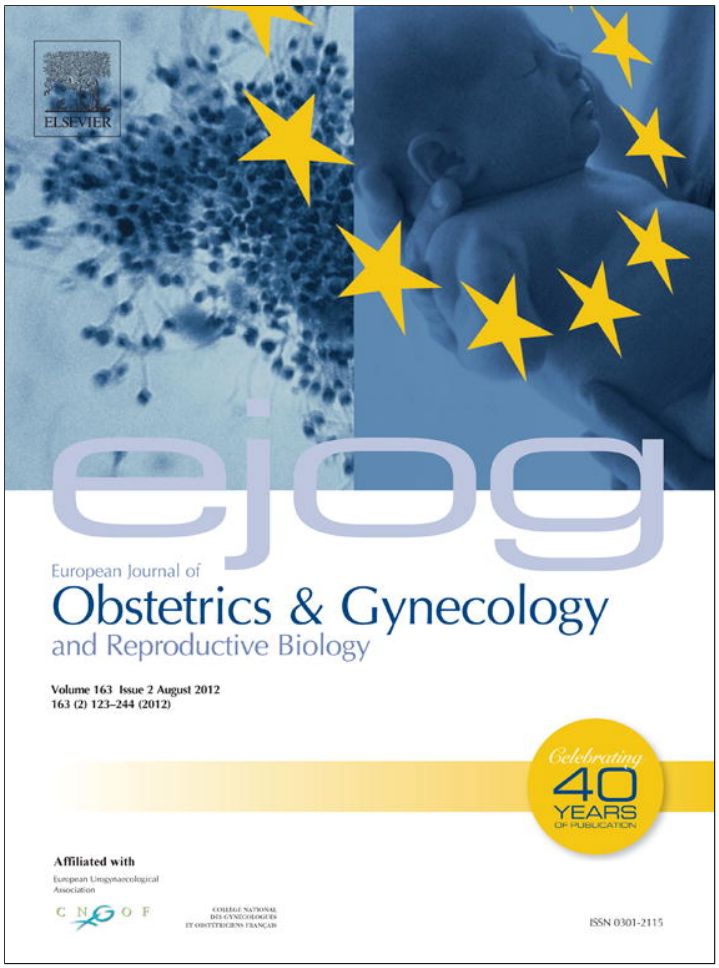

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Body mass index is negatively correlated with the response to controlled ovarian stimulation but does not influence oocyte morphology in ICSI cycles

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ABSTRACT

Objective: To investigate whether or not body mass index (BMI) is associated with oocyte dysmorphisms.
Study design: This retrospective study enrolled 1105 patients undergoing intracytoplasmic sperm injection (ICSI). The correlation between BMI and the response to controlled ovarian stimulation (COS) and ICSI outcomes was analysed. Oocyte morphology was determined in metaphase II (MII) oocytes retrieved from all cycles. The influence of BMI on the odds of having oocyte dysmorphism was also studied.
Results: A negative correlation was found between BMI and the number of oocytes retrieved, MII oocytes, oocytes injected, embryos obtained, high-quality embryos and oocyte recovery rate. In addition, a trend towards a negative correlation between BMI and implantation rate was observed. However, BMI did not influence oocyte dysmorphisms.
Conclusions: A negative correlation was found between BMI and the response to COS, and a trend towards a negative correlation was observed between BMI and implantation rate in the ICSI cycles. However, oocyte dysmorphisms were not influenced by BMI and, therefore, do not account for the reduced ICSI outcomes.

1. Introduction

Obesity is a rapidly growing worldwide phenomenon. It is estimated that more than 1.5 billion people worldwide are overweight, and 400 million are obese [1]. The increasing prevalence of obesity around the world is the result of a combination of increased caloric intake, dietary composition and reduced exercise [2].

The deleterious effects of obesity on general heath are well known. Obesity is also known to affect fertility because it perturbs the hormonal milieu that controls the menstrual cycle, ovulation and endometrial development [3]. The reproductive consequences of obesity include menstrual disorders and infertility [4]. As a result, obese women are almost three times as likely as non-obese women to be at risk of infertility [5] and to fail to become pregnant [6]. Moreover, obesity is associated with an increased risk of pregnancy complications [7].

High body mass index (BMI) is associated with lower success rates following assisted reproduction [8]. Obesity compromises the ovarian response to ovulation induction agents, such as gonadotropins [9], resulting in increased gonadotropin requirements during ovarian stimulation [10,11]. Moreover, overweight and obesity can have detrimental effects on oocyte quality and maturity. This includes retrieval of fewer oocytes [10], fewer mature oocytes [12] and poor oocyte quality, which subsequently leads to lower fertilization rates [4].

