Maternal Underweight Does Not Adversely Affect The Outcomes of IVF/ICSI and Frozen Embryo Transfer Cycles or Early Embryo Development

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Research Article

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Abstract

Purpose

To compare assisted reproductive technology (ART) outcomes and preimplantation embryo development between underweight and normal weight women.

Methods

This retrospective cohort study included 26 underweight women (body mass index [BMI] < 18.50 kg/m^2) and 104 normal weight women (BMI > 20 and < 24.9 kg/m^2) who underwent a total of 204 in vitro fertilization/intracytoplasmic sperm injection (IVF/ICSI) cycles and 358 fresh/frozen embryo transfers (ET) in our institution between January 2016 and December 2018. Statistical analyses compared selected ART outcomes (ovarian stimulation, fertilization, and pregnancy) between both weight groups. Morphokinetic and morphological parameters were also compared between 346 and 1467 embryos of underweight and normal weight women, respectively.

Results

The mean ± standard deviation age of the underweight and normal weight women was similar (31.6 ± 4.17 vs 32.4 ± 3.59 years; $p = 0.323$). There were no differences in the peak estradiol levels, the number of retrieved oocytes, the number of metaphase II oocytes, and the oocyte maturity rates between the two groups. The IVF/ICSI fertilization rates and the number of embryos suitable for transfer or cryopreservation were similar for both groups. All morphokinetic parameters that were evaluated by means of time-lapse imaging as well as the morphological characteristics were comparable between low and normal BMI categories. There were no significant differences in pregnancy achievement, clinical pregnancy, live births, and miscarriage rates between the suboptimal and optimal weight women.

Conclusion

Underweight status has no adverse impacts on the outcomes of IVF/ICSI with either fresh or frozen ET or on preimplantation embryo development and quality.

Introduction

The maternal nutritional status before and during early pregnancy plays a key role in reproductive health, early embryo developmental processes, and pregnancy outcomes. The body mass index (BMI) is used to identify underweight/overweight of adults and to reflect their nutritional status [1]. The association between overweight/obese (BMI > 25 kg/m^2) and impaired fertility [2], worse assisted reproductive

technology (ART) outcomes [3–5], and increased rates of miscarriage and obstetric risks in spontaneous [6–9] and ART pregnancies [10–12] is well-recognized. Similarly, underweight women (BMI < 18.50 kg/m^2) have higher rates of infertility compared to women with a normal BMI (18.50-24.99 kg/m^2) [13]. Additionally, a low BMI is associated with an increased risk of miscarriage in spontaneous pregnancies [14, 15] and with higher rates of obstetric complications, such as preterm delivery, preterm premature rupture of membranes, and low birth weight in the general population [9, 16, 17]. However, as was recently observed in a systematic review and meta-analysis, no association between prepregnancy subnormal body weight and ART outcomes has been established, and the conclusions in the studies conducted to date have been divergent [18]. While several studies have suggested a lack of a negative association between low BMIs and impaired ART outcomes [19–28], others have reported decreased numbers of collected oocytes and “good quality” oocytes [29], fewer usable embryos suitable for transfer or cryopreserve [30], an increased risk of miscarriage [15, 31–34], lower clinical pregnancy and live birth rates [32, 34, 35], and increased obstetric complications including preterm birth, low birth weight, and small for gestational age neonates [18, 36–38] in underweight compared to normal weight women undergoing ART. Based on these findings, many clinicians recommend weight gain in women with low BMIs who apply for in vitro fertilization (IVF) treatments.

Chronic energy and nutrient deficiencies can disrupt the hypothalamic-pituitary-gonadal (HPG) axis and lead to irregular menstrual cycles, ovulatory dysfunction, and thereby reduced reproductive function in underweight women [13]. However, the mechanisms by which underweight might affect ART outcomes, a process that bypasses the HPG axis, are far less clear and are probably related to multiple endocrine, adipokine, and metabolic alternations that can affect follicle growth, oocyte maturation, early embryo development, and endometrial receptivity. For example, leptin, a protein secreted by adipocytes, plays an important role in the embryo-maternal crosstalk at the time of implantation [39–43], and the low leptin levels found in underweight women [44] have been suggested as a mechanism responsible for implantation failure and early and recurrent miscarriages [45, 46].

The effect of female underweight on ART outcomes is still inconclusive. Previous studies included a variety of pathophysiologies underlying infertility, and most of those studies focused upon fresh embryo transfer (ET). Although several studies found impaired ART outcomes, known to be associated with impaired embryo development and low embryo quality, among underweight women undergoing ART [30–35], only one recent study explored embryo morphokinetics and morphology in this context [33].

