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The Relationship Between the Body Mass Index and the Controlled Ovarian Stimulation Outcomes

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Abstract

When assessing the impact of body mass index (BMI) values on controlled ovarian outcomes, high BMI tips the balance regarding negative impact. Although not all studies agree, it seems that both intermediary and definite endpoints are offset, and the effect is progressively more significant with increasing BMI. In addition, evidence suggests that oocyte quality and endometrial receptivity are lower in overweight and obese patients. Perfecting how increased weight is quantified and unifying definitions of parameters assessed emerge as ways in which a more concise view of the impact of BMI on in vitro fertilization (IVF) procedures could be achieved. The unifying viewpoint is that weight interventions could improve natural and assisted conception results and assure a safer pregnancy for both mother and child. Still, how weight loss could be achieved, especially in these women to whom time pressure is added, remain to be refined.

Keywords: BMI; IVF; controlled ovarian stimulation.

1. List of abbreviations

AFC, antral follicle count; AMH, anti-Mullerian hormone; ART, assisted reproductive techniques; BMI, body mass index; CPR, clinical pregnancy rates; COH, controlled ovarian hyperstimulation; ET, embryo transfer; GC, gestational carrier; GnRH, gonadotropin releasing hormone; HC, hip circumference; HCG, human chorionic gonadotropin; HPO, hypothalamic-pituitary ovarian; ICSI.

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Intra-cytoplasmatic sperm injection; IVF, in vitro fertilization; LBR, live birth rates; LH, luteinizing hormone; MII, metaphase II; OHSS, ovarian hyperstimulation syndrome; OR, odds ratio; PCOS, polycystic ovary syndrome; POR, poor ovarian response; TTP, time-to-pregnancy; WC, waist circumference; WHR, waist-hip ratio.

2. Introduction

Obesity pervades women of reproductive age with a staggering prevalence of more than 30% in the age category between 20-and 39 years old. During pregnancy, its implications are seen in both mother and child. Influences are echoed in both the ovarian and uterine environments and lower the likelihood of a successful pregnancy [1]. Especially in countries where fertility treatments are publicly founded, restrictions based on BMI value have been suggested or implemented. Obstetric complications and miscarriage rates are related to increasing BMI and other possible confounding factors such as age and polycystic ovary syndrome. Valuation assessments state that direct costs per live birth in overweight and obese women are not higher than those in lean counterparts, and restriction of services to this growing population would cause stigmatization. Also, currently, there is no proper protocol to help these women lose weight and improve their chances of having a child, as weight loss strategies are mainly unsuccessful in maintaining the weight loss and positively influencing ART outcomes. Currently, an agreement on the BMI threshold value from which the risks outweigh the benefits of reproductive treatments has not been reached. Also, not all studies unanimously agree on the impact of increasing BMI on unfavourable outcomes of reproductive technologies. Another concern is that studies using surrogate markers may not accurately picture substantive outcomes such as live birth [2].

This review describes the mechanism by which extreme values of BMI and especially high BMI affect reproductive outcomes and which parameters of ART procedures are most affected. Also, a brief illustration of the current weight intervention modalities and their efficiency in improving treatment endpoint is presented.

We performed a PubMed database search using the following terms "controlled ovarian stimulation" and "BMI" or "body mass index" and also consulted reference lists of the latest articles. We selected 35 studies and summarized and organized the information presented.

3. The impact of body mass index on reproductive function

Obesity affects various levels of the reproductive system.

The hypothalamic-pituitary axis is impaired, leading to abnormal follicular development [3]. Hyperinsulinemia in obese patients stimulates androgen production and subsequent aromatization to estradiol in peripheral tissues. This resulted in negative feedback on the HPO axis and decreased gonadotropins with clinical reverberations such as menstrual abnormalities and ovulatory dysfunction [4]. As demonstrated by animal and human studies, a central mechanism is implicated in reduced fertility in obese patients. This effect is mediated by leptin, which is present in increased amounts in obese women and may down-regulate leptin receptors in the hypothalamus and interfere with the amplitude of LH pulses. Higher serum leptin levels correlate with follicular leptin, impair steroidogenesis in granulosa cells, and decrease endometrial receptivity and lower implantation rates [4].

