

Effect of Body Mass Index on In Vitro Maturation Treatment Outcomes in Women without Polycystic Ovarian Syndrome

Baris Ata^{1,2*}, Ayse Seyhan¹, Jana Al-Shalaty¹, Alicia Marzal Escriva¹, Weon Young Son¹ and Seang Lin Tan^{1,3}

¹The McGill University Health Centre Reproductive Centre, Division of Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology, McGill University, Montreal, Quebec, Canada

²Assisted Reproduction Unit of the Uludag University School of Medicine, Bursa, Turkey

³Montreal Reproductive Centre, Montreal, Quebec, Canada

Abstract

Purpose: Previous studies have suggested that obesity can affect the oocyte yield, embryo quality and pregnancy rates following IVF. *In vitro* maturation differs from IVF in several ways including lack of controlled ovarian stimulation, oocyte retrieval when majority are expected to be still immature, and possibly different endometrial environment due to short secretory phase and the lack of exposure to supraphysiologic estrogen levels. Therefore female obesity can affect IVM and IVF cycles differentially. This study aims to assess the effect of female obesity on IVM outcomes in women without polycystic ovarian syndrome.

Methods: Retrospective chart review of 125 women who underwent an IVM cycle during a 5 year period. Women were divided to four categories based on Body Mass Index (BMI) according to the World Health Organization classification. Procedural and clinical outcomes were compared across different BMI categories. Independent effect of BMI on the odds of achieving a live birth was assessed using a multivariate logistic regression model.

Results: The numbers of cumulus corona complexes, *in vivo* matured and immature oocytes collected, metaphase two oocytes available for fertilization, good quality embryos available for transfer and embryos transferred were not statistically significantly different across BMI categories. Likewise, *in vitro* maturation rate of immature oocytes, fertilization rate, embryo implantation, clinical pregnancy and live birth rates were similar across the groups. BMI category did not have an independent effect after adjusting for possible confounders in the regression model.

Conclusions: BMI does not seem to affect IVM outcomes.

Keywords: Obesity; Body Mass Index (BMI); Assisted reproduction; *In vitro* maturation; *In vitro* fertilization

Introduction

Female fertility is affected by body weight; both underweight and overweight women are more likely to suffer from infertility than women with normal body weight [1,2]. Beyond its impact on ovulatory function and fecundity, obesity has been linked to lower success rates following *In Vitro* Fertilization (IVF) treatment [3-5].

However, studies investigating the effect of obesity on IVF outcome have yielded contradictory results [3,4,6,7]. Variations in the results can be attributed to different study populations, random effects due to small sample sizes in some studies, different cut-off values of Body Mass Index (BMI) used to categorize participants, varying definitions of relevant outcome measures including pregnancy and miscarriage, and the lack of adjustment for potential confounders such as female age, the presence of Polycystic Ovarian Syndrome (PCOS), number of prior failed cycles in some studies [8,9]. While some studies suggested obesity impacted IVF outcomes through its effect on ovarian response to gonadotropin stimulation [3], a recently published large scale study suggested obesity impacted embryo implantation and live birth rates through its effects on the uterine environment rather than on oocyte yield or embryo quality [4].

In Vitro Maturation (IVM) treatment involves collection of oocytes relatively earlier in the follicular phase when the majority is expected to be still immature and therefore does not require Controlled Ovarian Hyperstimulation (COS) [10,11]. Different follicular dynamics, the shorter duration of proliferative phase and the lack of exposure of endometrium to supraphysiological estrogen levels can lead to a different endometrial environment in IVM cycles than in conventional COS - IVF cycles. Therefore female obesity can be expected to

differentially affect IVM outcome than IVF outcome. A former study investigating effect of BMI on IVM outcome in women with Polycystic Ovarian Syndrome (PCOS) reported similar outcomes in different BMI categories [12]. Although IVM is most commonly performed for treatment of infertility associated with PCOS, it is also used for treatment of infertility due to other aetiologies. IVM is also used as a fertility preservation method for women with estrogen sensitive cancers who will receive gonadotoxic treatment. Moreover metabolic profiles and estrogenisation status of women with and without PCOS can differ, modifying an affect of BMI on IVM outcomes. Present study aims to assess the affect of BMI on outcome of IVM cycles undertaken for other indications than PCOS in order to provide further insight.

