Elevated body mass index impairs cumulative live birth rate and obstetric safety of younger women undergoing in-vitro fertilization/intracytoplasmic sperm injection treatment: A retrospective study

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Abstract

Objective: To evaluate the impact of elevated body mass index (BMI) on short- and long-term outcomes of in-vitro fertilization (IVF)/intracytoplasmic sperm injection (ICSI) treatments. Design: Retrospective cohort study. Setting: Teaching hospital. Population: Overall, 7229 patients undergoing IVF/ICSI fresh cycles and subsequent frozen embryo transfer cycles during 2014-2020. Methods: The patients were divided into normal (18.5–24.9 kg/m2) and high BMI ([?] 25 kg/m2) groups. Subgroup analyses were performed based on the boundary of 38 years old. Multivariate analysis was used to determine whether BMI was associated with live birth rate (LBR) or cumulative live birth rate (CLBR). Main Outcome Measure: Ovarian response, pregnancy outcomes, and safety for both mother and fetus. Results: For younger women (< 38y), CLBR was significantly reduced in the high BMI subgroup compared to the normal BMI control (73.7% vs 76.8%, p = 0.008) and was accompanied by fewer retrieved oocytes and available embryos. Meanwhile, the incidences of cesarean section (92.9% vs 87.1%, p < 0.001), hypertensive disorders of pregnancy (6.7% vs 3.1%, p < 0.001), fetal macrosomia (4.7% vs 2.8%, p = 0.002) and birth defects involving cleft lip and palate (0.4% vs 0.1%, p = 0.030) were significantly higher than the normal BMI group. However, no such differences were observed among older women ([?] 38y). Multivariate analysis revealed that high BMI was a risk factor for CLBR (OR = 0.837, 95% CI: 0.729–0.96). Conclusions: Elevated BMI has a greater adverse impact on younger women.

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Running title: High BMI affects IVF/ICSI outcomes

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Abstract

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Design: Retrospective cohort study.

Setting: Teaching hospital.

Population: Overall, 7229 patients undergoing IVF/ICSI fresh cycles and subsequent frozen embryo transfer cycles during 2014-2020.

Methods: The patients were divided into normal (18.5–24.9 kg/m^2) and high BMI ([?] 25 kg/m^2) groups. Subgroup analyses were performed based on the boundary of 38 years old. Multivariate analysis was used to determine whether BMI was associated with live birth rate (LBR) or cumulative live birth rate (CLBR).

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Conclusions: Elevated BMI has a greater adverse impact on younger women.

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Keywords: BMI, CLBR, obstetric complications, neonatal outcomes, birth defects

Tweetable abstract:

Elevated BMI has a greater adverse impact on CLBR and obstetric safety among younger women.

INTRODUCTION

The overweight and obesity epidemic continues to plague modern society due to the radical change of lifestyle and decreased physical exercise in recent years. Research has demonstrated that overweight and obesity are major causes of chronic diseases, such as cardiovascular disease and type 2 diabetes[1]. Obesity raises the risk of hypertension, dyslipidemia, diabetes, and coronary heart disease.

The burden of overweight and obesity is high in both developed and developing countries, with the proportion of overweight and obese women increasing from 29.8% in 1980 to 38.0% in 2013[2]. Elevated body mass index (BMI) in women affects every stage of reproductive life, including puberty, pregnancy, and delivery. This is related to menstrual and ovulatory disorders, impaired endometrial development and embryo implantation, increased abortion rates, and pregnancy complications, such as hypertensive disorders of pregnancy (HDP), pre-eclampsia, gestational diabetes mellitus (GDM), postpartum hemorrhage, and cesarean delivery[3]. Moreover, adverse perinatal outcomes, including fetal macrosomia and neural tube defects, are more likely to occur in obese women[4].

