Influence of Donor, Recipient, and Male Partner Body Mass index on Pregnancy Rates in Oocyte Donation Cycles

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ABSTRACT

Objective: A high body mass index (BMI) has been shown to associate with negative reproductive outcomes. Women with high BMI have in general lower chances of getting pregnant as well as higher risk of pregnancy complications. Several studies have described in the past the relationship between high BMI and the pregnancy outcome, however, some of them have a small sample size or fail to control for variables associated with a diminished probability of pregnancy. In the present study, we aim to analyze the role of the BMI of all parties involved in oocyte donation cycles (that is: the oocyte donor, the recipient woman, and the male partner) on pregnancy outcomes.

Methods: This study includes 1092 oocyte donation cycles. Inclusion criteria were: fertilization by ICSI, frozen semen, transfer of 2 embryos at day 3 of in vitro development. For statistical analysis, BMI was divided in: low weight (<20 kg/m²), normal (20-24 kg/m²), overweight (25-29 kg/m²) and obesity (≥30 kg/m²). Quantitative and categorical variables were assessed by squared-Chi test and one-way ANOVA. The association between the BMI (recipient, oocyte donor and partner) and pregnancy rate was assessed by multivariate logistic regression.

Results: Laboratory outcomes and pregnancy rates do not differ among the different BMI categories of recipient, oocyte donor or partner. After adjusted analyses (for oocyte donor age, for laboratory outcomes and for age and BMI of all the parties for pregnancy outcomes), no difference was found either.

Conclusion: In oocyte donation cycles, where donors BMI is by law mandated to be in the 18-30 range, the pregnancy rate of the oocyte recipient does not seem to be affected by the BMI of any of the parties involved.

Keywords: Body mass index, *In vitro* fertilization, Intracytoplasmic sperm injection, Embryo quality, Male obesity, Female obesity.

INTRODUCTION

A high body mass index (BMI) in women has been shown to negatively affect their reproductive outcomes, as these women have both lower chances of getting pregnant and higher chances of pregnancy complications (Garcia *et al.*, 2014). On one hand, a BMI higher than 25kg/m² has been reported to diminish both the number and quality of the MII oocytes obtained after controlled ovarian stimulation (Esinler *et al.*, 2008, Wittemer *et al.*, 2000), which in turn results in embryos of lower quality (Zhang *et al.*, 2010). Even when the female gamete is of high quality, such as in oocyte donation cycles, high BMI in the recipient is also associated with an increased abortion rate (Bellver *et al.*, 2003) and a lower ongoing pregnancy rates (Bellver *et al.*, 2007).

The endocrine changes associated with obesity can impact endometrial receptivity; obese women have more an-

drogen receptors in their endometrium (Okon *et al.*, 1998), and have altered levels of androstenedione, which depresses endometrial receptivity (Tuckerman *et al.*, 2000) and, through a decreased expression of glycodeilin, increases their susceptibility to abortion (Salim *et al.*, 2007).

Moreover, hyperinsulinemia associated with obesity decreases IGFBP1 levels in the uterus, an important molecule for embryonic adhesion (Butzow *et al.*, 2000, Fowke *et al.*, 2010). Finally, an increased concentration of leptin in the uterine environment in obese women has also been related to alteration in trophoblast invasion, implantation, and an increased risk of abortion (Castellucci *et al.*, 2000).

A lack of association between recipient BMI and pregnancy rate in oocyte donation cycles has been reported (Styne-Gross *et al.*, 2005); these results were confirmed in a meta-analysis (Jungheim *et al.*, 2013); however, the authors cautions against the over interpretation of their results, as they proceed from small and heterogeneous studies. A large study which analyzes reproductive outcomes in oocyte donation cycles, including BMIs of both donors and recipient, and also taking into account the increasingly important BMI of the male partner, is still lacking.

The relationship between male BMI and reproductive outcomes is much less studied; obese man have worse reproductive results with natural conceptions; male obesity is associated with low levels of androgens and high levels of estrogens, which result in hypergonadotropic hypogonadism associated with hypoandrogenemia (Colaci *et al.*, 2012). Hyperestrogenism causes an alteration in the pulsatile release of GnRH (Hammoud *et al.*, 2008). Both high weight and obesity in males have been associated to poor semen quality (Colaci *et al.*, 2012, Hammoud *et al.*, 2008) as well as to a higher proportion of DNA fragmentation in semen (Hammoud *et al.*, 2008; Colaci *et al.*, 2012), and infertility (Sallmen *et al.*, 2006).

