Reproductive Medicine; *Endocrinology and Infertility*

The Effect of Maternal Body Mass Index on in Vitro Fertilization-Intracytoplasmic Sperm Injection Treatment: A Prospective Comparative Study

Zeynep OZTURK INAL[1], Hasan Ali INAL[1]

Konya, Türkiye

ABSTRACT

OBJECTIVE: To evaluate whether or not maternal body mass index affects pregnancy rates following in vitro fertilization-intracytoplasmic sperm injection treatment.

STUDY DESIGN: A total of 869 patients who had undergone in vitro fertilization-intracytoplasmic sperm injection treatment between 2012 and 2017 were included in this study. The participants were stratified according to maternal body mass index as Group 1 (body mass index <25 kg/m^2; n=394), Group 2 (25 kg/m^2< body mass index <30 kg/m^2; n=303), and Group 3 (body mass index >30 kg/m^2; n=172).

RESULTS: While there were no differences between the groups in terms of age, smoking status, etiology of infertility, thyroid-stimulating hormone, prolactin levels, antral follicle count, and stimulation protocol (p>0.05), there was a significant statistical difference in terms of body mass index, duration of infertility, baseline follicle-stimulating hormone, luteinizing hormone, estradiol (E_2), duration of stimulation, total gonadotropin dose required, peak E_2 levels, progesterone levels, endometrial thickness on hCG administration, and cycle cancellation rate (p<0.05). In addition, the numbers of oocytes retrieved (groups 1 vs.. 3, p=0.011), metaphase II (groups 1 vs. 3, p=0.017) and 2 pronucleus (groups 1 vs. 3, p=0.010 and groups 2 vs. 3, p=0.010), and the rates of clinical pregnancy (40.1% vs. 33.2% vs. 23.8%, respectively), live births (33.6% vs. 23.7% vs. 13.9%, respectively), and miscarriages (17.7% vs. 28.6% vs. 44.7%, respectively) were also different between the groups (p<0.05).

CONCLUSION: Our data suggest that there is an inverse impact of increased body mass index on laboratory and reproductive outcome parameters of in vitro fertilization-intracytoplasmic sperm injection treatment. Taking cost-effectiveness into consideration, weight loss should be suggested before ovulation is induced.

Keywords: Assisted reproductive techniques, Body mass index, Clinical pregnancy rates, Ovulation induction

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[1] *Konya Training and Research Hospital, Department of Reproductive Endocrinology, Konya, Türkiye*

Address of Correspondence: *Hasan Ali Inal*
Konya Training and Research Hospital,
42090 Meram Yeni Yol Konya, Türkiye
dr.hasanaliinal@yahoo.com

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ORCID IDs of the authors: ZOI: 0000-0002-8766-2079
HAI: 0000-0002-8361-7908

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Introduction

Obesity is a serious public health problem in developed and developing countries. Historically more prevalent in more advanced age groups, it is now seen with increasing frequency in reproductive ages where endocrinological effects such as hypothalamic-pituitary-ovarian axis disorder can cause changes in the secretion of pulsatile gonadotropin, sex hormone-binding globulin, and ovarian androgen. This can prompt menstrual irregularity, anovulation, insulin resistance, have negative psychological and social effects, and can increase the risk of infertility by three times (1-3). It has also been demonstrated that weight loss can return women to spontaneous ovulation and pregnancy without any additional treatment (4-6). Elsewhere, it has been reported that obesity reduces fecundity and increases the rate of miscarriage through a negative effect on endometrial receptivity (7). The adverse

effects of pre-pregnancy obesity on perinatal (e.g., preeclampsia, gestational diabetes mellitus, preterm labor, and surgical delivery) and neonatal (e.g., macrosomic fetus) outcomes have also been reported (2). Additionally, obesity has been found to have a negative effect on serum testosterone and estrogen in men and to decrease sperm motility and quality (4,5)

There are conflicting results in the literature regarding the effects of maternal obesity on the success of assisted reproductive techniques (ART). Although some studies have found that maternal body mass index (BMI) has no negative effect on ART outcomes (8-11), others show that a higher BMI increases the amount of gonadotropin required, produces fewer oocytes, increases IVF-ICSI cancellation rate, decreases clinical pregnancy and live birth rates, and increases miscarriage rate (12-14). Since the effects of obesity on ART outcomes have not been fully elucidated, the current study sought to evaluate whether or not maternal BMI affects pregnancy rates following in vitro fertilization-intracytoplasmic sperm injection (IVF-ICSI) treatment.