Given the lack of consensus over the effect of maternal underweight on ART outcomes, the aim of the current study was to investigate the association between low BMI and ART outcomes in women undergoing fresh and frozen cycles for IVF/intracytoplasmic sperm injection (ICSI) due to genetic problems, unexplained infertility, and mechanical infertility. To strengthen the data, early embryo development and quality were also examined.

Materials And Methods

Ethical approval

This study was approved by the institutional review board (Helsinki) of the Tel Aviv Sourasky Medical Center (#0977-20-TLV). Informed consent was waived for this retrospective and anonymous analysis.

Study population and participant recruitment

This retrospective study was performed between January 2016 and December 2018 at the IVF Unit, Fertility Institute, Tel Aviv Sourasky Medical Center, a tertiary university-affiliated medical center. All consecutive women who underwent conventional IVF, ICSI, or IVF/ICSI cycles were included. Morphological and morphokinetic developmental patterns of 1813 embryos were assessed, and pregnancy outcomes from 358 ET cycles that included 513 transferred embryos were determined. Both fresh and frozen-thawed ET cycles were analyzed.

In order to prevent any influence of infertility factors on the outcome of IVF, we limited the analysis to the data of women who underwent IVF due to genetic indications for the performance of preimplantation genetic diagnosis (PGD: 56 cases, 43 %), unexplained infertility (61 cases, 47 %), and mechanical factor infertility (13 cases, 10 %). We excluded women who presented with the following: (1) uterine malformation, endometriosis, or hydrosalpinx; (2) a history of uterine and ovary surgery; (3) any thyroid disease, diabetes, or autoimmune disease; (4) more than three previous IVF/ICSI treatments; (5) a baseline follicle-stimulating hormone (FSH) level > 12 IU/L; (6) being a Fragile X carrier; and, (6) infertility due to male factor. All of the study women were weighed, and their heights were measured at initiation of their ART cycles, and their BMI was determined by the ratio of weight divided by the height squared in metric units. The study participants were divided into underweight (BMI < 18.5) and normal weight (BMI > 20 and < 24.9) groups. Women with a BMI < 18.5 and those with a BMI > 20 were not included in this study in order to clearly differentiate between “underweight” and “normal” weight.

Data collection

All relevant data were collected from the hospital computerized database. The data in the electronic charts included the following: clinical details [maternal age, weight, height, BMI, number of children, basal follicle-stimulating hormone (FSH) levels, thyroid-stimulating hormone (TSH) levels, prolactin levels, number of ovum pick-up (OPU) cycles prior to the initiation of the current study, and the reason for IVF], ART details and outcomes [number of OPU cycles per women, ovarian hyperstimulation protocol, ovarian stimulation duration, total FSH dose, peak serum estradiol, type of final maturation trigger, number of retrieved oocytes, number of metaphase II (MII) oocytes, fertilization method, number of 2 pronuclei (2PNs), number of usable embryos (either transferred or cryopreserved), ET protocol type, day the embryos were transferred, and number of embryos transferred], and pregnancy outcomes as detailed below.

A serum beta human chorionic gonadotropin (b-hCG) level > 25 IU/I was taken as positive for pregnancy. A clinical pregnancy was confirmed by the observation of an embryo pulse on transvaginal ultrasound

scanning at 6 to 12 weeks of gestation. Early miscarriage was diagnosed when a previously positive pregnancy test become negative before ultrasonographic detection of an embryonic pulse in the sixth week of pregnancy or later. Miscarriage was defined as a loss of clinical pregnancy before 12 full weeks of gestation. Live birth was defined as a live neonate born after 24 weeks of gestation. Pregnancy, clinical pregnancy, and live birth rates were on a “per embryo transfer” basis. Early miscarriage and miscarriage rates were calculated per pregnancy.

Ovarian stimulation, fertilization, embryo culture and embryo transfer

Controlled ovarian stimulation was carried out by the gonadotropin releasing hormone (GnRH) antagonist or the short GnRH agonist protocols [47]. Ovulation was triggered with 250 mcg of choriogonadotropin α (Ovitrelle; Serono, Geneva, Switzerland), 0.2 mg of triptorelin (Decapeptyl; Ferring Pharmaceuticals), or by a combination of both when at least three follicles achieved a diameter of 18 mm. Ovum pickup was performed 36 hours later, and the embryologists determined the total number of oocytes retrieved per cycle. The embryos in this study were fertilized by conventional IVF or ICSI [47]. In the ICSI cycles, cumulus cells were removed 2–3 hours after retrieval, and oocyte maturity was determined. Only MII oocytes were considered mature. Oocyte maturity was not determined systematically for the IVF cycles, nor was it used for statistical analysis. All of the embryos were incubated in the integrated EmbryoScope™ time-lapse monitoring system (EmbryoScope™; UnisenseFertiliTech A/S, Aarhus, Denmark, Vitrolyfe) from the time of fertilization until ET or freezing. Either ET or cryopreservation was carried out two to six days following oocyte retrieval. Endometrial preparation in the cases of frozen ET (FET) was performed with modified natural or artificial (hormonally substituted) cycle protocols [48]. Luteal support with progestin supplement (in various regimens) was continued in all cases until there was a negative b-hCG result or the ninth week of pregnancy. Serum b-hCG levels were confirmed on day 14 after ET.

