk *et al.*, 2021). However, some other studies have presented divergent results (Styne-Gross *et al.*, 2005; Levens and Skarulis, 2008; McClamrock, 2008; Norman *et al.*, 2008). A meta-analysis published by Metwally and co-workers reported no evidence for increased risk of miscarriage in obese patients undergoing IVF cycles (Metwally *et al.*, 2008).

A large study using the Latin American Registry of ART investigated the effect of obesity on pregnancy outcomes in more than 107,000 patients undergoing autologous IVF/ICSI treatments. It noted that BMI was not associated with the percentage of pregnancy, live birth and miscarriage (MacKenna *et al.*, 2017). Similar findings were described in a systematic review published by Jungheim and co-workers, indicating that obesity has no adverse effect on IVF outcomes in patients undergoing oocyte-donation programmes (Jungheim *et al.*, 2010).

A multicentre randomized study, published by Einarsson and colleagues in 2017, demonstrated that an intensive weight reduction programme prior to IVF treatment resulted in a substantial weight loss, but it did not increase live birth rates in moderately obese women scheduled for MAR treatments, compared with women undergoing IVF without weight loss (Einarsson *et al.*, 2017). However, the frequency of live births after spontaneous pregnancy was higher in the weight reduction group. The same authors in a subsequent follow-up trial published in 2019 showed that, for women with a BMI ≥ 30 and < 35 kg/m^2 and scheduled for IVF, the weight reduction did not increase their chance of a live birth. It needs to be mentioned that all data reported in this trial were self-reported by the participants, which could affect the results (Kluge *et al.*, 2019).

Another recent randomized, double-blinded study performed across 19 IVF units in China analyzed 877 infertile women scheduled for IVF who had a BMI ≥ 25 kg/m^2. The main aim of this paper was to investigate whether pharmacologic weight-loss intervention before MAR cycles could obtain an increase in live birth rate among overweight or obese women. Results showed that the live birth rate was not significantly different between the two groups (25.5% in the weight-loss group versus 25.6% in the groups without weight reduction), concluding that treating obese women with Orlistat, prior to IVF treatment induces a weight reduction, however, it did not increase the live birth rate among overweight patients (Wang Z *et al.*, 2021).

Furthermore, some authors have recently investigated gene expression profiles to identify whether the luteal phase endometrial transcriptome is altered in obese women during the window of implantation. Preliminary results, which need to be confirmed, have shown that during the window of implantation, obese women display endometrial dysregulation and a different gene expression compared with normal-weight control women (Bellver *et al.*, 2011; Metwally *et al.*, 2014).

Finally, the transcriptomic profile of endometrial genes in infertile obese women has been reported and results demonstrated that obesity is associated with significant endometrial transcriptomic differences compared with normal-weight patients. This variation in obese women might partially explain decreased implantation rates and a rise in the number of miscarriages observed in obese women undergoing MAR treatments (Comstock *et al.*, 2017).

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Conclusion

In the few last decades, obesity has firmly increased across the globe. This chronic condition can activate other diseases including type-2 diabetes or cardiovascular conditions. The effect of obesity on ovarian function, oocyte quality, and embryo and endometrial receptivity has been intensely investigated.

The adverse effect of obesity on the above conditions seems to be mainly due to a rise in inflammation and oxidative stress due to the combination of elevated LPS and ROS production. Women with a high BMI undergoing MAR treatments had lower pregnancy outcomes and a higher risk of miscarriage compared with women with a normal weight. Indeed, those concerns are still the object of debate, as the current literature shows contradictory results.

Therefore, further studies are required to clarify how those mechanisms adversely impair the ovarian function, and oocyte and embryo viability to implantation, and allow a pregnancy to reach term. Future investigations will describe targets that can be applied clinically and therapeutically to improve fertility concerns in obese women or patients with metabolic problems.

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