However, the relationship between BMI in male and reproductive outcomes in assisted reproduction has not been studied in depth and there is no general consensus (Thomson *et al.*, 2014).

The objective of the present study was to investigate the effect of the BMI of all parties involved on the pregnancy rates of women recipients of oocyte donation.

MATERIAL AND METHODS

This is a retrospective analysis of anonymized data from 1092 oocyte donation cycles between November 2010 and August 2013 at a large reproductive centre. This study did not require the approval of an Ethics Committee because the data were anonymous. Nevertheless, permission to conduct the study was sought and obtained from the Institutional Review Board of Clínica EUGIN.

Recipient characteristics

The indications for oocyte donation were failed IVF cycles with own oocytes, low ovarian reserve, poor oocyte

quality, genetic or chromosomal abnormalities transmissible to offspring and spontaneous or iatrogenic menopause. Women with menstrual cycles received a depot dose of GnRH agonist to suppress the pituitary. The estrogen endometrial preparation was started in the following menstrual cycle. An increasing dose of estrogens was administered orally or transdermally (from 2 to 6 mg, or from 75 to 150 mg, respectively) for a period of 15–40 days (average: 20.4; SD: 8; median: 17). This length of time was kept in all cases below 49 days, the limit above which a significant decrease in uterine receptivity has been demonstrated (Soares *et al.*, 2005).

Donor characteristics

All oocyte donors (age 18–35 years) had normally appearing ovaries at transvaginal ultrasound, adequate ovarian reserve as evidenced by an antral follicular count above 10, and displayed a correct response to ovarian stimulation, i.e. a progressive and gradual increase in follicular sizes, concordant with FSH administration. All donors were stimulated with exogenous gonadotrophins, while the pituitary suppression was based on two possible protocols: GnRH antagonists fixed from the sixth day of ovarian stimulation (most of the cycles) or GnRH agonists starting in the second phase of the preceding menstrual cycle. Regardless of the stimulation protocol, ovulation was triggered when three or more follicles ≥ 18 mm diameter were present on the ovaries. Ovulation trigger was performed with either 0.2 mg of the GnRH agonist Triptorelin (Decapeptyl Ipsen, Pharma Biotech, France) or 250 mg hCG (Ovitrelle, Merck, Germany) depending on the stimulation protocol. Oocyte collection was performed 36 hours after triggering by means of ultrasound-guided transvaginal follicular aspiration.

Partner characteristics

The inclusion criterion for this study was oocyte donation cycles with ICSI as a fertilization method. Exclusion criteria were semen coming from a sperm donor, semen obtained by testicular biopsy and semen frozen prior to treatment for a medical condition. All patients were requested to maintain 3–5 days of abstinence before providing the semen sample used for evaluation and fertilization. All sperm samples were analyzed (volume, concentration, motility) using the standard laboratory procedures of the World Health Organization (WHO, 2010).

Statistical analysis

For the statistical analysis, the following BMI categories were created (kg/m²): underweight (<20), normal weight (20–24), overweight (25–29) and obesity (≥ 30). Quantitative and categorical variables were assessed by squared-Chi test or one-way ANOVA, respectively. The association between the BMI categories (recipient, oocyte donor and partner) and the biochemical pregnancy rate was assessed by multivariate logistic regression (adjusting for recipient, donor, and partner age as well as recipient and donor BMI). The association between the donor BMI categories and the laboratory outcomes (number of COC, MII, and 2PN) was assessed by linear regression (adjusting for donor age). All analyses were performed using SPSS 20.

RESULTS

A total of 1092 cycles were included. Figure 1 shows the BMI distribution by recipient, oocyte donor, and partner.