Material and Method

Study participants and data collection

This retrospective comparative study was carried out at Ali Kemal Belviranlı Women's Health and Children's Hospital, IVF Unit. Outcomes of 757 fresh ICSI cycles were reviewed between January 2012 and December 2017. Inclusion criteria were participants aged 20-44 years, body mass index (BMI) between 18 and 35 kg/m^2, regular menstrual cycles, no uterine abnormalities in the ultrasound, and normal baseline hormonal levels. Participants were excluded from the study if they were >45 years, any diseases that affect the outcome of IVF/ICSI, such as hydrosalpinx and endometriosis. The ethical board approval was given from the institutional review board of Necmettin Erbakan University Meram Medical Faculty (2017/1082) and the study was performed in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. Written and oral informed agreement was given from the participants before the IVF-ICSI procedure for future use.

Data were obtained for age, BMI (kg/m^2), smoking status, infertility period, cause of infertility, the baseline at day 3 for follicle-stimulating hormone (FSH), luteinizing hormone (LH), and estradiol (E_2) levels, thyroid-stimulating hormone (TSH), prolactin, antral follicle count, stimulation parameters, cycle cancellation rate, IVF-ICSI outcomes, CPR, live birth, and miscarriage rates.

Ovarian stimulation and oocyte retrieval: Controlled ovulation stimulation was negotiated using the gonadotropin-releasing hormone agonist (GnRHa) or the flexible gonadotropin-releasing hormone antagonist (GnRHant) protocol.

The GnRHa protocol: First, pituitary down-regulation was performed with a GnRH agonist. Then, the ovaries were stimulated by exogenous gonadotropins. The GnRH agonist leuprolide acetate (Lucrin; Abbott Cedex, Istanbul, Turkey) was administered subcutaneously daily from day 21 of the preceding luteal phase (0.5 mg/day, sc) until menstruation, and then the dose was decreased to 0.25 mg/day until ovulation was triggered. Recombinant FSH (Puregon; Organon, Oss, the Netherlands, or Gonal F; Serono, Istanbul, Turkey) was used for stimulation. The initial gonadotropin dose used was individualized according to the patient's age, baseline serum FSH concentration on day 3, body mass index, and previous response to ovarian stimulation. The starting regimen was fixed for the first 3 days (100-225 IU recombinant FSH/day). Thereafter, the dose of gonadotropin was adjusted according to the individual ovarian responses, which were monitored by measuring serum estradiol levels and transvaginal ultrasonography (Logic 200 Pro, General Electric, Seoul, South Korea). Ovulation was triggered by the administration of 250 IU recombinant human chorionic gonadotropin (HCG) (Ovitrelle, Serono, Istanbul, Turkey) when at least two follicles reached 18 mm in diameter. Oocytes were retrieved 36 h after the HCG injection, and ICSI was performed for all IVF-ET patients.

The GnRHant protocol: The pituitary down-regulation was achieved and maintained using the flexible GnRHant protocol. Recombinant human FSH (r-FSH; Gonal-F, Merck-Serono, or Puregon, MSD) or human menopausal gonadotropin (hMG; Menogon or Menopur; Ferring) was used for COH. The initial gonadotropin dose used for ovarian stimulation was individualized according to the patient's age, baseline serum FSH concentrations on day 3, BMI, and previous response to ovarian stimulation. The starting regimen was fixed for the first three days (150-225 IU rec FSH/day), and thereafter, the gonadotropin dose was adjusted according to the individual's ovarian response. Serial estrogen levels and two-dimensional follicle measurements by transvaginal ultrasonography (Logic 200 Pro, General Electric, Seoul, South Korea) were performed. A daily dose of 0.25 mg of GnRHant (Cetrotide, Merck-Serono, or Orgalutran, MSD) was initiated when the leading follicle diameter was ≥13 mm or the serum E_2 level reached ≥ 300 pg/mL. When at least two dominant follicles reached dimensions of 18 mm or greater in diameter, hCG (250 µg, Ovitrell, Merck-Serono) was administered, and oocytes were retrieved 36 hours after the hCG injection. ICSI was then applied in accordance with our clinical procedures.

