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ASSISTED REPRODUCTION TECHNOLOGIES

Maternal body mass index affects embryo morphokinetics: a time-lapse study

Alessandro Bartolacci[1] · Jose Buratini[1,2] · Clarissa Moutier[1] · Maria Cristina Guglielmo[1] · Paola Vittoria Novara[1] · Fausta Brambillasca[1] · Mario Mignini Renzini[1] · Mariabeatrice Dal Canto[1]

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Abstract

Purpose To assess the effect of body mass index (BMI) on morphokinetic parameters of human embryos evaluated with time-lapse technology during in vitro culture.

Methods A retrospective analysis of ART cycles utilizing time-lapse technology was undertaken to assess the potential impact of maternal BMI on morphokinetic and static morphological parameters of embryo development. The cohort of patients was divided into four groups: 593 embryos from 128 underweight women in group A; 5248 embryos from 1107 normal weight women in group B; 1053 embryos from 226 overweight women in group C; and 286 embryos from 67 obese women in group D.

Results After adjusting for maternal age, paternal age, and cause of infertility, time to reach five blastomeres (t5) and time to reach eight blastomeres (t8) were longer in obese women compared with normoweight women [50.84 h (46.31–55.29) vs. 49.24 h (45.69–53.22) and 57.89 h (51.60–65.94) vs. 55.66 h (50.89–62.89), adjusted $p < 0.05$ and adjusted $p < 0.01$, respectively]. In addition, t8 was also delayed in overweight compared with normoweight women [56.72 h (51.83–63.92) vs. 55.66 h (50.89–62.89), adjusted $p < 0.01$]. No significant differences were observed among groups with regard to embryo morphology and pregnancy rate. Miscarriage rate was higher in underweight compared with normoweight women (OR = 2.1; 95% CI 1.12–3.95, adjusted $p < 0.05$).

Conclusion Assessment with time-lapse technology but not by classical static morphology evidences that maternal BMI affects embryo development. Maternal obesity and overweight are associated with slower embryo development.

Keywords BMI · Embryo development · Morphokinetics · Time-lapse

Introduction

In the last few years, the prevalence and incidence of obesity in women at the fertile age have increased dramatically all over the world [1, 2]. Obesity is well known to be associated with sub-fertility and infertility regardless the existence of ovulatory disorders, and with incidence of spontaneous abortions [3–6]. In addition, obesity is also strongly associated with perinatal complications, including preeclampsia, preterm delivery, and gestational diabetes [7, 8]. Nowadays, obese women failing to conceive naturally have access to assisted reproduction techniques (ARTs), but the literature is not clear regarding whether their outcomes might be compromised. While some studies suggest no direct negative impact [9, 10], but instead possibly decreased overall outcomes due to a higher percentage of poor responders in the obese population [11], others have provided evidence that obesity is associated with lower implantation, pregnancy, and live birth rates [12–15].

The mechanisms by which obesity influences female reproductive function are complex, not yet fully understood, and may involve detrimental effects at the endocrine, follicular, embryo, and uterine levels [16–18]. At the endocrine level, obesity is associated with hypogonadotropic hypogonadism and increased androgen:estrogen ratio, which are potential causes of irregular menstrual cyclicity and impaired follicle development [19]. Obesity can also perturb pancreas metabolism leading to the condition known as insulin resistance [20]. Studies in mice suggest that insulin resistance is associated with increased oxidative stress and impaired mitochondrial

✉ Mariabeatrice Dal Canto
dalcanto@biogenesi.it

[1] Biogenesi, Reproductive Medicine Centre, Monza, Italy

[2] Ovarian Molecular Physiology Laboratory, Department of Physiology, Institute of Biosciences, Sao Paulo State University, Botucatu, Sao Paulo, Brazil

function in the oocyte [21, 22], processes known to affect spindle formation, chromosome segregation, and thus oocyte developmental competence [23]. At the follicle level, obesity increases the concentration of lipids and inflammatory markers in the follicular fluid, alters cumulus cell gene expression, and induces endoplasmic reticulum stress [24], all of these reinforcing its negative influence on oocyte developmental competence.