Table 1: Laboratory outcomes. Univariate analysis (*P* One-way ANOVA)

Donor BMI	<20	20-25	25-30	≥ 30	<i>P</i>
Number of COC [median (IQR;Max-Min)]	8 (2;5-16)	8 (4;4-26)	8 (3;4-22)	3	0.50
Number of MII [median (IQR;Max-Min)]	6 (1;4-12)	6 (1;4-12)	6 (1;4-11)	6 (1;6-7)	0.88
Number of 2PN [median (IQR;Max-Min)]	5(2;2-10)	5 (2;2-10)	5 (2;2-8)	6 (4;2-7)	0.74

Table 2: Laboratory outcomes. Multivariate analysis. (Reference BMI category: 20-24)

		Effect	<i>P</i>
Number of COC	Donor BMI<20	-0.126	0.53
	Donor BMI ≥ 25	0.275	0.21
	Donor age	-0.012	0.49
Number of MII	Donor BMI<20	0.083	0.39
	Donor BMI ≥ 25	-0.010	0.92
	Donor age	0.012	0.18
Number of 2PN	Donor BMI<20	-0.020	0.86
	Donor BMI ≥ 25	0.115	0.34
	Donor age	-0.003	0.80

Table 3. Pregnancy outcomes. Univariate analysis (*P* Chi² test)

Recipient BMI	<20	20-24	25-29	≥30	<i>P</i>
βhCG-	85	318	116	54	0.67
	48.3%	52.9%	54.0%	54.0%	
βhCG+	91	283	99	46	
	51.7%	47.1%	46.0%	46.0%	
Oocyte donor BMI	<20	20-24	25-29	≥30	<i>P</i>
βhCG-	129	339	103	2	0.60
	51.4%	52.8%	53.6%	28.6%	
βhCG+	122	303	89	5	
	48.6%	47.2%	46.4%	71.4%	
Partner BMI	<20	20-24	25-29	≥30	<i>P</i>
βhCG-	9	266	242	56	0.12
	32.1%	51.6%	54.8%	52.8%	
βhCG+	19	250	200	50	
	67.9%	48.4%	45.2%	47.2%	

Table 4. Pregnancy outcomes. Multivariate analysis (Reference BMI category: 20-24).

	OR	95% CI OR		<i>P</i>
		Lower	Upper	
Recipient BMI<20	1.18	0.84	1.66	0.80
Recipient BMI 25-39	0.98	0.72	1.35	0.34
Recipient BMI ≥30	1.01	0.66	1.56	0.92
Recipient age	0.98	0.96	1.01	0.96
Donor BMI<20	1.03	0.77	1.38	0.86
Donor BMI 25-39	0.98	0.71	1.36	0.92
Donor BMI ≥30	2.64	0.50	14.02	0.25
Donor age	1.00	0.97	1.02	0.74
Partner BMI <20	2.20	0.97	4.98	0.06
Partner BMI 25-39	0.90	0.70	1.17	0.45
Partner BMI ≥30	0.97	0.63	1.48	0.87
Partner age	1.00	0.98	1.02	0.06

Laboratory outcomes

Laboratory outcomes, i.e. number of cumulus-oocyte complexes, mature (MII) and fertilized (2PN) oocytes recovered from the follicular puncture, do not differ among the different categories of oocyte donor BMI, as shown by univariate analysis (Table 1). After adjusting for donor age, and taking normal BMI (20-24) as reference, the association between donor BMI and laboratory outcomes remains no statistically significant (Table 2).

Pregnancy outcomes

Pregnancy rates (defined as a positive βHCG blood test taken 14 days after embryo transfer), do not differ among categories of recipient, oocyte donor, or partner BMI at univariate analysis (Table 3). In the same way, the multivariate analysis (Table 4) shows that, after adjusting for

recipient and donor age, and taking normal BMI (20-24) as reference, there is no effect of recipient, donor or partner BMI on pregnancy outcomes.

DISCUSSION**BMI and pregnancy**

The impact of BMI on fertility has been studied extensively, focusing mostly on the effect of high BMI (obesity) on fertilization rate, implantation, and pregnancy loss (Jungheim *et al.*, 2013, Luke *et al.*, 2011, Schliep *et al.*, 2014, Sobaleva & El-Toukhy, 2011, Styne-Gross *et al.*, 2005). While some authors describe lower oocyte and embryo quality in obese patients (Bu *et al.*, 2013, Valckx *et al.*, 2012), others did not find this association (Wang *et al.*, 2000). A report indicates the presence of fewer mature oocytes after controlled ovarian stimula-

Figure 1. BMI distribution for each of the parties involved in an oocyte donation cycle.