Materials and Methods

McGill University Health Centre – Reproductive centre records were retrospectively screened to identify IVM cycles conducted between 1st June 2005 and 1st June 2010. Royal Victoria Hospital Research Ethics Committee approved chart review. Only IVM cycles in which the

***Corresponding author:** Baris Ata, The McGill University Health Centre Reproductive Centre, Division of Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology, McGill University, Montreal, Quebec, Canada, E-mail: barisata@hotmail.com

Received April 25, 2013; Accepted June 23, 2013; Published June 25, 2013

Citation: Ata B, Seyhan A, Al-Shalaty J, Marzal Escriva A, Son WY, et al. (2013) Effect of Body Mass Index on *In vitro* Maturation Treatment Outcomes in Women without Polycystic Ovarian Syndrome. J IVF Reprod Med Genet 1: 104. doi:10.4172/2375-4508.1000104

Copyright: © 2013 Ata B, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

patient's BMI was recorded before starting the treatment and complete data available for variables analyzed were included in this study. BMI was calculated as the ratio of body weight (in kilograms) to height squared (in meters). Women were divided into four categories based on BMI: <18.5 kg/m², 18.5 – 24.9 kg/m², 25 – 29.9 kg/m², and ≥ 30 kg/m² according to the World Health Organization international classification for adults [13]. If a woman underwent more than one IVM cycle during the study period only the chronologically first cycle was included in the present study. IVM cycles conducted for the treatment of infertility associated with PCOS as well as with preimplantation genetic diagnosis were excluded.

IVM Protocol

The clinical and embryology laboratory IVM protocols exercised in our unit are described in elsewhere [10,11]. Briefly all women underwent a transvaginal ultrasound scan on the 2nd or 3rd day of a spontaneous or progestin induced menstrual bleeding to exclude ovarian cysts and endometrial pathology. A second scan was done when the leading follicle was anticipated to be 10 – 12 mm size. In case of arrested follicular growth some women were given 150 IU human menopausal gonadotropin injections for 3 days after the second scan. These women were excluded from the present study. When the leading follicle reached 10 – 12 mm 10,000 IU HCG i.m. was given and oocyte retrieval was scheduled 36 – 38 hours later.

Outcome Measures

The number of *in vivo* matured oocytes refers to oocytes that were at the metaphase II (MII) stage on the day of retrieval procedure. The number of immature oocytes refers to oocytes at the germinal vesicle and metaphase one stages on day of retrieval. *In vitro* maturation rate is calculated as the proportion of immature oocytes that reached MII stage following *in vitro* culture. Total number of MII oocytes includes both *in vivo* and *in vitro* matured oocytes which were available for fertilization. The denominator for two pronuclear (2PN) fertilization rates is the total number of MII oocytes injected with sperm. Embryo quality was determined by number and symmetry of blastomeres and extent of fragmentation [14]. Clinical pregnancy was defined as the presence of fetal heart beat during a transvaginal ultrasound exam at 6 – 7 weeks of gestation. Implantation rate is calculated as the number of fetuses with a heart beat divided by the number of embryos transferred per patient. Live birth is defined as the delivery of at least one living fetus. Other than clinical pregnancy and live birth rates all variables including implantation rate are calculated per patient and treated as continuous variables.

Women who underwent IVM for the purpose of oocyte vitrification were excluded.