Oocyte dysmorphisms have been associated with reduced intracytoplasmic sperm injection cycle (ICSI) outcomes [13–16]. Therefore, it can be hypothesized that a high BMI compromises an oocyte's morphological appearance and results in lower fertilization, implantation and pregnancy rates. The aim of this study was to investigate whether the reduced reproductive outcomes that are associated with high-BMI patients undergoing ICSI are associated with the morphological appearance of the oocytes retrieved.

2. Materials and methods

2.1. Study group

In total, 1105 ICSI cycles performed in patients from January 2006 to August 2010 at a private centre for assisted reproduction were evaluated. All the cycles included in this study were first in vitro fertilization (IVF) treatments.

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Inclusion criteria were: women of good physical and mental health; regular menstrual cycles of 25–35 days; presence of both ovaries and intact uterus; absence of polycystic ovaries, endometriosis or gynaecological/medical disorders; and a negative result in a screening for sexually transmitted diseases.

To minimize the influence of severe male factor infertility, all cases of sperm concentration $<1 \times 10^6$ million/ml and sperm motility <20% were excluded from the study. In addition, ICSI cycles with any female factors apart from tubal factor were also excluded from this study because female factors may significantly influence oocyte quality, pre-implantation embryo development and/or implantation.

The correlations between female BMI and the response to controlled ovarian stimulation (COS) and ICSI outcomes were analysed. For significant correlations, the influence of BMI on these variables was also assessed. Patients were categorized by their BMI as underweight (<19 kg/m^2), normal weight (19–24.9 kg/m^2), overweight (25–29.9 kg/m^2) or obese (≥ 30 kg/m^2), and ICSI outcomes were compared between the groups. Oocyte morphology was determined in metaphase II (MII) oocytes that were retrieved from all cycles. The influence of BMI on the odds of having oocyte dysmorphisms was studied.

Written, informed consent was obtained from the patients to share the outcomes of their cycles for research purposes. The study was approved by the local institutional review board.

2.2. Ovarian stimulation and oocyte retrieval

COS was achieved by long pituitary downregulation using a gonadotropin-releasing hormone agonist (Lupron Kit, Abbott S.A Societé Française des Laboratoires, Paris, France). This was followed by ovarian stimulation with recombinant follicle-stimulating hormone (Gonal-F, Serono, Geneva, Switzerland) using a step-down protocol until at least two follicles reached an average diameter of 18 mm. The protocols for pituitary downregulation, ovulation induction and administration remained consistent throughout the study period. Oocyte retrieval was performed 35 h after administration of recombinant human chorionic gonadotropin (Ovidrel, Serono, Geneva, Switzerland) through transvaginal ultrasonography.

2.3. Preparation of oocytes and morphology assessment

Retrieved oocytes were maintained in human tubal cultured medium (HTF, Irvine Scientific, Santa Ana, CA, USA) supplemented with 10% human synthetic albumin (HSA, Irvine Scientific), which was covered with mineral oil (Ovoil, Vitrolife) for 2–3 h before cumulus cell removal. Surrounding cumulus cells were removed with exposure to a HEPES buffered medium containing hyaluronidase (80 IU/ml, Irvine Scientific). The remaining cumulus cells were then removed mechanically by gentle pipetting with a hand-drawn Pasteur pipette (Humagen Fertility Diagnostics, Charlottesville, VA, USA).

Oocyte morphology was assessed using an inverted Nikon Diaphot microscope (Eclipse TE 300; Nikon, Tokyo, Japan) with a Hoffmann modulation contrast system under 400× magnification just before sperm injection (3–4 h after retrieval). The following intracytoplasmic and extracytoplasmic oocyte dysmorphisms were recorded: (i) increased cytoplasmic granularity (dark centre or homogeneous); (ii) smooth endoplasmic reticulum clusters; (iii) vacuoles in the ooplasm; (iv) large perivitelline space; (v) perivitelline space granularity; (vi) zona pellucida abnormalities; (vii) fragmented first polar body; and (viii) oocyte shape. Normal oocytes showed the following characteristics: clear cytoplasm with uniform texture and a homogenous, fine granularity that did not contain inclusions; a small perivitelline space without granularity; and a single, unfragmented first polar body [17].