Granulosa cell function and the intrafollicular fluid are modified in obese individuals, affecting oocyte maturation and oocyte quality [3]. The detrimental effect on oocytes is present at the organelles level with disrupted meiotic spindle formation, mitochondria and endoplasmic reticulum alterations. It is thought to be caused by the toxic effect of excess lipids and low-grade inflammation present in obese individuals [4]. Lipotoxicity and direct adverse leptin effects are also behind the poor-quality embryos obtained from obese women [4].

The effects of obesity on the endometrium are controversial. However, studies on mice and human subjects support the implication of obesity on decidualization defects which contribute to compromised endometrial receptivity and poor implantation and placentation [4].

Furthermore, placental steroid production, especially of estradiol and progesterone, is decreased in obese women. Although the clinical implications are unknown, it is presumed to be one cause of adverse perinatal outcomes [1]. Finally, there is concern about the transgenerational impact of maternal obesity in children. Epigenetic and genetic modifications in utero may translate to health issues in offspring starting from birth and continuing throughout their lifetime [4].

4. Obesity and IVF outcomes

An internet-based prospective Danish study of body size and time-to-pregnancy (TTP) concluded that overweight, obese, and very obese women have longer TTP than normal-weight women [5].

Because of the high rising prevalence of overweight and obesity in women of reproductive age and the difficulties in achieving live birth through natural conception in this group, many overweight or obese women resort to ART to increase their chance of having a child.

Inferior ART outcomes observed in women with higher BMI may be explained by lower ovarian response requiring higher doses of gonadotropins, decreased oocyte quality, lower implantation rates, impaired endometrial receptivity, and higher risk of miscarriages [6].

A large cohort study on BMI and IVF outcomes, comprising 239.127 in vitro fertilization cycles with autologous oocytes, reports higher success rates in women with low or normal BMI and worsening effects as BMI increased. The implantation rates, clinical pregnancy rates and live birth rates were gradually and progressively lower, and respectively pregnancy losses were higher as BMI increased. This study suggests that lower BMI does not have the same detrimental impact as high BMI has on reproductive outcomes. Also, the hypothesis that PCOS is the underlying cause of unfavourable effects in overweight and obese patients was disputed by the present study results, BMI coming out ahead as an independent variable affecting IVF success rate. Although higher BMI classes were associated with poor prognosis of live births, reaching 10% in morbidly obese individuals, this prognosis is still higher than females with other pathologies requiring ART, such as diminished ovarian reserve. Therefore, authors consider limiting access to obese individuals unwarranted [7].

In the systematic review of observational studies by Maheswari and his colleagues women with a BMI $\geq$ 25

kg/m2 had a lower chance of pregnancy following IVF (OR 0.71, 95% CI: 0.62, 0.81), required higher doses of gonadotrophins and were at higher risk of miscarriages (OR 1.33, 95% CI: 1.06, 1.68) compared with normal-weight women. However, data could not provide sufficient evidence for the role of BMI concerning live birth rate, cycle cancellation, oocyte recovery, and ovarian hyperstimulation syndrome. Authors regard the lack of standardized BMI categories and uniform outcome measures as impeding factors in interpreting and generating informed recommendations on treatment protocols and interventions [8]. However, not all studies are in agreement. In a retrospective cohort study performed on a French population (1588 women) undergoing IVF +/- ICSI, the impact of obesity and obesity severity on live birth rate per cycle and cumulative live per rate (all pregnancy attempts with both fresh and frozen embryos) was assessed. The protocol used involved either an agonist or antagonist according to the infertility cause, different among BMI categories, with obese women presenting more frequently with PCOS and ovulation disorders. Although the number of embryos transferred decreased with increasing BMI class during the first and second stimulation cycle, the live birth rate did not differ according to BMI category. The chance of obtaining a live birth adjusted for age, smoking status, infertility cause, and AMH levels was not influenced by either obesity or obesity severity. After adjusting for confounding factors, BMI also did not affect the miscarriage rate. A limitation of the study was the decreased number of women with a BMI over 35 kg/m2 and over 40 kg/m2 [10]. While analyzing the results of 1654 ICSI cycles, BMI did not significantly impact ART outcomes. Therefore authors suggested that treatment denial should not be based on the presence and level of obesity. Estradiol and progesterone levels at the time of hCG administration following COH, mean numbers of oocytes retrieved, fertilized, and the number of embryos transferred was not different between groups categorized according to their BMI. Although in patients with morbid obesity (BMI >35 kg/m2), endometrial thickness and LBR (live birth rates) per cycle and per ET (embryo transfer) were lower, no difference was observed in terms of implantation rate, clinical pregnancy rate (CPR) per cycle and ET, as well as live-birth rates, did not differ significantly between groups [6]. Elevated BMI does not seem to impact in vitro fertilization outcomes such as ovarian response adversely, number of oocytes retrieved, embryo transfer, implantation, and clinical pregnancy rates in younger women (under the age of 35), age being the strongest predictor of IVF success based on results of the study of Martinuzzi and his colleagues [11]

Regarding the specific alteration caused by obesity that determines poor IVF outcomes, sides have been taken between oocyte quality and uterine environment as being the principal culprit.