Statistics

Distributions of continuous variables were assessed with one sample Kolmogorov-Smirnoff test. One way analysis of variance (ANOVA) and independent samples Kruskal Wallis tests were used to compare continuous variables with or without normal distribution, respectively. Categorical variables were compared using chi-square test with or without Yates' correction where appropriate. Statistical significance was set at an alpha error rate of 0.05. A multivariate logistic regression analysis was done in order to assess the independent effect of BMI on the odds of achieving a live birth after adjusting for possible confounders. Live birth was included in the model as the dependent variable whereas female age, number of prior ART cycles, and BMI category (dummy variable, with normal BMI category being the referent) were included as the independent variables. Forward conditional analysis using the Wald method was done, i.e. only the variables which modified the effect of BMI category on the odds ratio of live birth by ≥ 10% were stepwise included in the model. All statistical analyses were done using PASW Statistics 18 (IBM, U.S.).

Results

One hundred twenty five women with complete data were included in the study. Forty six (36.8%) women underwent immature oocyte collection for fertility preservation and depending on the availability of a male partner or patient preference had their oocytes or embryos cryopreserved.

Comparisons of total number of oocytes collected, *in vivo* matured oocytes collected, immature oocytes collected, *in vitro* maturation rate for immature oocytes, and total number of metaphase 2 oocytes included all 125 women. Analyses of fertilization rate, number of cleaving embryos, number of good quality embryos excluded women who had their oocytes cryopreserved before fertilization. Analyses of number of transferred embryos excluded women who had their oocytes or embryos cryopreserved as well as women who had no embryos available for transfer due to other reasons, i.e. lack of MII oocytes, 2PN fertilization or cleaving embryos.

Demographic characteristics of the study groups are presented in Table 1. Mean female age was 33.2 years, and this was similar across different categories of BMI (One way ANOVA, p=0.49). Indications of treatment seemed to differ across the groups with more women with decreased ovarian reserve being present in the normal BMI category.

There were no statistically significant differences in the total number of oocytes retrieved, number of *in vivo* matured oocytes, number of immature oocytes, *in vitro* maturation rate of immature oocytes, total number of MII oocytes available for fertilization, 2 PN fertilization rate, number of cleaving embryos, number of good quality embryos between

| | <18.5 kg/m ² (n = 8) | 18.5 – 24.9 kg/m ² (n = 87) | 25 – 29.9 kg/m ² (n = 16) | ≥ 30 kg/m ² (n = 14) | Overall (n = 125) |
|---------------------------|------------------------------------|---|---|------------------------------------|----------------------|
| Indication (%) | | | | | |
| Male factor | 2 (25) | 16 (18.4) | 2 (12.5) | 3 (21.4) | 23 (18.4) |
| Unexplained infertility | 1 (12.5) | 17 (19.5) | 1 (6.2) | 2 (14.3) | 21 (16.8) |
| Tubal factor | 0 (0) | 13 (14.9) | 1 (6.2) | 3 (21.4) | 17 (13.6) |
| Decreased ovarian reserve | 1 (12.5) | 6 (6.9) | 2 (12.5) | 2 (14.3) | 11 (8.8) |
| Endometriosis | 1 (12.5) | 5 (5.7) | 1 (6.2) | 0 (0) | 7 (5.6) |
| Fertility preservation | 3 (37.5) | 30 (34.5) | 9 (56.2) | 4 (28.6) | 46 (36.8) |
| Female age (SD) | 30.9 (4.5) | 33.6 (4.9) | 33.3 (6.3) | 32.3 (6.5) | 33.2 (5.3)* |
| Mean BMI (SD) | 17.3 (0.9) | 21.4 (1.9) | 27.4 (1.6) | 33.7 (4.1) | 23.3 (4.9) |

* p = 0.49

Table 1: Baseline characteristics.