Numerous studies investigating the impact of elevated BMI on in-vitro fertilization (IVF)/intracytoplasmic sperm injection (ICSI) outcomes have been published, albeit with disparate results. Several studies found that an elevated BMI had no adverse effect on IVF/ICSI outcomes[5-8], while others demonstrated that elevated BMI was associated with adverse IVF outcomes, including lower ovarian response, inferior oocyte and embryo quality, higher cancellation rate, and lower clinical pregnancy rate (CPR) and LBR, as well

as higher rate of miscarriages[9-16]. Despite the broad research in this area, the effect of elevated BMI on IVF/ICSI outcomes is indeterminate.

Therefore, the aim of this study was to evaluate the impact of elevated BMI on both short- and long-term outcomes of fresh IVF/ICSI cycles and subsequent frozen embryo transfer (FET) cycles, particularly ovarian response, embryo quality, pregnancy outcomes, obstetric and neonatal complications, and congenital defects. This way, the impact of high BMI on assisted reproductive technology (ART) can be elucidated more comprehensively and inform pre-ART counseling of overweight and obese women.

METHODS

Patients

We performed a retrospective study on women who were first treated at the Reproductive Medicine Center of Tongji Hospital from January 1, 2014, to December 31, 2017. This was a non-interventional, single-center cohort study of patients undergoing routine long gonadotropin-releasing hormone (GnRH) agonist protocol. Patient information was anonymous without any identifier at the time of retrospective chart review.

BMI was expressed as the weight in kilograms divided by the square of the height in meters (kg/m^2). Based on the World Health Organization classification, all patients with normal (18.5–24.9 kg/m^2) and high ([?] 25 kg/m^2) BMI who underwent their first fresh IVF/ICSI cycles were included in the analysis. Moreover, women with polycystic ovary syndrome (PCOS) or uterine factors such as intrauterine adhesion and mediastinum uterus were excluded, and all cycles with IVF+ICSI fertilization, donor oocyte, freeze eggs, and preimplantation genetic diagnosis/preimplantation genetic screening were not included. Finally, a total of 7701 women were enrolled and were followed up to May 2020, until either delivery of one live infant or discontinuation of treatment. A total of 464 patients did not achieve live birth but had frozen embryos from the first stimulation, and eight women were pregnant. Finally, 7229 women completed the follow-up (Fig. S1).

Protocol for Ovarian stimulation

Controlled ovarian stimulation was performed using the routine long GnRH agonist protocol. Oocytes were retrieved transvaginally 34–36 h after human chorionic gonadotropin (hCG) administration, and fertilization was assessed 16–18 h after routine insemination or ICSI. Blastomere number and regularity, as well as the presence and volume of cytoplasmic fragmentation, were assessed 24 and 48 h later, respectively. According to the protocol developed by Chinese legislation, no more than two embryos were transferred on day 3 or 5 after oocyte retrieval. The remaining available embryos were cultured for blastocyst formation. Then, all patients received luteal support after embryo transfer, including intramuscular injections of progesterone in oil or vaginally administered micronized progesterone.

Embryo grading

The presence of two clearly distinct pronuclei, together with two individualized or fragmented polar bodies, 20 hours after IVF/ICSI, was considered normal fertilization. Day 3 embryos with 7–9 equal-sized cells, $< 10\%$ degree of fragmentation rate, were defined as high-quality embryos (HQE). Day 3 embryos with eight equal size blastomeres and no cytoplasmic fragments, derived from day 2 embryos with four equal size blastomeres and no cytoplasmic fragments were defined as top-quality embryos (TQE)[17].

Pregnancy outcomes

The primary pregnancy outcome was the cumulative live birth (CLB), defined as at least one liveborn baby at [?] 20 weeks gestation resulting from an ART-initiated cycle, including all fresh and subsequent FET cycles, until one live birth occurred or all embryos were used.

