The influence of body mass index on pregnancy outcome following single-embryo transfer

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Abstract

Purpose The association between obesity and reproductive outcome is controversial. The aim of this study is to evaluate the effects of obesity on clinical pregnancy rates following transfer of a single fresh embryo.

Methods A retrospective cohort study was conducted at a single tertiary medical center, including all first, fresh, single-embryo transfers using non-donor oocytes, during 2008–2013. We compared clinical pregnancy rate and pregnancy outcomes of singleton live births resulting from the transfer of a single fresh embryo in normal weight, overweight, and obese women, defined as body mass index (BMI) < 25 kg/m², ≥ 25 BMI < 30 kg/m², and BMI ≥ 30 kg/m², respectively.

Results Overall, 1345 cases met the inclusion criteria with 864 single-embryo transfers (SETs) in normal weight women, 292 in overweight women, and 189 SETs in obese women, resulting in 538 clinical pregnancies and 354 singleton births. The clinical pregnancy rate per transfer was similar among the three groups (41.3, 37.6, 37.5%, respectively, $p = 0.416$). Similarly, there were no significant differences in live births or ongoing pregnancies. On multivariate logistic regression analysis, BMI did not impact the likelihood for clinical pregnancy (OR 0.98, 95% CI 0.96–1.008, $p = 0.216$).

Conclusions Our study demonstrated that obesity has no detrimental effect on the clinical pregnancy rate resulting from the transfer of a single fresh embryo.

Keywords Single-embryo transfer · In vitro fertilization · Obesity · Pregnancy complications

Introduction

Obesity is a universal health problem. In some countries, over 50% of reproductive aged women are either overweight (body mass index (BMI) 25–29.9 kg/m²) or obese (BMI ≥ 30 kg/m²) [1–3]. Compared to normal weight women (BMI 18.5–24.9 kg/m²), obese women have a threefold risk for infertility [4, 5]. In addition, obesity is associated with increased risk for poor obstetrical outcome, including miscarriage, preeclampsia, gestational diabetes, induction of labor, operative delivery, fetal macrosomia, and congenital anomalies [6–8].

The effect of BMI on the outcome of in vitro fertilization (IVF) remains unclear. Although some authors have reported no negative effects of obesity on IVF outcome [9, 10], others have directly linked overweight and obesity to an adverse outcome. This includes the need for increased dose of gonadotropins, reduced number of oocytes collected, a high cancellation rate, and reduced pregnancy and live birth rates [11, 12].

Most studies that evaluated the impact of BMI on IVF outcome included transfer of multiple embryos at various stages

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of development, including more than 1 cycle per woman, and did not adjust for potential confounders [13, 14]. Recently, the trend towards SET has been increasing in order to minimize the risk for multiple gestations. While some studies showed a significantly lower live birth rate with a single cycle of SET versus a single cycle of double embryo transfer [15], others did not find any differences in the pregnancy rate [14].

The aim of our study was to evaluate the impact of obesity on clinical pregnancy rate following single-embryo transfers (SET) in fresh IVF cycles in young women.

Materials and methods

We conducted a retrospective study at the reproductive unit of the McGill University Health Center in Montreal, Quebec, Canada, evaluating SETs performed between December 2008 and December 2013. All first, fresh, SETs using non-donor oocytes in women ≤ 40 years old were included in the study. A woman was only included once. The study was approved by the institutional research and ethics board (Study 12-283-SDR).

We retrieved the data from our continuously updated computerized database, cross-checked with the patient's medical file. A detailed telephone survey was conducted by trained personnel to obtain missing information. The change in the Quebec policy for public funding of assisted reproductive technology in August 2010 expedited SETs, where SET is the rule apart for exceptional cases. We compared cycle outcome and singleton live birth outcomes of SET in non-obese and obese women. The BMI was measured for each woman prior to hormonal stimulation and calculated as weight in kilograms divided by the square of height in meters (kg/m^2).

The primary outcome was clinical pregnancy rate, defined as intrauterine gestational sac with embryonic pole with fetal heartbeat on transvaginal ultrasound. The secondary outcomes included live birth rates and neonatal and maternal outcomes in cases with live birth. Neonatal outcome included birth weight, small for gestational age (SGA), and large for gestational age (LGA), defined as birth weight < 10 th percentile and > 90 th percentile for gestational age, respectively, according to the Canadian live born infant birth weight curves [16], congenital malformations, admission to the neonatal intensive care unit, and respiratory and gastrointestinal complications.