Although lower pregnancy and birth rates following ART have been reported in obese women [25, 26], studies assessing the effects of BMI on embryological outcomes are often discrepant; while some suggest that BMI does not affect embryo development [27], others indicate negative effects on fertilization and embryo cleavage rates [28]. This discrepancy may result from the inaccuracy of methods based on static morphology, most commonly employed in IVF laboratories, to evaluate embryo development [13, 17]. Recently, the use of time-lapse technology has allowed a more precise approach taking into account morphokinetic parameters to assess embryo development. In fact, this technology has been reported to increase the accuracy in embryo selection, with positive impacts on pregnancy rates [29–32]. Time-lapse technology has been previously utilized to assess the impact of maternal BMI on embryo morphokinetics, but the examination of different time-windows of embryo development and statistical power concerns render this argument still unclear. While maternal obesity and overweight were reported to decrease embryo developmental potential and time to reach the morula stage [33], they did not affect cleavage stage morphokinetics in another study in which sample size was considered as a potential limitation by the authors [34].

In the present study, in order to assess the impact of maternal BMI on embryo development, we performed a retrospective analysis of ICSI cycles conducted at our clinic with the utilization of time-lapse technology, in which several morphokinetic parameters were compared across different BMI groups. In parallel, embryo static morphology was also retrospectively assessed and compared between BMI groups. We hypothesized that BMI affects embryo development and that the observation of such influence requires a dynamic evaluation.

Material and methods

Patients

This is a retrospective study including data from 1528 intracytoplasmatic sperm injection (ICSI) cycles in which time-lapse technology was utilized to assess morphological and morphokinetic developmental patterns of 7180 embryos with varying maternal BMI status. Clinical outcomes derive from 1366 embryos transferred on day 3 or 5 in single or double ETs. These data were obtained at the Biogenesi Reproductive Medicine Centre, Monza, Italy, from January 2012 to December 2017. Patients included in this study were in their first ICSI cycle using autologous oocytes and had their BMI calculated and registered in an electronic medical chart. Height and weight were measured with a standardized protocol. Body mass index was defined as weight in kilograms divided by the square of the height in meters (kg/m^2). The most recent World Health Organization (WHO) classification of BMI categories was used to divide the patients into four groups: group A, BMI < 18.50 kg/m^2 (underweight); group B, BMI 18.50–24.99 kg/m^2 (normal weight); group C, BMI 25.00–29.99 kg/m^2 (overweight); group D, BMI ≥ 30 kg/m^2 (obese) [35]. The numbers of embryos analyzed in each group are shown in Table 2. This study was approved by the locally competent ethical committee (ASST, Monza), and written consent was obtained from all participants.

Semen preparation

All male patients were required to undergo 2–7 days of abstinence before providing the semen samples for ICSI. After liquefaction of the semen (about 30 min at 37 °C), sperm samples were analyzed for volume, concentration, and motility according to WHO criteria (2010) [36]. Semen samples were prepared using Sil-Select (Ferti-Pro, Belgium) and Origio sperm medium (Måløv, Denmark). Sperm gradients of 90% and 45% were used throughout the study, and all procedures were conducted under sterile conditions. Subsequently, 1 mL of the lower layer (90% Sil-Select) was transferred into a conical centrifuge tube, to which 1 mL of the upper layer (45% Sil-Select) was gently added. The liquefied semen sample was then placed on top of the upper layer, and the tube was centrifuged for 14 min at 1400 rpm. Using a transfer pipette, 3 mL of sperm medium was added and the resuspended pellet was centrifuged for 10 min at 1200 rpm. The supernatant was removed; the sample was resuspended with 1 mL of sperm medium (Origio, Måløv, Denmark) and stored in an incubator at room temperature in unmodified atmosphere until use [37].