Other pregnancy outcomes assessed in the study included implantation rate, CPR, ongoing pregnancy rate (OPR), LBR, ectopic pregnancy rate, biochemical pregnancy rate, early spontaneous abortion rate (ESAR), late spontaneous abortion rate (LSAR), singleton pregnancy rate, and multiple pregnancy rate per fresh

embryo transfer cycle. Implantation rate was determined based on the number of gestational sacs detected by ultrasound scan 5–7 weeks after embryo transfer divided by the number of embryos transferred. Clinical pregnancy was defined as the presence of a gestational sac with observed fetal heart by ultrasound 5 weeks after embryo transfer, while ongoing pregnancy was defined as a pregnancy with fetal heart activity detected by ultrasound after 12 weeks of gestation. Live birth was defined as at least one liveborn baby at [?] 20 weeks gestation with fresh embryo transfer. Early spontaneous abortion was defined as miscarriage occurring during the first trimester of pregnancy, while late spontaneous abortion was defined as miscarriage occurring after the first trimester of pregnancy. Multiple pregnancy was defined as more than one gestational sacs detected by ultrasound scan 5–7 weeks after embryo transfer.

Perinatal outcomes, obstetric complications, andcongenital defects

Obstetric and perinatal complications, as well as congenital defects of deliveries from an ART stimulation cycle, including all fresh and subsequent FET cycles, were completely followed up. In this study, live births after fresh embryo transfer were referred to as fresh live births (FLBs); live births from all fresh and subsequent FET cycles were called CLBs.

Obstetric complications included in this study were HDP, GDM, pre-eclampsia, preterm premature rupture of membranes, placenta previa, polyhydramnios, oligohydramnios, postpartum hemorrhage, placental abruption, and placenta accreta.

Perinatal outcomes included mode of delivery, gestational age, weight at birth, neonatal asphyxia and infection, neonatal intensive care unit (NICU) admission, and early neonatal death. Specifically, very preterm birth and preterm birth were defined as a live birth or stillbirth occurring before 32 and 37 gestation weeks, respectively. Very low birth weight and low birth weight were respectively defined as birth weight lower than 1,500 grams and 2,500 grams. Fetal macrosomia was defined as birth weight $>$ 4,000 grams. Early neonatal death was defined as the death of a liveborn baby within 7 days of birth.

Based on the International Statistical Classification of Diseases Q codes (Q00-Q99)[18], 10th Revision, congenital malformations followed up in this study included cleft lip and cleft palate and congenital malformations originating from the nervous, circulatory, digestive, urogenital, and musculoskeletal systems.

Statistical analysis

Data were analyzed using SPSS 20.0 software. Normally distributed continuous data were presented as mean ± standard deviation, and non-normally distributed continuous data were expressed as median and quartile interval (M [P25-P75]). Categorical data were reported as the number of cases and frequency (%). Independent sample T-test was used for intergroup comparisons of normally distributed continuous data. Non-parameter test (rank-sum) was used for non-normal distribution. The Chi-square tests (or Fisher's exact tests, if appropriate) were used to determine the statistical significance between percentages for categorical data. A multivariate logistic regression model was used to determine odds ratios (ORs) and associated 95% confidence intervals (CIs) when comparing LBR and CLBR between two BMI groups. Models were adjusted for a series of possible confounders: maternal age, fertilization method, basal follicle-stimulating hormone (FSH), antral follicle count, and retrieved oocytes. Statistical significance was set at $P < 0.05$.

RESULTS

Patient characteristics

A total of 472 (6.5 %) were excluded due to lack of CLB results; therefore, of the 7701 women eligible for the study, 7229 women were included in the analysis (Fig. 1). The participants were divided into two BMI groups (normal BMI and high BMI); the baseline characteristics are summarized in Table 1. Overall, 6174 women had normal weight (18.5 [?] BMI [?] 24.9), while 1055 women were considered overweight and obese (BMI [?] 25). There were no significant differences in the type and etiology of infertility, fertilization method, and antral follicle count between the two BMI groups. The duration of infertility (3 vs 3, Z= 5.594, $p < 0.001$)

and basal FSH (6.66 vs 6.9, Z= -5.337, $p < 0.001$) were significantly longer and lower in the high BMI group than in the normal group, respectively.