One treatment cycle was defined by oocyte retrieval and all transfers (i.e., fresh and frozen-thawed) were derived from that ovarian stimulation. One complete treatment cycle was defined by a treatment cycle that achieved a live birth or in which all embryos were transferred but failed to achieve a live birth. Only the first delivery of each patient was considered in the analysis.

Time-lapse monitoring of embryo morphokinetics and morphology assessment

Embryo scoring and selection by means of time-lapse monitoring were performed by analysis of the time-lapse images of each embryo with software developed specifically for image analysis (EmbryoViewer workstation; UnisenseFertilitech A/S). Embryo morphology and developmental events were recorded in order to demonstrate the precise timing of the observed cell divisions in correlation to the timing of fertilization: specifically, time of pronuclei fading (tPNf), time of cleavage to a 2-blastomere (t2), a 3-blastomere (t3), a 4-blastomere (t4), etc. until an 8-blastomere (t8) embryo. The time point t8 was the last assessed parameter, even for embryos that were further cultured to be transferred or frozen on day 5. The other analyzed parameters were the lengths of the second and the third cell cycles (cc2 and cc3, respectively), and the synchrony in the division from 3 to 4 cell (s2) and 5 to 8 cells (s3). All the

assessments and annotations of the embryos were performed by senior embryologists, thereby ensuring a very low interobserver variation. Scores were allocated to day 3 embryos by means of the KIDScore algorithm [49].

Conventional morphology of the embryos was studied on day 3, taking into account the number of blastomeres, the symmetry among blastomeres, and the degree of fragmentation. The embryos were scored from grade 1 (high quality) to grade 4 (poor quality) accordingly [50, 51].

Statistical analysis

Data were analyzed with SPSS, version 25.0 (SPSS, Inc., Chicago, IL, USA). The baseline clinical characteristics as well as the ART and pregnancy data and outcomes were summarized as mean + standard deviation (SD), or number of responders (percentage) according to the variables. Significance was tested with the t-test, Mann-Whitney U test, $\chi 2$, and Fisher's exact test as appropriate. The effect of BMI status on morphokinetic parameters was assessed by a mixed model's analysis. A p value of < 0.05 was considered significant.

Results

Clinical characteristics of the study participants

In total, 130 women underwent 204 conventional IVF, ICSI, or IVF/ICSI cycles and were included in this study. Underweight (BMI < 18.5) women comprised 20% (26 out of 130) of our study participants. The clinical characterizations of the entire cohort are detailed in Table 1. Female age was similar for underweight and normal weight women (31.6 ± 4.17 vs 32.4 ± 3.59 years, respectively, $p = 0.323$). There were no clinical differences, including the ovarian reserve marker FSH (7.7 ± 2.11 vs 6.8 ± 2.38 mIU/mL; $p = 0.193$), the number OPU cycles prior to the current study period ($p = 0.93$), and the distribution between the indications of IVF ($p = 0.96$) between the two groups. The respective levels of TSH (2 ± 1.24 vs 2 ± 0.97 mIU/L; $p = 0.846$) and prolactin (254.6 ± 119.13 vs 244.2 ± 134.77 mIU/L; $p = 0.765$), hormones that at abnormal levels adversely affect fertility and are known to vary in underweight women, were similar between the two groups.

Ovarian stimulation data and outcomes

The 26 underweight women and 104 normal weight women underwent 42 and 162 OPU cycles, respectively. The ovarian simulation data and outcomes of both groups are summarized in Table 2. The number of OPU cycles per patient (1.6 ± 0.89 vs. 1.5 ± 0.83, respectively; $p = 0.867$), the distribution of ovarian stimulation protocols, including GnRH antagonist (83.3% vs. 77.8%), and the short GnRH analog (16.7% vs. 22.2%) did not differ between the two study groups ($p = 0.527$), nor did the total dosage (2434 ± 1343 vs. 2371 ± 1029 mIU/mL; $P = 0.744$) and duration (10.7 ± 2.56 vs. 10.8 ± 2.10 days; $p = 0.766$) of gonadotrophins. There were no statistically significant group differences in the peak estradiol levels (2352 ± 1426 vs. 2018 ± 1189 pg/mL; $p = 0.122$), the final maturation trigger type ($p = 0.051$), the number