Maternal adverse outcome included preeclampsia [International Classification of Diseases (ICD) 10 codes O.14, O.15], placenta previa (ICD 10 code O.44), placental abruption (ICD 10 code O.45), chorioamnionitis (according to placental pathology reports), and gestational diabetes (ICD code O.24.4).

Other variables collected were maternal and paternal age, gravidity and parity, and type of protocol used (microdose flare, fixed antagonist, a mid-luteal long agonist protocol, or

a natural-cycle IVF with no gonadotropin stimulation). Etiology of infertility was divided into six major categories: unexplained infertility, tubal factor infertility, endometriosis (laparoscopy or ultrasound findings of ovarian endometrioma were required for diagnosis), male infertility, polycystic ovarian syndrome, or poor ovarian response or reserve [17].

Embryo transfer day was determined based on the quantity and quality of embryos. All embryos were cultured in cleavage medium (Cook Medical, Sydney, Australia) until day 3, then transferred to blastocyst medium (Cook Medical, Sydney, Australia) for further culture to the blastocyst stage, when appropriate. All embryo cultures were performed under low-oxygen conditions (5% oxygen, 6% carbon dioxide, 89% nitrogen). Cleavage embryos were graded as good quality if they had four cells on day 2 or seven to eight cells on day 3, $< 20\%$ fragmentation, and exhibited no apparent morphological abnormalities [18]. Cleavage embryos were graded as good quality if they had four cells on day 2 or seven to eight cells on day 3, $< 20\%$ fragmentation, and exhibited no apparent morphological abnormalities [18]. Blastocysts were graded according to the level of expansion, the presence and the quality of inner cell mass, and quality of trophoctoderm. Top quality blastocysts were defined as ≥ 3 blastocysts with inner cell mass loosely grouped with several cells and few trophoctoderm cells forming a loose epithelium based on the Gardner and Schoolcraft scoring system [19]. The patients' age and the number and quality of cleavage embryos determined the allocation to blastocyst versus cleavage transfer. Ultrasound-guided embryo transfer was performed, and a serum beta human chorionic gonadotropin pregnancy (beta-hCG) test was performed 16 days after collection.

Statistical analysis was performed using SPSS version 21. Patient characteristics and clinical outcomes were tabulated into three BMI categories: normal weight, overweight, and obese women, defined as body mass index (BMI) $< 25 \text{ kg}/\text{m}^2$, $\geq 25 \text{ BMI} < 30 \text{ kg}/\text{m}^2$, and $\text{BMI} \geq 30 \text{ kg}/\text{m}^2$, respectively. Univariate analysis included chi-squared test for categorical variables and analysis of variants for continuous variables. To evaluate the effect of obesity on the clinical pregnancy rate, a multivariate logistic regression analysis was performed controlling for BMI and other confounders known to affect pregnancy rates (maternal age, smoking, cause of infertility, number of retrieved oocytes, and day of embryo transfer).

Results

The study included a total of 1345 first fresh IVF-SET cycles using non-donor oocytes. Of those, 864 patients were of normal weight, 292 overweight, and 189 were obese women resulting in 538 clinical pregnancies and 354 singleton births. We excluded seven women with monozygotic twins. In addition, 94 patients whose pregnancy outcome could not be

traced beyond the first trimester were considered ongoing pregnancies, and as a result, we could not calculate live birth rate per transfer.

Demographics and treatment characteristics of the three study groups are presented in Table 1. Polycystic ovary syndrome (PCOS) was more common in obese women than in overweight and normal weight women (16.3 vs. 6.5 and 5.6%, respectively, $p = 0.001$). Women of normal weights had a significantly shorter duration of stimulation and a lower total dose of FSH compared to overweight and obese women, with no significant difference in the number of retrieved oocytes (Table 1).

Table 2 summarizes the overall cycle outcome; no significant differences were found in the clinical pregnancy rate between normal weight, overweight, and obese women ($p = 0.416$). Table 3 summarizes the pregnancy outcomes of clinical pregnancies; there were no significant differences in live births or ongoing pregnancies among the three groups ($p = 0.706$, $p = 0.624$, respectively).

Pregnancy outcomes in cases with singleton live births are presented in Table 4. Maternal characteristics were similar among the groups. There were no significant differences in mean birth weight, gestational age, SGA, or preterm delivery among the three groups. There was a lower rate of preeclampsia in normal weight women compared with overweight and obese women ($p = 0.026$).