Parameters for ovarian response

The patients were further divided into two subgroups based on the cut-off age of 38 years. Comparisons of the parameters for ovarian response between the two different BMI categories are presented in Table 2 and Table S1. Younger women (< 38y) with high BMI received a significantly higher dose of Gn stimulation (29 vs 26, z = 10.255, $p < 0.001$) and had a slightly longer duration of Gn stimulation (10 vs 10, z = 1.975, p = 0.048) than those with normal BMI (Table 2). There were more retrieved oocytes (14 vs 13, z = -3.312, p = 0.001), metaphase II oocytes (12 vs 12, z = -3.322, p = 0.001), normally fertilized oocytes (8 vs 8, z = -3.324, p = 0.001), cleavage (10 vs 9, z = -3.816, $p < 0.001$), cleavage-stage embryos (8 vs 8, z = -2.978, p = 0.003), and blastocyst (4 vs 4, z = -2.621, p = 0.009) in the normal BMI group than in the high BMI group. However, in the older women ([?] 38y) subgroup, compared to the normal BMI group, the duration of Gn stimulation was shorter (10 vs 10, z = -2.802, p = 0.005), and the cleavage was lower (7 vs 7, z = -2.141, p = 0.032) in the high BMI group. In both age subgroups, serum peak estradiol and progesterone concentrations on hCG day in the normal BMI group were significantly higher than in the high BMI group. No significant differences in the numbers of HQE and TQE were observed between the two BMI groups (Table 2 and Table S1).

Pregnancy outcome measures

As indicated in Table 3, the CLBR and cancellation rate showed a statistically significant reduction in younger women with high BMI compared to those with normal BMI (73.7% vs 76.8%, p = 0.008; 28.6 % vs 34.8%, $p < 0.001$, respectively), but no significant differences were observed in the older women subgroup (Table S2).

Other pregnancy outcomes are presented in Table 3 and Table S2. There were no significant differences in implantation rate, CPR, OPR, LBR, ectopic pregnancy rate, biochemical pregnancy rate, ESAR, and LSAR for all age subgroups between the two BMI groups. No significant differences were found in the rates of singleton pregnancy and multiple pregnancy.

Perinatal outcomes, obstetric complications, and congenital defects

For younger women, details of perinatal outcomes resulting from FLBs, such as gestational age, birth weight, neonatal asphyxia and infection, NICU admission, and early neonatal death, are presented in Table S3a. These results were not significantly different between the two BMI groups. Besides, the rate of cesarean section was significantly higher in the high BMI group than in the normal BMI group (90.6% vs 83.2%, $p < 0.001$; Table S3a). In addition, obstetric complications, except for the rates of HDP and placenta previa, were largely similar between the two BMI categories. The incidences of HDP (4.4% vs 1.5%, $p < 0.001$) and placenta previa (0.6% vs 2.2%, $P < 0.001$) in the high BMI group were significantly higher and lower, respectively, than in the normal BMI group (Table S3a).

The rates of cesarean section (92.9% vs 87.1%, $p < 0.001$) and HDP (6.7% vs 3.1%, $p < 0.001$) resulting from CLBs in younger women with high BMI had similar trends to those of FLBs (Table S4a). Moreover, the incidence of fetal macrosomia (4.7% vs 2.8%, p = 0.002; Table S4a) and birth defects involving cleft lip and palate (0.4% vs 0.1%, p = 0.030; Table S5b) resulting from CLBs in younger women with high BMI was significantly higher than in those with normal BMI; these results were not significantly different compared to those of FLBs (Table S3a and S5a).

In contrast, no significant differences were found in perinatal outcomes, obstetric complications, and congenital defects resulting from FLBs and CLBs in older women subgroups (Table S3b, S4b, S5a, and S5b).

Multivariate logistic regression analysis of BMI-related LBR and CLBR

There was no statistical difference in the probability of FLB between the high BMI group and the normal BMI group after adjusting for differences in maternal age, basal FSH, fertilization method, antral follicle

count, and the number of retrieved oocytes (Table S6).

After adjusting for differences in maternal age, antral follicle count, fertilization method, and the number of retrieved oocytes, women with high BMI had significantly decreased odds of CLBR (Table 4). The adjusted OR (95% CI) of CLBR were 0.837 (0.729-0.96) for high BMI cohorts compared with normal BMI cohorts.