2.4. ICSI, fertilization assessment, embryo development and embryo transfer

ICSI was performed in all MII oocytes according to the technique described by Alikani et al. [18]. Oocytes were transferred into a micro-injection dish, which was prepared with 4-μl droplets of buffered medium (HEPES, Irvine Scientific) and covered with mineral oil, on a heated stage (37.0 ± 0.5 °C) of an inverted microscope. Approximately 16 h after ICSI, fertilization was confirmed by the presence of two pronuclei and extrusion of the second polar body. Embryos were kept in a 50-μl drop of HTF medium supplemented with 10% HSA covered with mineral oil in a humidified atmosphere (6% CO_2 in the air) and at 37 °C until transfer on day 3 of development. One to three embryos were transferred per patient.

High-quality embryos were defined as having the following characteristics: 8–10 cells on the third day of development, <15% fragmentation, symmetric blastomeres, and absence of multinucleation and zona pellucida dysmorphisms.

2.5. Statistical analyses

Results are expressed as mean ± standard deviation for numeric variables, and proportions are used for categorical variables. BMIs were correlated with the response to COS and ICSI outcomes using the Spearman correlation. The response to COS and ICSI outcomes were compared between the groups using analysis of variance and Chi-squared test. The influences of BMI on the response to COS, ICSI outcomes and oocyte/embryo morphology were calculated using linear and binary logistic regressions. All the analyses were adjusted for maternal age. Results are expressed as odds ratios (OR) with 95% confidence intervals (CI) or regression coefficients, standard error and R^2, correlation coefficient (R), and p-values. Results were considered significant at the 5% critical level ($p < 0.05$). Statistical analyses were performed using Minitab Release 14.

3. Results

From January 2007 to December 2010, 1105 ICSI cycles were performed. Table 1 presents the demographic characteristics and ICSI outcomes of all women included in the study.

The correlations between BMI and the response to COS and ICSI outcomes for all patients are shown in Table 2.

Linear regression analyses were performed for all significant correlations. These analyses demonstrated that a 1-point increase

Table 1
Demographic characteristics and intracytoplasmic sperm injection outcomes of the study group ($n = 1105$).

Variable	Values
Female age (years)	33.5 ± 5.2
Total dose of FSH administered (IU)	2342.6 ± 776.1
Mean number of follicles	18.0 ± 13.9
Mean number of oocytes retrieved	12.1 ± 9.4
Oocyte recovery rate (%)	68.2
Mean number of MII oocytes	8.3 ± 6.8
MII oocyte rate (%)	72.6
Fertilization rate (%)	65.0
Rate of high-quality embryos (%)	43.2
Mean number of embryos transferred	1.8 ± 1.2
Transferred cycles (%)	1037/1105 (93.8)
Implantation rate (%)	460/2003 (23.0)
Pregnancy rate (%)	359/1037 (34.6)
Miscarriage rate (%)	69/359 (19.2)

FSH, follicle-stimulating hormone; IU, international units; MII, metaphase II.
Values are mean ± standard deviation, unless otherwise indicated.

Table 2
Correlations between body mass index and the response to controlled ovarian stimulation and intracytoplasmic sperm injection outcomes.

Variable	Spearman correlation coefficient	*p*-Value
Follicle-stimulating hormone	0.032	0.271
Number of follicles	−0.055	0.069
Number of oocytes retrieved	−0.079	0.009
Oocyte recovery rate	−0.072	0.019
Number of MII oocytes	−0.076	0.014
MII oocyte rate	−0.013	0.582
Number of oocytes injected	−0.091	0.003
Fertilization rate	−0.013	0.575
Number of embryos obtained	−0.088	0.005
Number of high-quality embryos	−0.065	0.030
Number of embryos transferred	0.024	0.080
Implantation rate	−0.061	0.082

Table 3
Influence of body mass index on the response to controlled ovarian stimulation.

Variable	Regression coefficient	Standard error	R^2 (%)	*p*-Value
Number of oocytes retrieved	−0.17912	0.05330	0.5	0.001
Oocyte recovery rate	−0.46241	0.1627	0.7	0.005
Number of MII oocytes	−0.14069	0.03993	0.6	<0.001
Number of oocytes injected	−0.12961	0.04638	0.7	0.005
Number of embryos obtained	−0.10676	0.03774	0.7	0.005
Number of high-quality embryos	−0.06598	0.03071	0.4	0.032

MII, metaphase II.

in BMI decreased: (i) the number of oocytes retrieved (0.17); (ii) the retrieval rate (0.46%); (iii) the number of MII oocytes (0.14); (iv) the number of oocytes injected (0.13); (v) the number of embryos obtained (0.11); and (vi) the number of high-quality embryos (0.06). Regression analysis results are shown in Table 3.

BMI did not influence the pregnancy rate (OR 0.98, 95% CI 0.94–1.01, $p = 0.212$), miscarriage rate (OR 1.01, 95% CI 0.94–1.09, $p = 0.726$) or embryo transfer rate (OR 0.99, 95% CI 0.93–1.05, $p = 0.712$).