Table 1 Demographic and treatment parameters of the study groups

Variables	Normal weight BMI < 25 <i>N</i> = 864	Overweight ≥ 25 BMI < 30 <i>N</i> = 292	Obese BMI ≥ 30 <i>N</i> = 189	<i>p</i> value
BMI (mean)	21.5 ± 1.9	27 ± 1.3	35.3 ± 4.7	< 0.001
Age (years)	34.4 ± 4.1	34.2 ± 4.6	34.7 ± 4.2	0.528
Primary infertility	857/864 (99.2)	291/292 (99.3)	187/189 (98.9)	0.905
Causes of infertility				
PCOS (%)	23/409 (5.6)	9/138 (6.5)	14/86 (16.3)	0.094
Male (%)	156/409 (38.1)	61/138 (44.2)	36/86 (41.9)	
Unexplained (%)	131/409 (32)	41/138 (29.7)	17/86 (19.8)	
Mechanical (%)	32/409 (7.8)	16/138 (11.6)	8/86 (9.3)	
Endometriosis (%)	31/409 (7.6)	1/138 (0.7)	5/86 (5.8)	
Poor ovarian reserve (%)	25/409 (6.1)	7/138 (5.1)	5/86 (5.8)	
Anovulation (%)	11/409 (20.7)	3/138 (2.2)	1/86 (1.2)	
Smoking status (%)	32/409 (7.8)	20/138 (14.4)	10/86 (11.6)	0.056
Duration of stimulation (days)	16.4 ± 4.2	17.3 ± 5.4	17.0 ± 3.9	0.007
Total HMG used (units)	1616 ± 1418	1778 ± 1525	1722 ± 1310	0.424
Total FSH used (units)	2231 ± 1746	2603 ± 1695	2535 ± 1304	0.004
Antagonist protocol	526 (60.9)	152 (52.1)	113 (59.8)	0.185
Number of retrieved oocytes	10.4 ± 6.3	10.6 ± 6.7	10.0 ± 6.2	0.592
Assisted hatching	195 (22.6)	72 (24.7)	35 (18.5)	0.286
Embryo transfer day 5	545 (63)	178 (60.9)	111 (58.7)	0.264

Data is presented as *n* (%)

Table 2 Cycle outcome of women after single-embryo transfer

Cycle outcome	Normal weight BMI < 25 <i>N</i> = 864	Overweight ≥ 25 BMI < 30 <i>N</i> = 292	Obese BMI ≥ 30 <i>N</i> = 189	<i>p</i> value
Biochemical pregnancy	57 (6.5)	20 (6.8)	8 (4.2)	0.456
Clinical pregnancy rate	357 (41.3)	110 (37.6)	71 (37.5)	0.416
Ectopic pregnancy	3 (0.3)	0	1 (0.5)	0.526
Not pregnant	447 (51.7)	162 (55.4)	109 (57.6)	0.283

Data is presented as *n* (%)

After adjustment for potential confounders including BMI, maternal age, smoking, etiology of infertility, number of retrieved oocytes, and day of embryo transfer, obesity was not found to be an independent variable associated with lower rates of clinical pregnancies (Table 5). Day of transfer (cleavage stage vs. blastocyst stage) and maternal age were found to be independently associated with clinical pregnancies (OR 0.96, 95% CI 0.93–0.99, $p = 0.015$ and OR 0.29, 95% CI 0.22–0.38, $p < 0.001$, respectively). On stepwise, forward likelihood ratio analysis, day 3 embryo transfer (vs. day 5) was a significant negative predictor of clinical pregnancies (OR 0.38, 95% CI 0.25–0.57, $p < 0.001$).

Table 3 Pregnancy outcomes of clinical pregnancies in women after single-embryo transfer

Cycle outcome	Normal weight	Overweight	Obese	<i>p</i> value
	BMI < 25	≥ 25 BMI < 30	BMI ≥ 30	
	<i>N</i> = 357	<i>N</i> = 110	<i>N</i> = 71	
Live births ^a	231 (64.7)	73 (66.3)	50 (70.4)	0.706
Miscarriages	57 (16)	13 (11.8)	11 (15.5)	0.601
Stillbirths	3 (0.8)	2 (1.8)	1 (1.4)	0.673
Termination of pregnancies	2 (0.6)	1 (0.9)	0	0.725
Ongoing pregnancies ^b	64 (17.9)	21 (19.2)	9 (12.6)	0.624