| | <18.5 kg/m ² | 18.5 – 24.9 kg/m ² | 25 – 29.9 kg/m ² | ≥ 30 kg/m ² | p value |
|---|-------------------------|-------------------------------|-----------------------------|------------------------|---------|
| Total oocyte collected | 8.5 (5.5 -12.3) | 8.5 (5.8 – 16) | 7.5 (2 – 14) | 6.5 (3.5 – 17) | 0.64 |
| In vivo matured oocyte | 0.5 (0 – 1.75) | 1 (0 – 2) | 1 (0 -3) | 0.5 (0 – 1) | 0.15 |
| Immature oocyte | 8 (5.3 – 9) | 7 (4 – 14) | 7.5 (1.3 – 10) | 6 (3.5 – 14) | 0.79 |
| In vitro maturation rate | 69.1% (48.3 – 81.9) | 57.1% (37.5 – 71.4) | 66.7% (50 – 100) | 58.3 (44.7 – 78.8) | 0.34 |
| Total mature oocyte available for fertilization or cryopreservation | 5.5 (3.3 – 10) | 5 (3 – 11) | 5.5 (2 – 9) | 4 (1.8 – 10.5) | 0.73 |

Table 2: Oocyte yield and maturation.

| | <18.5 kg/m ² | 18.5 – 24.9 kg/m ² | 25 – 29.9 kg/m ² | ≥ 30 kg/m ² | p |
|---|-------------------------|-------------------------------|-----------------------------|------------------------|------|
| Fertilization rate ^a | 66.7% (54.8 – 80.8) | 77.8% (63.6 – 100) | 75.9 (65 – 100) | 81.5 (46.7 – 100) | 0.70 |
| Good quality embryos ^a | 2 (0.5 – 8.5) | 2 (1 – 3) | 2 (1 – 2.75) | 1 (0.5 – 3) | 0.86 |
| Embryos transferred ^b | 3 (2 – 4) | 3 (2 - 4) | 2 (1 – 4) | 2 (1 – 4) | 0.52 |
| Implantation rate ^b (25 th – 75 th percentile) | 5% (0 – 12.5) | 10.8% (0 – 29.2) | 0 | 15.6% (0 – 37.5) | 0.46 |
| Clinical pregnancy rate ^b | 20% (1/5) | 27% (14/52) | 0 (0/7) | 22% (2/9) | N/A |
| Live birth rate ^b | 20% (1/5) | 17.3% (9/52) | 0 (0/7) | 22% (2/9) | N/A |

^aExcluding women who had oocyte cryopreservation; ^bExcluding women who had oocyte or embryo cryopreservation without an embryo transfer

Table 3: Embryology and clinical outcome.

different BMI categories. Table 2 shows oocyte yield and maturation status across the categories of BMI. Number of embryos transferred, embryo implantation rate, clinical pregnancy and live birth rates were similar across different categories of BMI (Table 3).

After adjusting for the effects of female age and number of prior failed ART cycles, which are known to affect the chance of a live birth, women with abnormal BMI tended to have lower odds of achieving a live birth (OR = 0.685, 95% confidence interval: 0.179 – 2.676) but this was short of statistical significance (p = 0.58).

Discussion

The results of the present study demonstrate that neither laboratory nor clinical outcomes of IVM treatment cycles are affected by BMI alone, after adjusting for other factors. To the best of our knowledge this is the first study evaluating the independent effect of BMI on IVM outcomes in women without PCOS. Rigorous design with inclusion of 125 independent IVM cycles conducted in 125 women enabled reliable statistical analysis without introducing multiplicity into the data. WHO defined BMI classification was used rather than arbitrary cut – off values used in some of the previous IVF studies. This should make it possible to reliably compare and pool our data with future studies on the same issue.

Potential limitations of the present study are those common to retrospective studies. In order to prevent selection bias the investigators who collected BMI data from patient charts were blinded for laboratory data and pregnancy status at that stage. It is possible that obese or underweight women may have been reluctant to provide information on their weight or refuse being weighed and measured. Therefore some of such women treated in our center may have not contributed to the data. However, the sample with BMI info covers 77.8% of the 474 women who underwent 596 IVM cycles during the study period, which can be considered representative. Moreover the incidence of obesity in the study sample (11.2%) is very close to national average for similar age group (15). None of the outcome measures, with the exception of embryo quality, involve subjective assessment and hence ascertainment bias is unlikely.