5. Endometrial receptivity

In a 2010 study, no difference in insemination procedure, fertilization rate, day of ET, mean number of transferred and cryopreserved embryos, percentage of blastocyst transfers, or embryo quality on days 2 and 3 were found among groups defined by BMI value (underweight, average weight, overweight and obese). However, implantation, pregnancy, and live birth rates were poorer in obese women, with a progressive decrease for each increase in the BMI unit. Also, the cumulative pregnancy rate after four IVF cycles was reduced as BMI increased. Authors concluded that the IVF outcomes were decreased due to alteration in the uterine environment without impacting embryo quality [12]. To control the impact on oocyte quality, Bellver and his colleagues. They assessed the outcomes of 9.587 first ovum donation cycles from a typical weight

donor. Implantation, clinical pregnancy, twin pregnancy, and live-birth rates significantly decreased with increased BMI, suggesting that uterine receptivity is the principal malefactor [13]. A previous 2007 study of Bellver on 2656 cycles with ovum donation of good quality embryos stated that the role of the endometrium and its environment should be considered when assessing poor ART outcomes [14]. In obese women, there is a dysregulation of endometrial gene expression during the window of implantation. These genes are implicated in the development and regulation of different biological functions, and some have been previously related to implantation and unexplained infertility. This human luteal phase endometrial transcriptomic profile alteration is more pronounced when obesity is associated with PCOS or infertility [15]. These studies are supported by a 2019 systematic review and meta-analysis, encompassing 21 studies and almost 700 000 cycles, which stated that female obesity negatively impacted the live birth rate following IVF and the association with PCOS further harmfully affected prognosis, possibly because of exacerbated metabolic dysregulations. In contrast, oocyte origin (donor or non-donor) did not impact IVF outcomes, suggesting that endometrial receptivity rather than oocyte quality is preferentially affected by obesity [3]

The gestational carrier (GC) model allows assessment of uterine receptivity independently of ovarian environment and under controlled conditions of hormonal support and embryo quality. A retrospective analysis of 163 patients suggests that obesity does not impact reproductive outcomes such as clinical pregnancy rates and live birth rates in gestational carrier cycles. Authors also suggest that the metabolic profile of the carriers may be more important than BMI in explaining the differences in pregnancy outcomes [16].

6. Oocyte quality

Obesity and the subsequent metabolic dysfunction generate a substandard environment for embryo development as measured by blastocyst formation. The lower blastocyst formation rate may be one of the culprits for dissatisfying results of reproductive technologies. In a study performed on 120 patients, authors reported that patients who were overweight or obese had significantly lower blastocyst formation rates than normal-weight controls, despite similar embryo development up until day 3. Also, PCOS, more frequently encountered in patients with higher BMI, did not affect oocyte/embryo quality, signifying an independent effect of increased weight and metabolic disturbances on embryo development [17]. Follicular fluid composition seems to partly reflect metabolic changes in serum and influence oocyte quality, irrespective of BMI. Metabolic aberrations rather than BMI-related changes are probably responsible for decreased oocyte quality in obese patients [18]

Jungheim's systematic review and meta-analysis on IVF outcomes in obese donor recipients concluded that oocyte quality, not endometrial receptivity, may be the overriding factor influencing reproductive outcomes in obese women using autologous oocytes [19]. Similarly, a study assessing more than 45 000 cycles suggested that obesity affects embryo quality, reducing pregnancy rates reported with autologous but not with donor oocytes. Obesity seems to impair oocyte quality in early pregnancy. Still, later, a damaged intrauterine environment may surpass the initial advantage provided by donor oocytes in obese women and may lead to fewer live births [20].