Embryo grading and ET procedure: Embryos were classified according to a simplified system based on Veeck's morphological criteria: Grade I embryos have equal-sized blastomeres and no cytoplasmic fragmentation, grade II embryos have blastomeres of equal size and minor cytoplasmic fragmentation covering <10% of the pre-embryo surface, grade III embryos have blastomeres of distinctly unequal size and vari-

able fragmentation, grade IV embryos have blastomeres of equal or unequal size and moderate-to-significant cytoplasmic fragmentation covering >10% of the pre-embryo surface, and grade V embryos have few blastomeres of any size and severe fragmentation covering >50% of the pre-embryo surface. None of the embryos were classified as grade V in this study. Blastocyst quality was categorized as excellent (AA), good (AB, BA, BB), fair (BC, CB), or poor (CC), based on trophectoderm and inner-cell-mass quality scores (11). The highest quality embryos were selected for embryo transfer on days 2, 3, and 5 after fertilization. The number of embryos transferred (two or fewer per patient) complied with national regulations in Turkey.

ET Procedure: Two senior physicians performed the ETs accompanied ultrasonographic appearance (Logiq 200 Pro, General Electric, Seoul, South Korea) using an embryo transfer catheter system. A sterile speculum was introduced to the vagina in the lithotomy position and the vagina and the cervix were cleared using sterile cotton swabs.

An embryologist loaded the embryos into a soft transfer catheter which was advanced to the ET physician who deposited the embryos approximately 10 mm from the uterine fundus under USG. The catheter was gently removed after 5 seconds. In cases of ET with external guidance, an initial catheter with inner sheath was inserted into the external cervical os and then advanced through the cervical canal and internal os to 10 mm of the uterine fundus using USG. The internal sheath was withdrawn, and a second catheter loaded with embryos was introduced in its place and advanced to approximately 10 mm from the uterine fundus where the embryos were deposited. Difficult transfers required the use of a stylet in addition to this form of external guidance.

All catheters were immediately checked for retained embryos, blood, and the patient remained in the Trendelenburg position for about 10 minutes. Patients in whom tenaculum was excluded from the study. Luteal phase support was provided with progesterone in the form of Crinone 8% gel (Serono, Istanbul, Turkey) at a daily dose of 90 mg. Baseline parameters and IVF-ICSI outcomes were compared between the groups. Biochemical pregnancy was detected with hCG levels in venous blood tests performed 12-14 days after embryo transfer and clinical pregnancy was accepted as those with a gestational sac accompanying fetal heart-beat on ultrasound examination at 4-5 weeks after embryo transfer. Live birth was defined as the birth of a live fetus after 22 weeks of gestational age. The subjects were stratified according to the maternal BMI as Group 1 (BMI<25 kg/m^2; n=394), Group 2 (25 kg/m^2 < BMI <30 kg/m^2; n=303), and Group 3 (BMI >30 kg/m^2; n=172). Basal parameters, clinical and laboratory IVF-ICSI outcomes, and reproductive outcome parameters were compared between the groups.

Statistical analysis

The statistical analyses were performed using SPSS 15.0 for Windows (SPSS, Chicago, IL, USA). The Kolmogorov-Smirnov test was used for examining the continuous variables with normal and non-normal distributions. The one-way analysis of variance (ANOVA) for normally distributed variables and the Kruskal-Wallis test for not-normally distributed variables were used to compare groups. Categorical data were examined by Pearson's chi-square test, and Fisher's exact test was applied if the expected frequency was less than 5 in >20% of all cells. The continuous variables were presented as the mean±standard deviation (SD) and the categorical variables were demonstrated as the number of cases and percentages. The Bonferroni-adjustment was used to control the type I errors for all possible multiple comparisons. A p<0.05 value was established as statistically significant.

Results

A total of 51 patients were excluded from the study, specifically those with age >45 (n=19), BMI >35 kg/m^2 (n=14), systemic disease (n=9), endocrine or metabolic disorders (n=6), and concomitant medication (n=3). The remaining 869 participants were classified into three groups and their outcomes were analyzed (Figure 1).