Data is presented as *n* (%)

^a Known live births calculated clinical pregnancy

^b Ongoing pregnancy beyond the first trimester

Table 4 Pregnancy outcomes and complications in cases with live births after the transfer of a single embryo stratified by BMI groups

Pregnancy outcome	Normal weight	Overweight	Obese	<i>p</i> value
	BMI < 25	≥ 25 BMI < 30	BMI ≥ 30	
	<i>N</i> = 231	<i>N</i> = 73	<i>N</i> = 50	
Maternal age	33.2 ± 3.6	32.7 ± 4.2	34.1 ± 4.0	0.131
Paternal age	36.5 ± 5.8	37.1 ± 6.3	37.2 ± 5.6	0.693
BMI	21.3 ± 2.0	27.0 ± 1.4	34.3 ± 3.9	< 0.0001
Smoking	14/221	11/71	5/49	0.056
Primary infertility	224 (96.9)	71 (97.2)	48 (96)	0.919
ICSI	167 (72.2)	59 (80.8)	43 (86)	0.153
Embryo transfer day 5 (%)	185 (80)	61 (83.5)	42 (84)	0.701
Etiology of infertility	<i>n</i> = 223	<i>n</i> = 73	<i>n</i> = 48	0.276
PCOS (%)	17 (7.6)	7 (8.2)	8 (16.7)	
Male infertility (%)	95 (42.6)	35 (47.9)	21 (43.8)	
Tubal factor infertility (%)	20 (9)	10 (13.7)	6 (12.5)	
Endometriosis (%)	14 (6.3)	0	2 (4.1)	
Poor ovarian reserve (%)	12 (5.4)	4 (5.5)	3 (6.3)	
Unexplained (%)	65 (29.1)	17 (23.3)	8 (16)	
Gestational age at delivery (weeks)	37.9 ± 2.8	38.2 ± 2.6	37.9 ± 2.1	0.782
Birth weight (g)	3117 ± 682	3297 ± 682	3202 ± 542	0.135
Male gender	112 (50.7)	30 (42.9)	21 (47.7)	0.517
C/S	88 (38.1)	22 (30.1)	21/50 (42)	0.642
SGA	22/222 (9.9)	7/70 (10)	3/44 (6.8)	0.559
PTD	36/222 (16.2)	9/70 (12.9)	6/44 (13.6)	0.497
Preeclampsia	3/222 (1.3)	5/70 (7.1)	3/44 (6.8)	0.026
Placental abruption	3 (1.3)	1 (1.4)	0	0.716
Gestational diabetes	3 (1.3)	0	2 (4.0)	0.176
LGA	11/222 (5)	7/70 (10)	2/44 (4.5)	0.293
Chorioamnionitis	3 (1.3)	0	2 (4.0)	0.176
Genetic disorder/malformation	3/222 (1.4)	0	0	0.438
Maternal complications	19 (8.2)	9 (12.3)	7 (14)	0.341
Neonatal complications	74 (32)	23 (31.5)	11 (22)	0.369
Any maternal or neonatal complication	84/221 (38)	25/70 (35.7)	15/44 (34.1)	0.858

For all variables, categorical data is presented as *n* (%) and continuous variables are presented as mean ± SD

BMI body mass index (at the start of infertility treatment), *ICSI* intracytoplasmic sperm injection, *PCOS* polycystic ovarian syndrome, *C/S* cesarean section, *SGA* small for gestational age (< 10%), *PTD* preterm delivery (< 37 weeks), *LGA* large for gestational age (> 90%)

Table 5 Multivariate logistic regression analysis for clinical pregnancies as a dependent variable

Variable	OR (95% CI)	P value
BMI	0.98 (0.96–1.01)	0.22
Age	0.96 (0.93–0.99)	0.01
Number of retrieved oocytes	1.014 (0.99–1.03)	0.17
Smoking	0.86 (0.76–1.35)	0.13
Day 3 vs. day 5 transfer	0.29 (0.22–0.38)	< 0.001

BMI body mass index (at the start of infertility treatment)

Discussion

In this study, we evaluated the effect of obesity on clinical pregnancy rate following transfer of a single fresh embryo. Our key findings are as follows: (1) Obesity did not affect the clinical pregnancy rate, number of live births, or ongoing pregnancies following the transfer of a single fresh embryo; (2) pregnancy outcome and obstetric complications were similar among normal weight, overweight, and obese women, apart for a lower rate of preeclampsia in normal weight women; and (3) younger maternal age and day 5 embryo transfer were the only significant factors associated with higher rates of clinical pregnancies.