Protocol for ovarian stimulation

Pituitary downregulation and ovarian stimulation were achieved with GnRH antagonist (Ganirelix, Merck Sharp & Dohme, Rome, Italy) and rFSH (Puregon, Merck Sharp & Dohme, Rome, Italy or Gonal-F, Merck, Rome, Italy) [38]. The initial dose and dose adjustments during treatment were chosen on a case-by-case basis according to patients' characteristics and response to gonadotrophins. Ovulation was triggered with 10,000 IU hCG, administered 36 h prior to oocyte collection (Ovitrelle Merck, Rome, Italy), when follicles reaching diameters ≥ 17–18 mm were first observed.

ICSI and embryo culture

ICSI was carried out according to conventional methodology. After retrieval, cumulus-oocyte complexes were cultured in fertilization medium (Sequential Fert, Origio, Måløv, Denmark). Cumulus cells were removed by brief exposure to cumulase (80 U/mL; ICSI Cumulase, Origio, Måløv, Denmark), followed by mechanical action with the use of plastic pipettes (denuding pipettes; Vitromed). For ICSI, oocytes were positioned with the first polar body at the 12 o'clock position, and the injecting needle was inserted at the 3 o'clock position. Microinjected oocytes were transferred to Embryoslide™ Culture slides (Vitrolife, Göteborg, Sweden), into 30-μL microdrops of cleavage medium, and covered with paraffin oil (Origio, Måløv, Denmark). Embryos were cultured and analyzed for morphokinetic parameters in an integrated embryo culture TLM system (EmbryoScope™ Time-lapse System; Vitrolife, Göteborg, Sweden) [31]. No changes in embryo culture conditions were made throughout the study. Image acquisition was set for every 10 min at seven different focal planes for each embryo. Depending on the day chosen for transfer, embryos were morphologically assessed on day 3 or day 5 according to the Istanbul consensus [39], and were classified according to a quality score (1 = poor; 2 = fair; 3 = good) previously validated as explained below.

Embryo transfer

Embryo transfer strategy was decided considering maternal age, couple history, and embryo quality. Fresh ET was performed 3 or 5 days after fertilization according to the American Society for Reproductive Medicine guidelines [40], with abdominal ultrasound guidance. For younger patients (≤ 35 years old), without any major male infertility factor and at least three top quality embryos, considering both morphological score and morphokinetic parameters, a single embryo was transferred on the fifth post-fertilization day. In all other cases, one or two embryos were transferred on the third day after fertilization and the other embryos were further cultured and then frozen.

Evaluation of time-lapse images

Embryo image acquisition was performed with the software EmbryoViewer (Unisense FertiliTech, Aarhus, Denmark). Cleavage time was considered the moment when cell division was completed and the two originating cells were completely segregated and invested by their respective cytoplasmic membranes. The definitions of the timepoints assessed in the study were as follows: t2, time at which the embryo presented two separate and distinct cells; t3, time at which a three-blastomeres embryo was achieved; t4, time at which a four blastomeres embryo was achieved; t5, time at which a five blastomeres embryo was achieved; t8, time at which an eight blastomeres embryo was achieved. The time point t8 was the latest parameter assessed even for embryos further cultured to be transferred on day 5. Other parameters analyzed were Cc2 (interval between t3 and t2) and Cc3 (interval between t5 and t3), reflecting the duration of the second and third cell cycles, and s2 and s3, reflecting the synchrony of cell divisions from two to four blastomeres (s2) and from five to eight blastomeres (s3).

Outcome measures

The primary outcome was embryo morphokinetics, which parameters were the timepoints listed above. Embryo quality score, ongoing pregnancy, and spontaneous abortion were secondary outcomes. To generate the embryo quality score, we first utilized retrospective data from all single transfers performed in our center with clinical pregnancy diagnosis, in which embryos were evaluated according to the Istanbul consensus [39] either on day 3 or day 5. A regression model linking histological parameters with embryo implantation potential was generated as previously described [41], and based on the coefficients generated by this regression model, score scales ranging from 1 to 3 (1 = poor, 2 = fair, and 3 = good) were established to classify embryos on day 3 and day 5. The main parameters of assessment on day 3 were degree of fragmentation, number of blastomeres, and symmetry among blastomeres, while on day 5, the main parameters were degree of expansion, hatching status, inner cell mass, and trophectoderm quality (Istanbul Consensus [39]). Ongoing pregnancy was defined as the presence of fetal heartbeat at 6 to 12 weeks of gestation. Spontaneous abortion was defined as loss of clinical pregnancy before 20 weeks of gestation.