According to the BMI classifications, the majority of cycles were in women of normal weight (738 patients, 66.8% of all treatment cycles). The underweight, overweight and obese groups comprised 39 (3.5%), 242 (21.9%) and 86 (7.8%) patients, respectively. Demographic characteristics and the ICSI outcomes of the study groups, which were divided into four subgroups according to BMI, are shown in Table 4.

In terms of oocyte morphology, BMI did not influence the presence of granular cytoplasm (OR 1.01, 95% CI 0.99–1.03, $p = 0.379$), smooth endoplasmic reticulum aggregates (OR 1.03, 95% CI 0.84–1.27, $p = 0.775$), vacuoles (OR 1.02, 95% CI 0.95–1.10, $p = 0.605$), perivitelline space size (OR 0.87, 95% CI 0.81–1.04, $p = 0.387$), granularity (OR 1.00, 95% CI 0.96–1.05, $p = 0.883$), zona pellucida abnormalities (OR 0.92, 95% CI 0.85–1.00, $p = 0.058$), fragmented first polar bodies (OR 1.02, 95% CI 0.98–1.06, $p = 0.362$) or oocyte shape (OR 1.03, 95% CI 0.89–1.18, $p = 0.720$). Moreover, BMI did not influence the odds of having a high-quality embryo (OR 1.00, 95% CI 1.00–1.01, $p = 0.785$).

4. Comments

Reduced fecundity in obese women is probably related to multiple factors, including abnormalities in endocrine and metabolic functions that can affect follicular growth, implantation and the achievement of a clinical pregnancy. In some studies, obesity is associated with lower success rates of patients undergoing IVF. In contrast, other studies have found that obesity has no effect on the need for gonadotropins [19,20] or the number of days of ovarian stimulation [19,21]. Therefore, the aim of this study was to analyse the association between BMI and the response to COS and ICSI outcomes, and to verify whether there is a connection between BMI and oocyte dysmorphisms.

The results demonstrated that BMI is negatively correlated with the number of oocytes retrieved, MII oocytes, oocytes injected, embryos obtained, high-quality embryos and oocyte recovery rate. In addition, a trend towards a negative correlation between BMI and implantation rate was observed. However, when the patients were divided into groups according to their BMI, almost all variables were similar between the analysed groups. The variables that differed between groups included the number of follicles and oocytes, and the fertilization and implantation rates. Also, underweight patients had more follicles and retrieved oocytes compared with the other groups.

No differences were observed in the total administered dose of follicle-stimulating hormone between the underweight group and the other groups; however, the lower mean female age in the underweight group could explain the higher number of follicles and retrieved oocytes in these patients. In addition, the fertilization

Table 4
Demographic characteristics and intracytoplasmic sperm injection outcomes of the four body mass index subgroups.

Variables	Underweight ($n = 39$)	Normal weight ($n = 738$)	Overweight ($n = 242$)	Obese ($n = 86$)
Female age	32.5 ± 4.4^a	34.5 ± 4.6^b	35.2 ± 4.6^b	35.8 ± 5.1^b
Infertility type				
Male factor (%)	23 (59.0)[a]	285 (38.6)[a]	97 (40.1)[a]	32 (37.2)[a]
Female factor (%)	11 (28.2)[a]	264 (35.8)[a]	85 (35.1)[a]	28 (32.6)[a]
Male and female factor (%)	4 (10.2)[a]	99 (13.4)[a]	30 (12.4)[a]	20 (23.2)[a]
Unexplained (%)	1 (2.6)[a]	90 (12.2)[a]	30 (12.4)[a]	6 (7.0)[a]
Duration of infertility (years)	2.1 ± 3.9^a	2.5 ± 3.7^a	2.8 ± 4.3^a	2.9 ± 4.1^a
Follicle-stimulating hormone administered (IU)	2106.6 ± 469.2^a	2314.0 ± 666.1^a	2322.4 ± 676.5^a	2318.7 ± 647.6^a
Mean number of follicles	24.2 ± 16.7^a	17.8 ± 13.8^b	17.8 ± 13.9^b	17.8 ± 12.5^b
Mean number of oocytes	8.4 ± 6.0^a	6.4 ± 4.7^b	6.1 ± 4.6^b	5.7 ± 4.0^b
Oocyte recovery rate (%)	72.3[a]	69.3[a]	66.2[a]	64.4[a]
MII oocyte rate (%)	73.5[a]	71.8[a]	75.0[a]	69.8[a]
Fertilization rate (%)	60.0[a]	69.8[b]	64.5[a,b]	64.8[a,b]
High-quality embryo rate (%)	61.3[a]	58.1[a]	64.3[a]	61.1[a]
Transferred embryos	1.8 ± 1.2^a	1.8 ± 1.2^a	1.9 ± 1.3^a	1.9 ± 1.2^a
Transferred cycles (%)	36/39 (92.3)[a]	694/738 (94.0)[a]	225/242 (93.0)[a]	82/86 (95.3)[a]
Implantation rate (%)	11/70 (15.7)[a]	327/1310 (25.0)[a]	86/462 (18.6)[b]	36/161 (22.4)[a,b]
Pregnancy rate (%)	9/36 (25.0)[a]	250/694 (36.0)[a]	71/242 (29.3)[a]	29/82 (35.4)[a]
Miscarriage rate (%)	2/9 (22.2)[a]	43/250 (17.2)[a]	19/71 (26.8)[a]	5/29 (17.2)[a]