Flowchart of the study

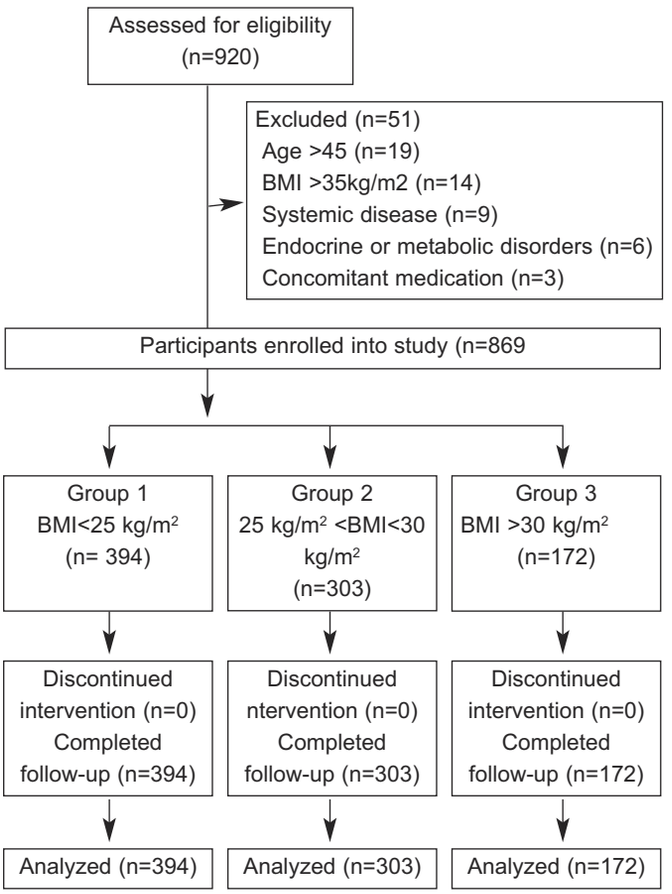

Figure 1: *Enrollment and follow-up of the study subjects.*

A comparison of the sociodemographic and stimulation characteristics of the participants is provided in table I. While there were no differences between the groups in terms of age, smoking status, etiology of infertility, thyroid-stimulating hormone, prolactin levels, antral follicle count, and stimulation protocol (p>0.05), there was significant statistical difference (p<0.05) in terms of BMI (21.9+81.99 vs. 27.23+1.43 vs. 32.88+2.38, respectively; p<0.001), duration of infertility (5.51+3.33 vs. 6.20+3.78 vs. 7.39+3.89, respectively; p<0.05), baseline follicle-stimulating hormone (groups 1 [7.45+2.28] vs. 3 [6.74+2.45], p=0.003), luteinizing hormone (groups 1 [5.93+2.77] vs. 2 [5.14+2.80], p=0.001 and groups 1 [5.93+2.77] vs. 3 [5.08+3.11], p=0.003), estradiol (E_2) (groups 1 [46.50+16.6] vs. 2 [42.69+16.79], p= 0.007 and groups 1 [46.50+16.6] vs. 3 [42.63+15.28], p=0.027), duration of stimulation (groups 2 [9.62+1.51] vs. 3 [10.17+1.86], p=0.001), total gonadotropin dose required (groups 1 [1929.63+912.79] vs. 3 [2234.60+1019.92], p=0.001 and groups 2 [2008.26+ 883.51] vs. 3 [2234.60+1019.92], p=0.030), peak E_2 levels (groups 1 [2015.65+1140.77] vs. 2 [1802.17+1063.92], p=0.043 and groups 1 [2015.65+1140.77] vs. 3 [1705.64+ 1323.19], p=0.010), progesterone levels (0.89+0.39 vs. 0.79+0.37 vs. 0.69+0.37, respectively: p<0.05), endometrial thickness on hCG administration (groups 1 [10.3+1.62] vs. 3 [9.86+1.65], p=0.002 and groups 2 [10.28+1.74] vs. 3 [9.86+1.65], p=0.028), endometrial thickness on hCG administration on transfer day (10.52+1.66 vs. 10.44+1.83 vs. 10.02+1.74, respectively; p<0.05), and