Discussion

Main findings and Interpretations

In the current study, elevated BMI was associated with fewer mature oocytes and available embryos in younger women, but we did not observe a statistically significant decline in blastocyst formation rate, HQE rate, and TQE rate in overweight and obese individuals versus normal-weight controls, which is inconsistent with the research results of Ioanna et al. [9]. Despite previous studies reporting that elevated BMI can be associated with poor pregnancy outcomes of fresh IVF cycles, no significant effects of maternal BMI on implantation rate, CPR, OPR, and LBR in all groups and subgroups were observed in fresh cycles. This finding may be related to the lack of differences in the number of HQE and TQE, which could also explain the absence of statistical differences in the abortion rates of fresh cycles. Unlike the recent study demonstrated that obesity was associated with spontaneous abortion[19], compared to women with normal weight, the odds of early miscarriage were 1.45 times higher among obese women[20].

CLBR was significantly lower among younger women with high BMI relative to the normal BMI group; this may be due to a reduced number of available embryos at cleavage and blastocyst stages in the high BMI group. Nevertheless, the decrease in the number of embryos was triggered by a reduction in the number of retrieved oocytes and mature oocytes, which was statistically different for younger women among different BMI groups. Thus, we speculated that the obesity microenvironment has a greater adverse effect on oocyte maturation and development in younger women than in older women.

Previous animal studies have indicated that obesity adversely affects oocyte maturation and embryonic development [21-25]. This could be due to direct damage of the oocytes and indirect effects of dysfunctional systemic maternal endocrinology and metabolism. Murine models fed a high-fat diet (HFD-mice) were used to mimic the effects of obesity and metabolic dysfunction observed in obese humans. In addition to the body weight gain of the HFD-mice, hypercholesterolemia, elevations in glucose, insulin, or free fatty acids, and changes in adipokines may affect oocyte quality[21]. The adverse effects of maternal obesity have been observed as early as the oocyte and two-cell embryo stages, and there are more apoptotic follicles and smaller and fewer mature oocytes in obese mice compared with control mice[26]. Oocytes from HFD-mice tend to have meiotic aneuploidy, spindle and chromosome alignment defects, and mitochondrial abnormalities, which are a major cause of early embryonic loss[23, 24]. In addition, bidirectional communication of the oocyte with the surrounding cells is critical for oocyte development, and several studies have attempted to evaluate the impact of obesity on these ovarian cells. HFD-mice exhibited increased anovulation and decreased fertilization rates in vivo, which is accompanied by remarkably increased apoptosis, endoplasmic reticulum stress, lipid accumulation, and mitochondrial dysfunction in granulose and cumulus cells[27]. Increased apoptosis of granulose cells might explain the low peak estradiol levels among obese women of any age, despite the increased Gn dose for younger women. But research evidence from human studies is limited, Jungheim et al. demonstrated that obesity does not affect IVF outcomes in women using donor oocytes[28]. Recent study using the Time-Lapse system indicated that human oocytes from overweight and obese women were smaller and less likely to complete fertilization; the resulting embryos were more likely to reach the morula stage, and the trophectoderm of blastocysts had fewer cells[29]. Thus, the adverse effect of elevated BMI on oocyte quality rather than endometrial receptivity may be the major factor impairing IVF/ICSI outcomes. However, further research is needed to confirm and consolidate the above ideas.

Moreover, the long-term adverse effects of obesity are mainly reflected in the birth safety and health of the offspring. In the present study, maternal HDP and fetal macrosomia were more likely to occur among younger women with high BMI. Liu et al.[30] also reported that obesity might raise the risk of some poor prenatal outcomes through the development of GDM and HDP. Therefore, the fetus is more likely to be

exposed to an adverse intrauterine environment, resulting in an increased incidence of fetal macrosomia and cesarean delivery, which, in turn, increases the risk of childhood and adult obesity. In addition, no significant difference in congenital defects between different BMI groups except for cleft lip and cleft palate in younger women was observed in our study.