of retrieved oocytes (13.4 ± 7.50 vs. 13.6 ± 8.91; $p = 0.868$), the number of MII oocytes (13.1 ± 8.50 vs. 13.7 ± 9.15; $p = 0.775$), and the oocyte maturity rates (80.4 ± 15.31% vs. 88.3 ± 13.58%; $p = 0.091$). The type of fertilization procedure (IVF, ICSI, or IVF + ICSI) was almost equally distributed between the two groups ($p = 0.582$), and there was no significant group difference in fertilization rate with either IVF (54.8 ± 20.34% vs. 55.3 ± 22.56%; $p = 0.938$) or ICSI (77.4 ± 17.45% vs. 75.4 ± 17.08%; $p = 0.617$). Likewise. there was no significant group difference in the total number of embryos (3.9 ± 4.31 vs. 4.4 ± 3.98; $p = 0.279$), the number of cryopreserved embryos (2.9 ± 4.54 vs. 3.1 ± 4.34; $p = 0.741$), and the number of ETs (1.07 ± 0.87 vs. 1.27 ± 0.93; $p = 0.226$).

A total of 71 and 287 ETs were performed in the underweight and normal weight women, respectively, with no differences in the number of ET cycles per subject (2.7 ± 2.03 vs. 2.7 ± 1.93; $p = 0.917$), or the distribution of ET modality (including fresh ET, modified natural FET, and hormonally substituted FET) between groups ($p = 0.434$). A mean of 1.4 embryos was transferred each time ($p = 0.870$), and no significant difference was detected in the distribution of the number of ETs ($p = 0.764$) or their developmental stage ($p = 0.115$).

Morphokinetic and morphological characteristics

Three-hundred forty-six embryos of underweight women were compared morphokinetically to 1467 embryos of normal weight women. Early embryonic development was recorded by time-lapse imaging. The mean timings of tPNf, and t2 to t8, along with cc2, cc3, and s2 to s3 were not significantly different in the maternal BMI group comparison (Table 3A).

The KIDScore was calculated for 278 embryos from underweight women and 1305 embryos from normal weight women. All of those embryos were available for embryoscopic analysis at 66 h and were fit to be graded according to the model in which each embryo receives a score between 1–5 (1 indicating the lowest potential for pregnancy and 5 indicating the highest). The mean scores were similar for embryos from the underweight and from the normal weight women (3.7 ± 1.50 vs. 3.63 ± 1.51, respectively; $p = 0.670$) (Table 3A). There was also no significant group difference between the proportion of embryos graded either 4 or 5 or 2 or less ($p = 0.593$) (Table 3B).

To complete the embryo development assessment, we performed a conventional morphological evaluation on day 3. We examined the number of blastomeres, the symmetry among blastomeres, and the degree of fragmentation, and each embryo received a score between 1–4 (1 indicating the highest potential for pregnancy and 4 indicating the lowest). The mean scores were similar for embryos from the underweight and the normal weight women (1.82 ± 1.04 vs. 1.95 ± 1.10, respectively; $p = 0.230$) (Table 3A). There was also no significant group difference between the proportion of embryos graded 1 or 2, or those graded 3 or more ($p = 0264$) (Table 3B). Finally, no significant group difference was found in the percentage of embryos whose development was stopped before day 3 (8.4% vs. 8.2%; $P = 0.910$) (Table 3A).

Pregnancy outcomes

One hundred and one embryos from underweight women and 412 embryos from normal weight women were transferred, and the pregnancy outcomes were assessed (Table 4). The respective rates of pregnancy (35.3 ± 43.20% vs. 25.8 ± 39.53%; $p = 0.11$), clinical pregnancy (24.4 ± 40.32% vs. 23.3 ± 39.54%; $p = 0.89$), live births (23.7 ± 40.30% vs. 19.5 ± 37.35%; $p = 0.42$), early miscarriage (37.5 ± 49.18% vs. 26.3 ± 44.30%; $p = 0.23$), and miscarriage (4.7 ± 21.82% vs. 11.5 ± 32.15%; $P = 0.36$) were not significantly different.