A study of retrospective design on 1105 patients undergoing ICSI sought to find whether body mass index

affected oocyte morphology. BMI negatively correlated with the number of oocytes retrieved, MII oocytes injected, embryos obtained, high-quality embryos, and oocyte recovery rate. In addition, there was a trend towards lower implantation rates. However, neither gonadotropin requirements (increased gonadotropin doses being known to cause oocyte dysmorphisms) nor different parameters of oocyte morphology appeared to be influenced by body mass. Still, the limited number of patients in the underweight and obese categories and the study's retrospective nature impair the formation of a definitive conclusion [9].

In the category of patients with a poor ovarian response (POR), a retrospective study exploring the role of overweight and obesity found that although MII oocytes, gonadotropin dose, COH duration and embryo counts were similar between groups, fertilization rates and clinical pregnancy rates were lower in the obese group compared to controls with normal weight. Obesity had a strikingly higher impact than overweight on the outcomes of IVF in POR patients. Obese patients had a lower concentration of LH, probably because of increased aromatization of androgens to estrogens. Also, hyperleptinemia causes central leptin resistance and hypogonadotropic hypogonadism with altered pulsatile LH amplitude. Decreased LH concentrations may impair follicular growth. The study proposed a cutoff value of 4 mIU/ml with an 86% specificity to predict IVF failure. Reduced fertilization rate with normal oocyte numbers suggests that the quality of the oocytes is impaired in obese women [21].

7. Choice of stimulation protocols in obese patients

A comparative study of stimulation protocol used during ovarian stimulation in normal-weight women compared with obese women undergoing IVF reported that in both agonist and antagonist groups, a higher dose of gonadotropins was needed in patients with a BMI ≥ 25 kg/m2 than in patients with normal BMI. Still, no significant differences were found in the length of stimulation, the number of oocytes retrieved, or the number of embryos transferred. In both the antagonist and agonist groups, the number of clinical pregnancies was higher in patients with normal BMI, suggesting an impairment of ovarian response to gonadotropins secondary to obesity. Although the study found no significant differences between the two stimulation protocols, the authors propose antagonist use as the better alternative, especially in patients at risk for ovarian hyperstimulation syndrome and those considered poor responders [22]. A nomogram allowing individualization of gonadotropin starting dose in GnRH antagonist protocol was proposed. Based on multivariate analysis, It takes into account BMI, AFC (antral follicle count) and AMH, thereby facilitating clinical decisions for adjusting the gonadotropin starting dose to optimize the number of oocytes obtained, pregnancy rate and protection from unwanted outcomes such as insufficient follicular recruitment in case of inadequate low dosage, and increased risk of OHSS, unsynchronized development of the endometrium and chromosomal aberration of oocytes due to excessive dosage [23].

8. Miscarriage risk

The pooled analysis from a systematic review of 6 studies and 28. Five hundred thirty-eight women revealed a higher miscarriage rate in obese women (13.7%) versus normal-BMI women (10.9%) who conceive spontaneously [24]. Also, another meta-analysis focusing primarily on miscarriage risk after assisted conception

suggested that the risk is increased in overweight and obese women after oocyte donation and ovulation induction. Still, there was no evidence of an increased risk of miscarriage after intracytoplasmic sperm injection (ICSI) [25]. Both analyses address the problem of the clinical heterogeneity of studies as an impediment to making a clear conclusion and state that there is insufficient evidence for the relationship between increased BMI and recurrent miscarriages [24, 25].

The study of Goldman and his colleagues failed to show an impact of obesity on oocyte quality involving alterations in normal mitotic check-points and abnormalities in cell division, thereby leading to aneuploidy [26]. Still, recurrent early pregnancy loss with euploid chromosomes (46, XX or 46, XY) are higher in obese women and are associated with an increased risk of recurrent miscarriage as compared to non-euploid miscarriages, which were shown to occur on a random basis and generally do not increase the risk of subsequent miscarriage. Associated endocrine changes and metabolic abnormalities in the obesogenic environment are presumed to cause suboptimal implantation and subsequent miscarriage. Still, the authors did not find a higher frequency of these disorders in their cohort of individuals with higher BMI. Further studies are needed to determine why euploid miscarriages are more frequent in the obese population [27]. A study assessing more than 700 cycles of recipients of ovum donation concluded that obesity, independently of the presence of PCOS, was associated with a four-fold increase in the risk of spontaneous abortion, suggesting uterine receptivity was the culprit for poor reproductive outcomes [28].