A). Recipient

B). Oocyte donor

C). Partner

tion in obese patients, lower fertilization rate, and lower number of transferred embryos (Bellver *et al.*, 2010). A study evaluating 6500 in vitro fertilization cycles with patient own oocytes found that obese women had significantly higher gonadotropin consumption during controlled ovarian stimulation (Bellver *et al.*, 2010). Moreover, the researchers found lower implantation, pregnancy, and live birth rates as the BMI increased. However, oocyte quality, evaluated by embryo quality on day 2 and 3 of development, was not affected by the patient BMI in this study. Taken together, these results suggest that obesity can either alter embryo quality by mechanisms which are not reflected in embryo morphology, or that the effect is mostly exerted on the endometrium.

The donor-recipient model allows for the uncoupling of the two factors that have been mostly suspected of being altered by high BMI: oocyte quality and endometrial receptivity.

BMI in donation cycles

We did not find any relationship between BMI of recipient and the partner and pregnancy rate, and this is in agreement with what found by other researchers when analyzing the effect of body mass index (BMI) on implantation, pregnancy, and incidence of spontaneous miscarriage using the donor oocyte recipient model (Styne-Gross *et al.*, 2005, Wittemer *et al.*, 2000). Similar results were found in the study by Schliep *et al.* (2014), where they reported no significant associations between male, female, or couple BMI and fertilization rate, embryo score, clinical pregnancy, or live birth after adjustment for relevant confounders. A study evaluating 536 oocyte recipients (Styne-Gross *et al.*, 2005) did not found significant differences in implantation rate, ongoing pregnancy or abortion rate across recipient BMI categories. These results confirmed what found in a previous, smaller study (Bellver *et al.*, 2003). A subsequent larger study by the same group (Bellver *et al.*, 2007) comprising 2656 recipient, 122 of which obese, found a tendency to a lower implantation rate and pregnancy rate, as well as higher rates of ectopic pregnancy and abortion as the recipient BMI increased. Moreover, there was a significantly lower ongoing pregnancy rate for started cycle in obese women compared to those of normal BMI. Finally, Dessolle *et al.* (2009) evaluated 450 donation cycles, and found a significant drop in pregnancy rate in recipient with BMI over 30 kg/m², regardless of age.

In our study, we found that when the embryo is derived from a donor of BMI <30, i.e. not obese, there is no effect of the recipient BMI on pregnancy rates, which indicates that the worse reproductive outcomes in obese patients using their own oocytes should be due to oocyte quality rather than an effect on the endometrium.

BMI in the male partner

The relationship between semen characteristics and male BMI is unclear; morphological sperm defects have been related to high BMI (Hammoud *et al.*, 2008) while more recent studies did not find a relationship between male BMI and seminal parameters and sperm binding ability, in a population of male with low or moderate idiopathic infertility (Sermondade *et al.*, 2013, Thomsen *et al.*, 2014), as well as pregnancy rates (Isa *et al.*, 2014, Thomsen *et al.*, 2014). Interestingly, pregnancy rates of obese patients increased after ICSI but not after conventional IVF (Merhi *et al.*, 2013). However, a study by Colaci *et al.* (2012) reports that male obesity might have a negative effect on pregnancy rates after ICSI as well. The cycles analyzed in this study were all carried out with ICSI as fertilization technique, and in agreement with the study by

Merhi we did not find an effect of male BMI on pregnancy rates, strengthening the hypothesis that the worse reported outcome in conventional IVF might be due to functional alteration in the sperm such as motility or the ability to penetrate the zona pellucida.

CONCLUSION

In conclusion, we found that a high BMI in oocyte recipient and her male partner do not impact pregnancy rates when the oocytes come from young women with normal BMI, and when the fertilization technique is ICSI. We suggest that both these factors might ease some of the effect of high BMI, such as low oocyte quality and altered sperm function, thus allowing for high pregnancy rates across the BMI spectrum. As pregnancy complications are more frequent in obese patients, counseling should be extended to high BMI women regardless of their chance to attain a pregnancy.

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CONFLICT OF INTERESTS

No conflict of interest have been declared.

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