Statistical analysis

Data analysis was performed with the Statistical Package for Social Sciences (SPSS) version 21.0 (SPSS Incl., USA). Baseline characteristics of the different BMI groups were compared with the use of Kruskal-Wallis test. To assess the effect of BMI status on morphokinetic parameters, a general linear regression model was utilized to compare mean times, in which group B (normoweight) played the reference role and all other BMI groups were considered as dummy variables. As a variable number of embryos from each patient were analyzed configuring repeated measures, we have included the number of embryos per patient in the regression model as an independent variable. Logistic regression was applied to analyze the effect of BMI status on ongoing pregnancy and miscarriage rates. We performed adjustments for the following potential confounders: maternal age, paternal age and cause of infertility. Odds ratio for ongoing pregnancy and miscarriage rate was corrected also for day of transfer and number of

transferred embryos. All p values < 0.05 were considered statistically significant. Results are expressed as mean ± standard deviation (SD) or median [interquartile range (IQR)] and odds ratio (OR) with 95% confidence interval (CI).

Statistical power analysis was performed using G*power 3 [42] and revealed that the study has a power equal to 80% to detect differences in morphokinetics parameters larger than 2% (assuming a type I error of 0.05).

Results

A total of 1528 patients with varying BMI status undergoing their first fresh IVF cycle at our Fertility Center were included in the analysis. From these patients, 7180 embryos were assessed for histological and morphokinetic parameters, while clinical outcomes derive from 1366 embryos transferred on day 3 or 5 in single or double ETs. Baseline women characteristics across BMI groups are presented in Table 1. No statistical differences were found for female age, male age, number of retrieved oocytes, percentage of mature oocytes, fertilization rate, and embryo quality score. Overweight women showed a significantly increased risk of tubal factor infertility when compared with normal weight women, while all other infertility causes did not differ across BMI groups.

After adjusting for maternal age, paternal age, and cause of infertility, two morphokinetic parameters, t5 and t8, varied significantly across different BMI groups (Table 2). Embryos from obese women (group D) had cleavage time 5 (t5) delayed in relation to the control normoweight group (group B) [50.84 h (46.31–55.29) vs. 49.24 h (45.69–53.22), adjusted $p < 0.05$)]. Moreover, cleavage time 8 (t8) was delayed in embryos from overweight women (group C) and obese women (group D) compared with embryos from normoweight women (group B) [56.72 h (51.83–63.92) and 57.89 h (51.60–65.94) vs. 55.66 h (50.89–62.89), respectively, adjusted $p < 0.01$].

Embryo morphology, as assessed by quality scores, did not vary significantly across BMI groups (Table 3). The only clinical parameter significantly affected by maternal BMI was miscarriage rate, which was reduced in underweight women (group A) in relation to normoweight women (Table 3). Nevertheless, the likelihood of pregnancy reflected by the OR was numerically lower in underweight and obese women compared with the control group.

Discussion

In the present study, we have assessed the impact of maternal BMI on embryo development utilizing time-lapse technology. This was motivated by the fact that previous studies assessing static morphology or morphokinetic parameters were not able to clearly answer if maternal BMI influences embryo development. We report for first time evidence of slower development of cleavage stage embryos from overweight and obese mothers.