Discussion

There is no consensus over the effect of maternal underweight on IVF outcomes, and numerous studies have demonstrated conflicting conclusions. The value of this information is its contribution in establishing recommendations, if any, regarding the lower weight threshold for optimal IVF outcomes. The present study has demonstrated that underweight women undergoing IVF treatment do not appear to be at greater risk of impaired IVF outcomes than normal weight women. We base this on the absence of any significant differences in the peak estradiol levels, the number of retrieved oocytes, the number of mature oocytes, the maturity rate of the oocytes, and the fertilization rate between the underweight and normal weight IVF women. Furthermore, the rates of pregnancy, clinical pregnancy, live births, and miscarriages were similar, and the pre-implantation embryo development was comparable between the two study groups.

Two meta-analyses summarized the association between maternal underweight and pregnancy outcomes. The first one [15] explored the association between underweight and miscarriages and concluded that maternal subnormal body weight prepregnancy is associated with a slightly increased risk of clinical miscarriage compared with normal weight women. However, it should be borne in mind that this meta-analysis included spontaneous pregnancies as well as conception via ART, and the types of pregnancy among underweight women did not yield significantly different outcomes. Furthermore, the conclusions were limited by not showing any association between prepregnancy subnormal body weight and other critical outcomes of ART, such as clinical pregnancy and live birth rates. The second meta-analysis was published more recently [18], and it focused solely upon autologous IVF pregnancies, exploring the association between subnormal body weight prepregnancy and multiple obstetrical outcomes. That study included 38 mostly retrospective cohort studies, and the authors concluded that there were no differences in terms of miscarriage or live birth rates between underweight and normal weight patients, but that clinical pregnancy rates were slightly impaired among the underweight women. However, none of the 38 studies independently demonstrated a significant reduction in clinical pregnancy, and a modest reduction emerged only when all of them were combined. As Xiong et al. [18] commented, their findings should be interpreted with caution because the results were potentially underpowered due to the small number of studies included in the adjusted analyses.

Inconsistency about the effects of maternal underweight on IVF outcomes remained after Xiong et al.'s [18] meta-analysis as well. Similar to our results, however, most of these recent studies failed to find any association between underweight and negative IVF outcomes [24–28]. Contrarily, Tang et al. found that

being underweight was linked to reduced implantation, clinical pregnancy, and ongoing pregnancy rates in women undergoing FET-based IVF [34]. We consider that the influence of biological differences among different ethnicities might explain these differences in outcomes between studies. Indeed, Tang et al.'s study of a Chinese population observed a negative influence of low BMIs among Asian women on IVF outcomes, and Cai et al [32] had earlier reported that a low BMI was associated with reduced live birth rates and increased miscarriage rates compared with normal weight in a Chinese population. The other studies [24–28], as well as ours, had been conducted in a non-Asian population, and none observed any correlation between low prepregnancy maternal weight with IVF outcomes. An exception is the Italian study of Bartolacci et al. [33], who reported a higher miscarriage rate in underweight compared with normal weight women undergoing IVF and suggested that the mechanisms underlying a higher risk of miscarriage included differences in embryo quality and endometrial receptivity. Embryo quality assessment was traditionally based upon morphology, however, several studies argued that static morphological parameters are not sufficient and suggested adding morphokinetics parameters for analyzing embryo quality. For example, embryo dynamics employing time-lapse imaging was shown to improve embryo selection by adding useful quality parameters of embryo development timings [52, 53]. Furthermore, various patterns of embryo cleavage have been related to different success rates of embryo implantation, clinical pregnancy, and live birth [54–56]. Before our current work, only Bartolacci et al. [33] had examined the effect of underweight on embryo morphokinetics and those authors found no significant differences in time-lapse imaging parameters between underweight and normal weight women. Our results confirmed that there is no significant relationship between female underweight and embryo developmental kinetics, thereby supporting the similar clinical pregnancy and miscarriage rates we found between underweight and normal weight women. Another mechanism raised by Bartolacci et al. [33] was that low leptin levels, as described in underweight woman [44], may impair endometrial function. Leptin receptors are expressed in the secretory endometrium [39–43] where they may regulate uterine angiogenesis [57] and embryo implantation [39–43]. Low plasma leptin levels have been associated with early miscarriage and recurrent miscarriage [45, 46] and may explain why underweight women would conceivably have an increased miscarriage rate. We did not test leptin levels, and therefore, we cannot contribute to that discussion. The discrepancy between the two studies with regard to miscarriage rate could be due to different sample sizes and/or methodologies. The women in Bartolacci 's study (mean age of 36 years) were older than the participants in the current study (mean age of 32 years). Advanced maternal age (≥ 35 years) may have undesirable effects upon endometrial receptivity and thereby reduce embryo implantation and successful pregnancy rates [58, 59]. Bartolacci et al., unlike us, had included various infertility causes that are known to impair IVF outcomes, such as polycystic ovary syndrome, which is an endocrine-metabolic disorder that negatively affects the endometrium receptivity, leading to implantation failure and miscarriages [60, 61]. The differences between the results of our study and theirs may also be due to a synergistic effect of these factors and underweight.