9. BMI - not a perfect measure for assessing obesity implications on COS

Body mass index is not an ideal marker to evaluate obesity. Because it cannot accurately assess body composition and discern between fat mass and lean mass and weight distribution, other anthropometric indicators such as waist and hip circumference (WC, HC), waist-hip ratio (WHR), body fat quantification using bioimpedance (BF%), and body composition are proposed to assess female reproductive parameters more accurately. A cutoff value of 80 cm for WC could predict pregnancy rates in eutrophic women. WHR of 0.85 appeared as a valuable indicator of ART results such as oocytes retrieved, mature oocytes and fertilization in obese women. It seems that fat amount and distribution are more critical than that absolute weight regarding fertility parameters and may cause divergent study results [29].

Is low BMI as detrimental as high BMI?

Supposedly, the association between BMI and IVF outcomes takes the form of an “inverted U shape”. It is presumed that both underweight, as well as overweight and obese individuals have poorer ART outcomes compared to individuals with a normal BMI. Still, current literature appears to at least partially debunk this conception. The study of Wise stated that fecundability in underweight women varied by parity status with an increase in parous women and a decrease in nulliparous women, although overall associations were weak [5]. A large study examining the effect of low body mass index on outcomes of IVF found no difference compared to normal weight individuals. Although some disparities existed in COS characteristics between groups, evaluation of clinical outcomes failed to show any difference between groups, particularly with patients who underwent single euploid frozen embryo transfer [30].

10. Obesity interventions

Current guidelines have a concordant view on achieving a healthy weight (based on BMI) before pregnancy using nutritional intervention and physical activity [1]

An open-label, single-centre, randomized pilot study brought out promising results regarding the impact of a brief, intensive weight loss intervention on reproductive outcomes in obese women (BMI between 35-45 kg/m2) with anovulatory infertility. Although authors reported an increased reluctance of women to undergo a dietary intervention, which led to a small study sample, the intensive weight loss approach appeared to be safe and more effective than nutritional counselling regarding weight loss, metabolic parameters, and pregnancy achievement [31].

A systematic review and meta-analysis of 40 studies on both men and women stated that a combination of dietary counselling, with a decreased calorie amount for fat and refined carbohydrates coupled with aerobic exercise, was more likely than counselling to result in weight loss, ovulation improvement and pregnancy. In the case of IVF conceptions, there was no difference between intervention and control groups [32]. However, another systematic review focusing specifically on weight loss intervention in obese women undergoing ART stated that despite the overall poor overall quality of studies included, including the clinical recommendation of weight loss using diet and lifestyle changes, non-surgical medical intervention and bariatric surgery, before ART prevails. Higher pregnancy and live birth rates and improved intermediate outcomes (decreased cancellation rates, an increase in the number of embryos available for transfer, a reduction in the number of ART cycles required to achieve pregnancy and a decrease in miscarriage rate) were associated with weight-loss interventions. The authors also emphasize the need for prospective RCTs to establish which intervention is more appropriate for this category of patients [33].

Despite this, extensive studies do not replicate these findings. Although an intensive weight reduction intervention (low-calorie diet for 12 weeks followed by weight stabilization for 2-5 weeks) resulted in a significant weight loss (mean weight change -9.44 kg), it did not substantially affect live birth rates in women with a BMI between 30 and 34.9 kg/m2, scheduled for IVF [34]. In the follow-up of this prospective, multicenter, randomized controlled study, weight reduction in obese infertile women on cumulative live birth rate two years after was assessed using questionnaires regarding current weight, live births, and ongoing pregnancies. Female patients randomized to weight loss intervention before performing IVF did not have a better chance of live birth in the following two years after the initial intervention than the group of women with IVF only. Also, most women have regained their pre-study weight [35].

11. Conclusion

As the global pandemic of obesity expands, its effects are seen on multiple levels. Not surprisingly, reproductive competency is among the ones gravely affected and, at first look, assisted reproductive techniques seem to offer an option for these women. But even using ART cannot overcome the deep reverberations obesity has. Whether primary defective oocyte quality, uterine environment, or both are guilty of poor reproductive outcomes remains

an open debate. In the aftermath, further clarifications are needed to offer target solutions and improve the chances of achieving pregnancy and live birth.

Despite overweight and obesity being in many cases a modifiable factor, particularly when comparing it with age, the primary influence for bad ART outcomes, change has never been easy. Many controversies concerning obesity and reproductive results are deep-seated, but, if anything, we must be conscious of the grave impact obesity has and implement solutions on a global scale for a global problem.

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