Studies assessing IVF outcomes in obese women have reported discrepant results and there is still no single consensus in the medical literature. While some suggest no negative effects [17], others have identified alterations in several parameters such as fertilization, cleavage rates [28], and embryo quality [43]. A large study including 6500 cycles reported reduced implantation, pregnancy, and live birth rates in obese women undergoing IVF treatment, although no significant differences in oocyte or embryo quality were observed [13]. This is in agreement with the absence of differences among BMI groups with regard to embryo quality score in the present study. Taken together, these data suggest that classical morphological parameters routinely utilized to assess embryo quality may not be accurate enough to detect potential impacts of maternal BMI on oocyte and embryo developmental competence [13, 17]. In the face of such limitation, the present study utilized time-lapse technology to assess the influence of maternal BMI on embryo development. Previous studies have already demonstrated the utility of time-lapse technology to improve the accuracy of embryo selection for transfer. In these studies, temporal patterns of embryo cleavage have been particularly related to different success rates of embryo implantation [29, 32].

The present data suggest slower progression of cell divisions in embryos from overweight and obese women compared with normoweight women, with significant differences between the four-blastomere and five-blastomere stage embryo (t5), and subsequently at the time the eight-blastomere stage is achieved (t8). In contrast, a previous study failed to find any association between maternal BMI and morphokinetic parameters of cleavage stage embryo development [33]. This discrepancy is likely due to the low number of embryos assessed in the previous study (71 embryos from 13 obese women), leading the authors to suggest that further larger studies would be needed to confirm their results. On the other hand, the discrepancy between the present data and another previous study indicating decreased time to morula in embryos from obese and overweight mothers is intriguing and difficult to explain [34]. We speculate that maternally inherited genomic instability could delay embryo development during early cleavage stages as discussed below [44], which could then be followed by dysregulation of embryogenesis. In fact, in spite of reaching the morula stage faster, embryos derived from obese and overweight mothers presented lower cell numbers and disturbed glucose and amino acid metabolism [34].

Table 1 Baseline characteristics by female BMI

Variable	Group A (< 18.50)	Group B (18.50–24.99)	Group C (25.0–29.99)	Group D (≥ 30)	*p* value
Number of patients	128	1107	226	67	
Female age, years (mean ± SD)	36.43 ± 4.59	36.98 ± 4.0	36.74 ± 4.53	37.75 ± 4.4	0.15
Male age, years (mean ± SD)	39.1 ± 5.3	39.2 ± 5.5	39.5 ± 5.3	39.7 ± 5.9	0.57
BMI (kg/m^2)	17.64 ± 1.58	21.39 ± 1.68	26.80 ± 1.48	31.55 ± 1.49	n/a
Number of retrieved oocytes (mean ± SD)	10.2 ± 5.19	10.10 ± 5.1	9.90 ± 4.71	9.38 ± 4.26	0.65
Mature oocytes, percentage (mean ± SD)	67.26 ± 1.98	67.18 ± 1.85	67.31 ± 2.01	67.33 ± 2.15	0.96
Fertilization rate (mean ± SD)	72.4 ± 24.62	75.0 ± 21. 77	73.2 ± 25.52	72.1 ± 28.67	0.84
Cause of infertility, OR (< IC95%)					
Endometriosis	0.64 (0.27–1.79)	1	1.01 (0.58–2.01)	0.28 (0.38–2.05)	
Male factor	0.96 (0.59–1.55)	1	0.85 (0.58–1.25)	1.39 (0.78–2.47)	
Mixed	1.05 (0.68–1.61)	1	0.98 (0.70–1.38)	1.18 (0.68–2.05)	
Polycystic ovarian syndrome	2.38 (0.78–7.30)	1	2.34 (0.95–5.82)	1.05 (0.14–8.05)	
Tubal factor	1.21 (0.61–2.43)	1	1.86 (1.16–3.0)**	0.85 (0.30–2.40)	
Unexplained infertility	0.91 (0.60–1.37)	1	0.80 (0.58–1.11)	0.83 (0.48–1.44)	