Table I: *Demographic and stimulation characteristics of the patients.*

		BMI<25 (Group 1) (n=394)	25<BMI<30 (Group 2) (n=303)	BMI>30 (Group 3) (n=172)	*p*		
					1 vs. 2	1 vs. 3	2 vs. 3
Age (years)		30.03+4.55	30.31+4.96	30.94+4.56		0.109	
BMI (kg/m^2)		21.9+81.99	27.23+1.43	32.88+2.38	<0.001	<0.001	<0.001
Smoking rate (%)		7.4%	7.3%	5.8%		0.775	
Duration of infertility (years)		5.51+3.33	6.20+3.78	7.39+3.89	0.038	<0.001	0.004
Etiology of infertility (%)	Male factor	39.4%	38.1%	29.7%		0.116	
	Tubal factor	1.3%	2.6%	1.7%			
	Unexplained	34.4%	36.8%	36.1%			
	Poor responder	24.9%	22.5%	32.6%			
Baseline-FSH (IU/mL)		7.45+2.28	7.14+2.52	6.74+2.45	0.205	0.003	0.187
Baseline-LH (IU/mL)		5.93+2.77	5.14+2.80	5.08+3.11	0.001	0.003	0.975
Baseline-Estradiol (pg/mL)		46.50+16.65	42.69+16.79	42.63+15.28	0.007	0.027	0.996
Antral follicle count		6.06+2.60	6.41+2.72	5.67+2.55		0.064	
TSH (µIU/mL)		2.22+1.12	2.09+1.03	2.29+1.23		0.144	
Prolactin (ng/mL)		16.70+9.40	16.0+28.01	15.34+9.37		0.231	
Stimulation protocol (%)	Long	17.8%	19.5%	20.5%		0.875	
	Antagonist	81.4%	80.1%	78.9%			
	Microdose	0.8%	0.3%	0.6%			
Duration of stimulation (days)		9.76+1.52	9.62+1.51	10.17+1.86	0.528	0.147	0.001
Gonadotropin dose (IU)		1929.63+912.79	2008.26+883.51	2234.60+1019.92	0.511	0.001	0.030
Estradiol levels on day hCG (pg/mL)		2015.65+1140.77	1802.17+1063.92	1705.64+1323.19	0.043	0.010	0.660
Progesterone levels on day hCG (pg/mL)		0.89+0.39	0.79+0.37	0.69+0.37	0.002	<0.001	0.031
Endometrial thickness on day hCG (mm)		10.3+1.62	10.28+1.74	9.86+1.65	0.651	0.002	0.028
Endometrial thickness on transfer day (mm)		10.52+1.66	10.44+1.83	10.02+1.74	0.042	0.006	0.019
Cyle cancellation rate (%)		1.7%	2.6%	6.9%	0.444	0.004	0.031

BMI: body mass index; FSH: follicle-stimulating hormone; LH: luteinizing hormone; TSH: thyroid-stimulating hormone; hCG: human chorionic gonadotropin.
p<0.05 is statistically significant

cycle cancellation rate (groups 1 [1.7%] vs. 3 [6.9%], p=0.004 and groups 2 [2.6%] vs. 3 [6.9%], p=0.031).

The laboratory and reproductive outcomes of the participants are summarized in table II. The numbers of oocytes retrieved (groups 1 [9.41+6.01] vs. 3 [7.90+5.50], p=0.011), MII (groups 1 [7.46+4.15] vs. 3 [6.33+4.58], p=0.017) and 2PN (groups 1 [5.11+3.42] vs. 3 [4.06+2.88], p=0.010 and groups 2 [4.98+3.24] vs. 3 [4.06+2.88], p=0.010), and the rates of clinical pregnancy (40.1% vs. 33.2% vs. 23.8%, respectively; p<0.05), live births (33.6% vs. 23.7% vs. 13.9%, respectively; p<0.05), and miscarriages (17.7% vs. 28.6% vs. 44.7%, respectively; p<0.05) were also different between the groups.

Discussion

We found that overweight and obese patients with higher BMIs had worse responder rates, lower peak E_2 levels, and less endometrial thickness and required higher gonadotropin doses than the normal weight group. In addition, lower numbers of MII and 2PN oocytes were retrieved, the clinical pregnancy and live birth rates were lower, and the miscarriage rate was higher.

Obesity has historically been observed more frequently in adult and advanced age groups. It is now a global epidemic and has become an important public health problem in younger age groups, too (2). Infertile women, including obese patients, in the reproductive age group, benefit from ART to fulfill their fertility requirements, and so the possible effects of increased BMI on ART are of great importance for the clinician, the patient, and public health (3).

Endocrinological and paracrinological factors play a role in the interaction between embryo and endometrium for successful implantation and live birth (15). Hyperandrogenemia, insulin resistance, and abnormal hormone levels that occur with increased BMI can negatively affect this process (1,16). A higher BMI also affects the levels of inflammatory markers such as insulin-like growth factors, tumor necrosis factor-alpha, and interleukine-6 which play roles in cell differentiation and differentiation, folliculogenesis, oocyte maturation, and embryo development. As a result, embryo implantation can be negatively affected and the risk of miscarriage can increase (17-19). Previous studies have shown that increased BMI is associated with poor IVF-ICSI outcomes through the effect of these endocrinological factors (2,20-21) with one study reporting that a reduction of one BMI unit can increase the chance of pregnancy by 19% (22). It has also been found that advanced maternal age and smoking negatively affect live birth rates (23), although the mean age and smoking rates were similar between the groups in our study.