IU, international units.
In each row, different letters mean significant differences ($p < 0.05$).
Note: $a \neq b$, $a = ab$, $b = ab$.

rate was significantly lower in the underweight group compared with the normal-weight group. It has been suggested that the association between body weight and IVF/ICSI outcome is an 'inverted U shape'. This implies that being underweight has as deleterious an effect on assisted reproductive treatment outcomes as does overweight and obesity [22,23]. A significant difference between implantation rates in the normal-weight and overweight groups was also observed (25.0% vs 18.6%, respectively), but the obese group had similar implantation rates to the normal-weight group.

The present data do not suggest that obesity has a significant impact on the response to COS and ICSI outcomes. A possible explanation could be the infrequency of treatment cycles (86 cycles) in obese women.

High BMI has been shown to compromise the ovarian response to gonadotropin stimulus, leading to increased gonadotropin requirements during COS [9–11]. Further, it has been shown that the presence of oocyte dysmorphisms is gonadotropin dose-dependent [24,25] and associated with reduced ICSI outcomes [13,14,24,26]. Therefore, the present authors wanted to verify the association between high BMI and oocyte dysmorphisms. The results demonstrated, however, that BMI did not influence the chance of an oocyte displaying morphological abnormalities. In addition, no significant difference between the groups in terms of gonadotropin requirements was observed, and no correlation was found between BMI and gonadotropin requirements. This could explain the lack of association between BMI and the presence of oocyte dysmorphisms.

Previous studies have suggested that women with extreme BMIs have fewer oocytes [10], lower fertilization rates [27] and lower implantation rates [28]. Therefore, being underweight or overweight may interfere with infertility treatment (IVF) and ICSI. Furthermore, it has been reported that, in younger patients undergoing IVF, BMI has a significantly negative impact on fertility, but its impact diminishes as patients reach their mid-30s [29]. Therefore, the effects of age appear to be stronger than BMI in older patients. In the present study, apart from the underweight and normal-weight groups, the other groups had mean female ages of >35 years. This could explain why this study failed to demonstrate reduced outcomes in the overweight and obese patients.

Most studies that have shown a negative association between obesity and success rates following IVF have reported on intermediate outcomes, such as the response to COS, rather than more definitive endpoints such as pregnancy and live birth. Balen et al. [30] showed that a higher BMI was associated with increased doses of gonadotropin but not with reduced pregnancy rates. This demonstrates a clear discrepancy between surrogate and substantive outcomes. A recent, retrospective analysis failed to demonstrate a weight-related reduction in the number and maturity of oocytes retrieved. However, fewer implantations, pregnancies and live births were observed in obese women [2].

Weight loss has been shown to improve reproductive function in overweight and obese women [31–33]. Even modest weight loss (up to 10% of the initial body weight) can effectively improve menstrual cycle regularity, ovulation and pregnancy rates [34]. Therefore, overweight and obese women attending assisted reproductive technology centres should be given the necessary advice and support to achieve their weight loss.

A strength of this study is the large database that was used, which encompassed a broad spectrum of patients representing typical infertility patients presenting for assisted reproduction. Also, a total of 1105 ICSI cycles were analysed. Furthermore, this is the first study to evaluate the relationship between BMI and oocyte morphological abnormalities. This study is limited, however, by its retrospective design. The small numbers of patients in the underweight (3.5%) and obese (7.8%) groups prevented any meaningful interpretation of the data.

In summary, BMI is negatively correlated with the response to COS, and trends towards a negative correlation with implantation rate in ICSI cycles. Oocyte dysmorphisms, however, are probably not influenced by BMI and, therefore, may not account for reduced ICSI outcomes.

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