** $p < 0.01$ vs group with normal BMI

SD standard deviation, *OR* odd ratio, *n/a* not applicable

The impact of BMI on embryo development observed in the present study is likely a consequence of compromised oocyte quality. Oocytes from obese women are smaller [34], and oocyte diameter has been suggested as a predictor of embryo development [45]. Follicular fluid from obese women undergoing IVF contains increased levels of insulin, inflammation markers, triglycerides, and nonesterified fatty acids (NEFA) [22, 46]. Accumulation of triglycerides and NEFA indicate lipotoxicity, which has been recognized as an important cause of organelle damage in oocytes [46, 47]. Further studies in women and animal models indicate that obesity leads to abnormal mitochondria distribution and increased levels of reactive oxygen species (ROS) in the oocyte, which can compromise spindle formation and chromosomal alignment [44, 48, 49]. However, the exact mechanisms by which maternal overweight and obesity determine slower and potentially poorer embryo development are still unknown. It is tempting to speculate that they may involve maternally inherited genomic instability, particularly due to telomere attrition, a phenomenon resulting from increased oocyte oxidative stress. In the cleavage stage embryo, inefficient telomere reconstitution would be expected to cause anaphase lag, mosaicism, and copy number variants, leading to slower and poorer development [50].

Table 2 Embryo morphokinetic parameters in different maternal BMI groups

BMI Number of embryos	Group A (< 18.50) 593	Group B (18.50–24.99) 5248	Group C (25.0–29.99) 1053	Group D (≥ 30) 286
t2	26.39 (24.51–28.42)	25.95 (23.99–28.10)	26.06 (24.47–28.45)	26.17 (24.41–28.77)
t3	36.97 (34.76–39.55)	36.81 (34.39–39.48)	37.26 (34.91–39.76)	37.42 (34.74–39.97)
t4	38.18 (36.10–40.90)	37.91 (35.46–40.82)	38.37 (35.98–41.26)	38.51 (35.99–41.84)
t5	50.01 (46.53–53.45)	49.24 (45.69–53.22)	50.12 (46.42–53.90)	50.84 (46.31–55.29)*
t8	55.49 (51.37–63.48)	55.66 (50.89–62.89)	56.72 (51.83–63.92)**	57.89 (51.60–65.94)**
Cc2	11.05 (10.26–11.82)	11.06 (10.25–11.86)	11.23 (10.33–12.16)	11.26 (10.25–12.10)
Cc3	12.84 (11.46–14.30)	12.74 (11.29–14.26)	13.03 (11.55–14.46)	13.16 (11.76–15.07)
s2	0.67 (0.33–1.25)	0.66 (0.33–1.27)	0.65 (0.32–1.33)	0.75 (0.33–1.50)
s3	4.07 (2.50–12.96)	4.50 (2.33–13.72)	5.00 (2.67–14.18)	5.00 (2.66–14.13)

Data presented in hours: median and IQR (interquartile range). *$p < 0.05$, **$p < 0.01$, in comparison with group B (normal BMI)

Values presented are cleavage times from a zygote to a 8-cell embryo. t2, time at which the embryo presented two blastomeres; t3, time at which a three-blastomeres embryo was identified; t4, time at which a four blastomeres embryo was identified; t5, time at which a five blastomeres embryo was identified; t8, time at which an eight blastomeres embryo was identified; Cc2, interval between t3 and t2; Cc3, interval between t5 and t3; s2, synchrony of cell divisions from two to four blastomeres; s3, synchrony of cell divisions from five to eight blastomeres

Table 3 Embryo morphology scores and ICSI outcomes across maternal BMI groups

	Group A (< 18.50)	Group B (18.50–24.99)	Group C (25.0–29.99)	Group D (≥ 30)
Number of embryos	593	5248	1053	286
Embryo quality score (mean ± SD)	1.92 ± 0.68	1.97 ± 0.73	1.89 ± 0.75	1.87 ± 0.77
Number of embryo transfers	113	989	201	63
Number of embryos per transfer (mean ± SD)	1.96 ± 0.71	1.91 ± 0.65	1.96 ± 0.67	1.97 ± 0.72
Day of embryo transfer				
Embryo transfers on day 3 (%)	98/113 (86.7)	854/989 (86.3)	179/201 (89)	58/63 (92.1)
Embryo transfers on day 5 (%)	15/113 (13.3)	135/989 (13.65)	22/201 (10.9)	5/63 (7.9)
Ongoing pregnancy, OR (< IC95%)	0.73 (0.43–1.25)	1	1.34 (0.94–1.94)	0.81 (0.41–1.62)
Miscarriage rate, OR (< IC95%)	2.1 (1.12–3.95)*	1	0.94 (0.47–1.90)	1.64 (0.62–4.02)