In the literature, conflicting results exist regarding the effects of increased BMI on ART outcomes. For example, Fedorcsák P, et al. (13) evaluated 5019 IVF-ICSI cycles and found no significant difference in live birth rates between

Table II: *Laboratory and reproductive outcome parameters of the patients.*

		BMI<25 (Group 1) (n=387)	25<BMI<30 (Group 2) (n=295	BMI>30 (Group 3) (n=160	*p*		
					1 vs. 2	1 vs. 3	2 vs. 3
Number of oocytes retrieved		9.41+6.01	8.97+5.11	7.90+5.50	0.576	0.011	0.126
Number of MII oocytes		7.46+4.45	7.19+4.22	6.33+4.58	0.712	0.017	0.115
2 Pronucleus		5.11+3.42	4.98+3.24	4.06+2.88	0.868	0.010	0.030
Fertilization rate (%)		68.48+24.5	68.80+23.67	67.09+25.17		0.768	
Grade I embryo (%)		67.2%	66.5%	65.1%		0.231	
Number of embryo transfers (%)	Single	82.7%	78.2%	75.2%		0.105	
	Multiple	17.3%	21.8%	24.8%			
The days of embryo transfer (%)	2	3.9%	5.1%	10.1%			
	3	84.8%	85.6%	79.9%		0.117	
	5	11.3%	9.3%	10.0%			
The embryo transfer technique (%)	Easy transfer with a soft catheter	22.1%	21.5%	16.8%			
	After external guidance transfer	71.9%	69.1%	78.5%		0.173	
	Difficult transfer with a stylet	6.0%	9.4%	4.7%			
Clinical pregnancy rate (%)		40.1%	33.2%	23.8%	0.042	<0.001	0.041
Live birth rate (%)		33.6%	23.7%	13.9%	0.005	<0.001	0.017
Miscarriage rate (%)		17.7%	28.6%	44.7%	0.045	0.001	0.042

BMI: Body mass index, MII: metaphase p<0.05 is statistically significant

obese and normal-weight women (41.4% vs. 50.3%). Similarly, Wittemer C, et al. (24) and Dokras A, et al. (25) show that BMI has no negative effect on rates of clinical pregnancy or live birth. On the other hand, however, Luke B, et al. (26) evaluated approximately 45,000 embryo transfers and show that an increased BMI decreases clinical pregnancy and live birth rates and that this effect is especially pronounced in women under 35 years of age. A separate meta-analysis of 33 studies and 47,967 IVF-ICSI cycles found that obese and overweight patient groups had poorer outcomes compared to normal-weight women and that the obese group was worse than the overweight patient group (1). These findings were in agreement with our results. Sartorius and Nieschlag (27) demonstrate that an increased BMI can have other negative perinatal outcomes such as preeclampsia, preterm birth, and surgical delivery, as well as reducing live birth rates. Relatedly, Pinborg A, et al. (6) evaluate 1,417 IVF-ICSI cycles and show that the cancellation rate increases with increased BMI, the two key reasons being that obesity makes the oocyte pick-up procedure more difficult and insufficient follicles are developed despite the use of high gonadotropin doses.

The possible negative effects of an increased BMI on ART should be explained to overweight and obese women who are scheduled for IVF-ICSI treatment. Before the process begins, it should also be explained that weight loss can increase the chance of success in terms of pregnancy and live birth. Overweight and obese women should consequently be encouraged to lose weight, and clinicians planning ART should implement weight loss programs involving diet and exercise. In addition, it should be understood that the gonadotropin dose required will increase with higher BMIs meaning that treatment costs will also grow despite the increasingly negative perinatal outcomes.

The strong point of the current study consists of the adequate number of subjects in each group and the prototypical sample from central Turkey. The results can be generalized to most of the country's population. However, the potential limitations of the study are that it was conducted in a tertiary single care institution, a retrospective study and that the cumulative CPR was not evaluated because no frozen ETs were included.

In conclusion, this study found that an increased BMI has a negative effect on ART outcomes as shown in decreasing clinical pregnancy and live birth rates and increasing miscarriage rates. Further studies with more participants are needed to elucidate this effect.

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