Interestingly, our findings indicate no significant differences in pregnancy outcomes, obstetric and neonatal complications, and congenital defects between different BMI groups among older women ([?] 38y), whether undergoing fresh cycles or subsequent FET cycles. Therefore, we believe that age is still a major factor affecting IVF/ICSI outcomes. Obesity has a greater adverse impact on younger women ($<$ 38y) compared to older women ([?] 38y). Kort et al.[31] showed that 10% weight loss could enhance LBR in overweight/obese women. Liu et al.[30] also suggested a 10%–15% reduction in pre-pregnancy maternal BMI for obese women and a 5% reduction for overweight women to lower the incidence of prenatal outcomes. Based on the above evidence, younger women with elevated BMI should consider losing weight before pregnancy, but older women do not have to delay pregnancy to achieve weight loss as they need to balance against the risk of age-related fertility decline. Notably, our weight loss recommendations are based on age boundaries. However, it remains to be tested whether weight management interventions could improve the short- and long-term outcomes of IVF/ICSI treatment.

Strengths and limitations

To our knowledge, this is the first large-scale study to comprehensively assess the impact of elevated BMI on the short- and long-term outcomes of IVF/ICSI treatment and subsequent FET cycles in a Chinese population. Unlike other studies which have focused exclusively on pregnancy outcomes of fresh cycles as primary outcomes, the most meaningful finding in our study was CLBR. CLBR is a more accurate indicator of the state of oocytes following IVF/ICSI stimulation, which lend credibility and persuasiveness to the results. In addition, to reduce the heterogeneity of the study, only the routine long protocol was included, and PCOS patients were excluded. Nevertheless, there are a few limitations to this study. Our study was race- and region-restricted; a larger and diverse dataset may provide additional insights into the impact of elevated BMI on IVF/ICSI outcomes. In addition, as our birth defects data were gathered through telephone follow-up, many minor defects may have been overlooked, although the overall conclusion is less likely to be affected. Moreover, due to the retrospective nature of the current study, further randomized controlled trials are needed to validate the results.

CONCLUSION

In conclusion, obesity could impair oocyte quantity and quality in younger women through altered endocrinology and poor follicular microenvironment, which, in turn, impairs CLBR. Maternal obesity is also closely associated with HDP and fetal macrosomia among younger women, which could raise the birth risk and economic burden. Since being overweight and obese adversely affects IVF/ICSI outcomes, weight loss management may improve pregnancy outcomes and safety among younger women with elevated BMI. Further randomized controlled trials of lifestyle or pharmacological interventions prior to IVF/ICSI procedures in overweight and obese women are needed to determine whether the short- and long-term adverse effects for both mothers and their offspring could be reduced.

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Disclosure of interests

The authors confirm that there are no conflicts of interest.

Contribution to authorship

HD participated in the conception and design of the study and drafting the article. HB and XM participated in the acquisition of data, analysis, and interpretation of data. YJN participated in revising the article

critically for important intellectual content. YSL participated in the acquisition of data, analysis, and interpretation of data.

WRX participated in revising the article critically for important intellectual content.

ZHW and ZYQ carried out the study design and approved the final version to be submitted. All authors reviewed and approved the final manuscript.

Ethics approval

The study was approved by the institutional review board of Tongji Hospital (reference no. 20201203)

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Supporting Information

Additional supporting information may be found online in the supporting information section at the end of the article.

Figure S1. Flowchart of data selection.

Table S1. Parameters of ovarian stimulation and embryos ([?] 38y subgroup).

Table S2. Pregnancy outcomes of FLBs ([?] 38y subgroup).

Table S3a. Perinatal outcomes and obstetric complications of FLBs (< 38y subgroup).

Table S3b. Perinatal outcomes and obstetric complications of FLBs ([?] 38y subgroup).

Table S4a. Perinatal outcomes and obstetric complications of CLBs (< 38y subgroup).

Table S4b. Perinatal outcomes and obstetric complications of CLBs ([?] 38y subgroup).

Table S5a. Congenital defects of FLBs.

Table S5b. Congenital defects of CLBs.

Table S6. Multivariate logistic regression analysis of BMI-related LBR.

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