* $p < 0.05$ vs group B (normal BMI)

SD standard deviation, *OR* odd ratio

Embryo quality score: mean score based on morphological parameters examined on day 3 or day 5. Data were obtained from all embryos produced

No statistically significant differences were observed in pregnancy rates among different BMI groups in the present study. Nevertheless, the numerically inferior ongoing pregnancy rate provided by embryos from obese mothers coincided with slower early development, which reinforces our suggestion that obesity may indeed compromise embryo developmental competence. It is important to point out however, that the present study was not designed to assess the effects of BMI on pregnancy rates, which would require a much larger number of patients. In addition, embryos from all BMI groups were selected for transfer considering morphological and morphokinetic parameters. Therefore, the selection of the fastest embryos from all BMI groups for transfer may have minimized differences in embryo quality and thus in pregnancy rates, particularly between maternal normoweight and obesity. The impact of obesity on pregnancy rates is a controversial topic in the literature. A recent large multi-center retrospective analysis including 51,198 women in their first autologous IVF cycle reported an overall negative impact of high BMI on ongoing pregnancy rate [15]. Another large retrospective study assessing the outcome of 9587 oocytes donated by normoweight donors and transferred to women with different BMI reported decreased implantation, pregnancy, and live birth rates associated with higher BMI, suggesting that maternal obesity may also compromise uterine receptivity [51]. In contrast, other studies failed to demonstrate significant differences in live birth rates between normoweight and obese patients, although the majority of these studies have assessed a much lower number of patients [52, 53].

Finally and interestingly, a higher miscarriage rate was observed in underweight women, and a similar trend was also observed in obese women. The underweight condition appears to negatively affect IVF outcomes, but studies assessing this phenomenon are scarce and conflicting [54–56]. The higher miscarriage rate in underweight women may be due to decreased levels of leptin, which was previously suggested to impair embryo implantation [57]. Plasma levels of leptin are positively correlated with BMI both in pregnant [58] and non-pregnant women [59]. Leptin and its receptor are expressed in the secretory endometrium [60] and may influence uterine angiogenesis and embryo implantation [61]. In fact, low serum levels of leptin have already been linked to recurrent abortions [62].

The present results are potentially valuable in the context of clinical practice. Since obesity was associated with slower embryo development, particularly prolonging time intervals to reach five and eight blastomeres, these parameters can be potentially utilized to improve embryo selection and transfer prognosis in obese IVF patients. Time-lapse technology has been previously shown to be a useful tool to improve embryo selection in ART [29–32]. We now reinforce this concept by demonstrating its value in the context of obesity. In parallel, our data also reinforce that standard static morphology is not capable to discriminate embryo quality in this context.

We acknowledge that our study is limited by its retrospective nature and by the utilization of data generated in a single IVF center. On the other hand, the large number of embryos analyzed for all BMI groups strengthens the soundness of our study.

In conclusion, time-lapse assessment of embryos from women with different BMI allowed us to observe slower embryo development associated with maternal overweight and obesity. This study also suggests that, in the context of maternal overweight and obesity, static morphology appears not accurate enough to distinguish embryo quality, while morphokinetic parameters provided by time-lapse technology may be valuable to improve embryo selection and prognosis. The present data motivate further studies assessing the mechanisms underlying the impact of obesity on embryo quality, and their relative importance in the overall decrease in fertility associated with obesity.

Compliance with ethical standards

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

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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