Our study has several strengths: Firstly, to minimize possible confounding effects of the underlying infertility diagnosis, our study group included women who underwent IVF due to conditions that are less likely to impair fertility, such as genetic problems that require PGD and unexplained and mechanical

infertility. Secondly, to overcome the argument of a less natural uterine environment in fresh ETs following ovarian stimulation, we included both fresh and frozen-thaw ETs. Thirdly, we examined the morphology and the morphokinetics characterizations of a large number of embryos in order to evaluate the effects of a low maternal BMI on embryo development that are known to influence implantation.

This study also has several important limitations. Firstly, it is retrospective in design, which reduces its direct application to clinical practice. Secondly, the statistical analyses were performed in relatively small subgroups, which could compromise the strength of the conclusions, thus calling for further studies on larger populations. Thirdly, we did not examine the effects of pre-pregnancy maternal underweight on pregnancy/perinatal outcomes following IVF due to lack of access to these data, and this, too, awaits further studies.

In conclusion, we demonstrated that maternal underweight is not associated with poorer IVF/ICSI/FET outcomes or with impairment of preimplantation embryo development, thus supporting the findings of others [19–28] in this ongoing controversy. It should be borne in mind, however, that a suboptimal BMI before IVF was found to be an independent risk factor for many adverse obstetric outcomes, including preterm birth, preterm premature rupture of membranes, intrauterine growth restriction, low birth weight, and small for gestational age neonates [18, 35–37]. Therefore, dietary and lifestyle counseling intended to achieve optimal body weight prior to IVF is recommended in order to improve not only IVF pregnancy rates but also the chances of an uncomplicated pregnancy, childbirth, and postnatal period.

Declarations

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Conflict of Interest The authors declare that they have no conflict of interest.

Availability of data and material Data are available upon request.

Code availability Not applicable.

Authors' Contribution D.H. and H.A. were involved in the conception, study design, data acquisition and analysis and, manuscript preparation. Y.K. collected and managed the database and provided her expertise in the critical reading of the manuscript. N.S., and E.H.H. were involved in the conception, managed the database and, provided their expertise in the critical reading of the manuscript. S.L. managed and statistically analyzed the database. A.G., and F.A. contributed to the interpretation of the data and provided their expertise in the critical reading of the manuscript. All contributors reviewed and edited the manuscript and gave their approval of the final version.

Ethics approval: This study was approved by the institutional review board (Helsinki) of the Tel Aviv Medical Center (#0977-20-TLV).

Consent to participate: Anonymous questionnaire - no consent form is required. Approved by the institutional review board (Helsinki) of the Tel Aviv Medical Center.

Consent for publication: Not applicable.

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Tables

Table 1
Comparison of clinical parameters between the studied underweight and normal weight women

Characteristic	Underweight (BMI < 18.5) (*n* = 26)	Normal weight (BMI > 20 and < 24.9) (*n* = 104)	*p* value
Age (y)	31.6 (4.17)	32.4 (3.59)	0.323
Height (cm)	165.2 (6.55)	163.7 (7.14)	0.328
Weight (kg)	47.7 (3.99)	59.7 (5.98)	< 0.001
BMI (kg/m^2)	17.4 (0.71)	22.2 (1.40)	< 0.001
Children (*n*)	0.65 (0.94)	0.59 (0.82)	0.86
Number of children	15 (57.7)	61 (58.7)	0.99
0	7 (26.9)	28 (26.9)	
1	4 (15.4)	15 (14.4)	
≥2			
Day 3 FSH (mIU/mL)	7.7 (2.11)	6.8 (2.38)	0.193
TSH (μIU/mL)	2 (1.24)	2 (0.97)	0.846
Prolactin (mIU/L)	254.6 (119.13)	244.2 (134.77)	0.765
Number of OPU cycles prior to the study period			0.93
0	21 (80.8)	88 (84.6)	
1	3 (11.5)	8 (7.7)	
2	1 (3.8)	4 (3.8)	
3	1 (3.8)	4 (3.8)	
Cause of IVF			0.96
PDG	11 (42.3)	45 (43.3)	
Unexplained	12 (46.2)	49 (47.1)	
Mechanical factor	3 (11.5)	10 (9.6)	

Values are presented as mean (standard deviation) or number (%). A *p* value of < 0.05 was considered significant.