Previous studies that addressed the correlation between obesity and reproductive outcomes have been controversial. Some studies reported decreased implantation and pregnancy rates, increased miscarriage rates, and poor pregnancy outcomes in obese women [7, 11, 13]. Those unfavorable outcomes have been attributed to multiple factors including adverse effects of obesity on oocyte and embryo quality, poor ovarian response necessitating increased gonadotropin injections, and lower numbers of collected oocytes [20, 21], as well as impaired endometrium [22]. However, other studies using the donor-oocyte recipient model have not found any association between increased BMI and reduced pregnancy rate or increased miscarriage rate [23].

Systematic reviews have concluded that obese women have a lower likelihood of pregnancy and live birth with an increased risk of miscarriage. However, there is insufficient evidence whether this affects cycle cancelation and oocyte recovery rates [14]. Cases included in those reviews had considerable clinical and methodological heterogeneity in the transfer of multiple embryos and transfer of fresh or frozen embryos, with an inconsistent adjustment for risk factors. Studies on single-embryo transfers showed that obesity was negatively associated with the occurrence of live birth [24]. A retrospective study found that morbid obesity significantly increased miscarriage rates and reduced live birth rates [25]. However, in contrast to our research, their study included only blastocyst transfer and fresh and frozen embryos.

The results of our study showed that the clinical pregnancy rates resulting from transfer of fresh SET were comparable in normal weight, overweight, and obese women and that increased BMI was not associated with increased adverse obstetric and perinatal outcome. These findings remained negative after adjusting for potential confounders. Our results are consistent with a previous study performed based on the Latin American Registry that found no association between overweight and obesity and the likelihood of pregnancy, live birth, or miscarriage in women undergoing assisted reproductive technology [26]. Similarly, Insogna et al. [27] reported no impact of BMI on implantation rates or clinical pregnancy rates in frozen-thawed blastocyst transfer. Nonetheless, the lack of statistical differences in our study could also be due to the possibility of type I statistical error.

Previous studies that examined the impact of obesity on obstetric outcome have demonstrated increased risk for adverse outcome including preeclampsia, gestational diabetes, operative delivery, and more [6, 7]. In our study, we did not find any differences in maternal and neonatal outcome between obese and overweight women, though normal weight women had a lower rate of preeclampsia in comparison.

The only independent factors found to be associated with increased clinical pregnancy rate were maternal age and day of embryo transfer. While this was not the primary outcome of our study, it is an important finding. As previous studies have shown, blastocyst embryo transfer is associated with increased implantation and live birth rate compared to cleavage-stage embryo transfer [28, 29]. In our study, this finding remained significant even after adjusting for potential confounders including BMI.

The main limitation of our study lies in its retrospective design and the inherent risk for undetected selection bias. Furthermore, we did not have data regarding other potential confounders such as ethnicity, prior obstetrical complications, and family history. We used Canadian population growth curves to assess the rate of SGA (< 10% percentile) to mitigate the lack of ethnicity data. Over 80% of our populations were nulliparous women, thereby minimizing the potential effect of previous pregnancy complications on pregnancy outcome. Moreover, while pregnancy outcome and obstetric complications were similar among normal weight, overweight, and obese women, the groups might be too small to draw definite conclusions and large-scale studies are needed.

The strengths of our study are these were singletons as a result of the transfer of a single embryo performed in a single-center study with a SET policy for all patients, thus minimizing the bias of good-prognosis patient selection and without the possibility of a deleterious effect of the vanishing twin phenomenon on the pregnancy outcome. Furthermore, the same culture media was used, eliminating the possible different effects of various culture media on the subsequent neonatal outcome [30]. Finally, we included only fresh embryos to

minimize any potential effects attributed to freeze-thawed embryos [31]. Our findings can be used to reassure physicians in our field that the transfer of a single fresh embryo in obese women should result in similar implantation and pregnancy rates compared to transfers in normal weight and overweight women. Obesity does not appear to be associated with increased adverse obstetric and perinatal outcomes in this subset population.

In conclusion, our study demonstrates that obesity does not impact the clinical pregnancy rates resulting from the transfer of a single fresh embryo.

Compliance with ethical standards

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

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