BMI, body mass index; FSH, follicle-stimulating hormone; TSH, thyroid stimulating hormone; OPU, ovum pick-up; IVF, in vitro fertilization; PGD, preimplantation genetic diagnosis; SD, standard deviation
Note: Standard reference ranges: FSH: 1-9.2 mIU/mL; TSH: 0.5-4.8 μIU/mL; Prolactin: 108.78-557.13 mIU/L

Table 2
Comparison of ovarian stimulation data and outcomes between underweight and normal weight women

Characteristic	Underweight (BMI < 18.5) (*n* = 26)	Normal weight (BMI > 20 and < 24.9) (*n* = 104)	*p* value
Number of OPU cycles	42	162	
OPU cycles per patient	1.6 (0.89)	1.5 (0.83)	0.867
Total OPU cycles	16 (61.5)	63 (60.6)	0.24
1	5 (19.2)	30 (28.8)	
2	4 (15.4)	5 (4.8)	
3	1 (3.8)	6 (5.8)	
4			
Ovarian stimulation protocol	35 (83.3)	126 (77.8)	0.527
GnRH antagonist	7 (16.7)	36 (22.2)	
Short GnRH agonist			
Ovarian stimulation duration (days)	10.74 (2.56)	10.85 (2.10)	0.766
FSH total dose (mIU/mL)	2434 (1343)	2371 (1029)	0.744
Peak E2 (pg/mL)	2352 (1426)	2018 (1189)	0.122
Final maturation trigger	32 (76.2)	145 (89.5)	0.051
hCG	7 (16.7)	14 (8.6)	
GnRH agonist	3 (7.1)	3 (1.9)	
hCG + GnRH agonist			
Oocytes retrieved	13.4 (7.50)	13.6 (8.91)	0.868
MII oocytes	13.1 (8.50)	13.7 (9.15)	0.775
Maturity rate	80.4 (15.31)	88.3 (13.58)	0.091

Values are presented as mean (standard deviation) or number (%). A *p* value of < 0.05 was considered significant.

MII and maturity rate pertains to ICSI cycles; 2PN and fertilization rate pertains to all cycles.

BMI, body mass index; OPU, ovum pick-up; GnRH, gonadotropin-realizing hormone; FSH, follicle-stimulating hormone; E2, estradiol; hCG, human chorionic gonadotropin; MII, metaphase II; IVF, in vitro fertilization; ICSI, intracytoplasmic sperm injection, 2PN, 2 pronuclei; ET, embryo transfer; FET, frozen embryo transfer

Characteristic	Underweight (BMI < 18.5) (*n* = 26)	Normal weight (BMI > 20 and < 24.9) (*n* = 104)	*p* value
Fertilization methods	16 (38.1)	49 (30.2)	0.582
IVF	22 (52.4)	92 (56.8)	
ICSI	4 (9.5)	21 (13)	
IVF + ICSI			
2PN embryos	8 (5.41)	8.6 (6.89)	0.565
Fertilization rate	54.8 (20.34)	55.31 (22.56)	0.938
IVF	77.4 (17.45)	75.43 (17.08)	0.617
ICSI			
Total number of embryos	3.9 (4.31)	4.4 (3.98)	0.279
Transferred	1.07 (0.87)	1.27 (0.93)	0.226
Frozen	2.9 (4.54)	3.1 (4.34)	0.741
Number of ET cycles	71	287	
ET cycles per patient	2.7 (2.03)	2.7 (1.93)	0.917
ET protocol type	30 (42.3)	128 (44.6)	0.434
Fresh ET	11 (15.4)	29 (10.1)	
Modified natural FET	30 (42.3)	130 (45.3)	
Hormonally substituted FET			
Number of embryos transferred per transfer	1.4 (0.60)	1.4 (0.59)	0.870

Values are presented as mean (standard deviation) or number (%). A *p* value of < 0.05 was considered significant.

MII and maturity rate pertains to ICSI cycles; 2PN and fertilization rate pertains to all cycles.

BMI, body mass index; OPU, ovum pick-up; GnRH, gonadotropin-realizing hormone; FSH, follicle-stimulating hormone; E2, estradiol; hCG, human chorionic gonadotropin; MII, metaphase II; IVF, in vitro fertilization; ICSI, intracytoplasmic sperm injection, 2PN, 2 pronuclei; ET, embryo transfer; FET, frozen embryo transfer

Characteristic	Underweight (BMI < 18.5) (*n* = 26)	Normal weight (BMI > 20 and < 24.9) (*n* = 104)	*p* value
Number of embryos transferred	44 (62)	176 (61.3)	0.764
1	25 (35.2)	99 (34.5)	
2	1 (1.4)	10 (3.5)	
3	1 (1.4)	2 (0.7)	
4			
Day of ET	20 (28.2)	88 (30.7)	0.115
Day 2 or 3	43 (60.6)	139 (48.4)	
Day 5 or 6	2 (2.8)	5 (1.7)	
Day 3 and 5	6 (8.5)	55 (19.2)	
Day 4			
Values are presented as mean (standard deviation) or number (%). A *p* value of < 0.05 was considered significant.			
MII and maturity rate pertains to ICSI cycles; 2PN and fertilization rate pertains to all cycles.			
BMI, body mass index; OPU, ovum pick-up; GnRH, gonadotropin-realizing hormone; FSH, follicle-stimulating hormone; E2, estradiol; hCG, human chorionic gonadotropin; MII, metaphase II; IVF, in vitro fertilization; ICSI, intracytoplasmic sperm injection, 2PN, 2 pronuclei; ET, embryo transfer; FET, frozen embryo transfer			

Table 3 A. Comparison of embryo morphokinetic parameters of the studied underweight and normal weight women.

Parameter	Underweight (BMI <18.5) (*n* = 26)	Normal weight (BMI >20 and <24.9) (*n* = 104)	*p* value
Number of embryos	346	1467	
tPNf	25.17 (3.79)	25.33 (4.42)	0.496
t2	28.70 (5.93)	28.38 (5.29)	0.448
t3	38.96 (5.70)	38.76 (5.90)	0.820
t4	40.77 (6.14)	41.11 (6.61)	0.676
t5	52 (8.23)	51.26 (8.52)	0.529
t6	54.53 (8.16)	54.25 (8.57)	0.890
t7	57.13 (8.84)	56.80 (9.44)	0.825
t8	59.81 (9.56)	59.26 (9.90)	0.974
cc2	10.33 (4.94)	10.53 (4.29)	0.317
cc3	12.91 (7.53)	12.84 (6.53)	0.941
s2	1.97 (3.68)	2.26 (4.48)	0.138
s3	8.17 (10.74)	8.87 (9.43)	0.368
KIDScore[a]	3.70 (1.50)	3.63 (1.51)	0.670
Morphological score[a]	1.82 (1.04)	1.95 (1.10)	0.230
Number of embryos whose development was stopped before day 3 (%)	29 (8.4)	120 (8.2)	0.910

Values are presented as mean (standard deviation). A *p* value of < 0.05 was considered significant.

Pronuclei fading (tPNf), t2, t3, t4, t5, t6, t7, t8 = time (hours) between fertilization and pronuclei fading, two-, three-, four-, five-, six-, seven-, and eight-cell stage, respectively; cc2, cc3 = length (hours) of the second and third cell cycle, respectively; s2, s3 = synchrony (hours) in the division from three to four and five to eight cells, respectively.

BMI, body mass index

[a]Morphokinetic data were obtained from all embryos while KID and morphological scores were allocated to day 3 embryos.

B. Distribution of the KIDScore and the morphology score of the studied underweight and normal weight women

Embryo category	Underweight (BMI <18.5) (*n* = 26)	Normal weight (BMI >20 and <24.9) (*n* = 104)	*p* value
KIDScore			0.593
1 (low quality)	38 (13.7)	191 (14.6)	
2	42 (15.1)	186 (14.3)	
3	15 (5.4)	104 (8)	
4	53 (19.1)	254 (19.5)	
5 (high quality)	130 (46.8)	570 (43.7)	
Morphology score			0.264
4 (low quality)	19 (6.7)	128 (9.8)	
3	74 (26.1)	375 (28.6)	
2	27 (9.5)	113 (8.8)	
1 (high quality)	163 (57.6)	694 (53)	

Values are presented as number (%). A *p* value of < 0.05 was considered significant.

KID and morphological scores were allocated to day 3 embryos.

BMI, body mass index

Table 4
Comparison of pregnancy outcomes between the studied underweight and normal weight women

Characteristic	Underweight (BMI < 18.5) (*n* = 26)	Normal weight (BMI > 20 and < 24.9) (*n* = 104)	*p* value
Pregnancy rate	35.33 (43.20)	25.87 (39.53)	0.11
Clinical pregnancy rate	24.41 (40.32)	23.39 (39.54)	0.89
Live birth rate	23.71 (40.30)	19.51 (37.35)	0.42
Early miscarriage rate	37.5 (49.18)	26.3 (44.30)	0.23
Miscarriage rate	4.7 (21.82)	11.5 (32.15)	0.36
Values are presented as % (standard deviation). A *p* value of < 0.05 was considered significant.			
Pregnancy, clinical pregnancy, and live birth rates were on a “per embryo transfer” basis.			
Early miscarriage and miscarriage rates were calculated per pregnancy.			