While some studies on IVF reported less oocytes being collected from women with higher BMI [7,8,15-18] Perhaps the response to exogenous gonadotropins administered during a stimulated cycle

varies by patients' BMI and this can affect the oocyte yield. In our study the number of oocytes collected in an unstimulated IVM cycle was not affected by the patient's BMI.

Wittemer et al. reported oocyte quality, as assessed by proportion of metaphase I and metaphase II oocytes to total number of oocytes (including oocytes at the germinal vesicle stage, postmature oocytes and oocytes with fractured zona pellucida), was decreased in over- and underweight women in IVF cycles [19]. Our findings do not suggest that oocytes' potential for nuclear maturation is compromised by abnormal BMI. In the present study *in vitro* maturation rate of immature oocytes collected seems unaffected by BMI. Two large studies reporting fertilization rates in IVF cycles have yielded contradictory results [4,7]. This can be perhaps attributed to ethnic differences between study cohorts. Our findings do not suggest a difference in fertilization rates and numbers of cleaving embryos across BMI categories. The numbers of good quality embryos seem to be similar as well. Based on these observations laboratory parameters seem to be unaffected by BMI in IVM cycles.

Neither the clinical pregnancy nor live birth rates were statistically significantly different across BMI categories in our analyses. Although women with normal BMI had the higher absolute clinical pregnancy rates than women in other BMI categories, an unexpectedly high pregnancy loss rate (5/14, 35%) in the normal BMI category coupled with the absence of pregnancy losses in other categories led to similar live birth rates across BMI categories. The small numbers of pregnancies in each category prevent further comment and these observations can be due to chance alone. The observed differences can be regarded clinically relevant and can reach significance, if maintained, in a larger sample. Therefore a negative effect of abnormal BMI on clinical outcome cannot be excluded. Despite the differences between IVM and IVF cycles, our results should also be considered in the context of previous studies investigating effect of BMI on IVF outcomes, as both treatments also share common steps to successful implantation and delivery [3-7,20,21].

In conclusion, based on our data BMI seems to lack an effect on the laboratory and clinical outcome measures of IVM cycles. Nevertheless, abnormal pre-pregnancy BMI is a well-recognized risk factor for pregnancy complications such as gestational diabetes and pregnancy induced hypertension associated with high BMI, and small for gestational age birth associated with low BMI. Therefore women

contemplating a pregnancy should be counseled about these risks and encouraged to maintain a normal BMI regardless of its effects on assisted reproduction treatments.

References

1. Zaadstra BM, Seidell JC, Van Noord PA, te Velde ER, Habbema JD, et al. (1993) Fat and female fecundity: prospective study of effect of body fat distribution on conception rates. *BMJ* 306: 484-487.
2. van der Steeg JW, Steures P, Eijkemans MJ, Habbema JD, Hompes PG, et al. (2008) Obesity affects spontaneous pregnancy chances in subfertile, ovulatory women. *Hum Reprod* 23: 324-328.
3. Maheshwari A, Stofberg L, Bhattacharya S (2007) Effect of overweight and obesity on assisted reproductive technology—a systematic review. *Hum Reprod Update* 13: 433-444.
4. Bellver J, Ayllón Y, Ferrando M, Melo M, Goyri E, et al. (2010) Female obesity impairs *in vitro* fertilization outcome without affecting embryo quality. *Fertil Steril* 93: 447-454.
5. Rittenberg V, Seshadri S, Sunkara SK, Sobaleva S, Oteng-Ntim E, et al. (2011) Effect of body mass index on IVF treatment outcome: an updated systematic review and meta-analysis. *Reprod Biomed Online* 23: 421-439.
6. Li Y, Yang D, Zhang Q (2010) Impact of overweight and underweight on IVF treatment in Chinese women. *Gynecol Endocrinol* 26: 416-422.
7. Zhang D, Zhu Y, Gao H, Zhou B, Zhang R, et al. (2010) Overweight and obesity negatively affect the outcomes of ovarian stimulation and *in vitro* fertilisation: a cohort study of 2628 Chinese women. *Gynecol Endocrinol* 26: 325-332.
8. Maheshwari A (2010) Overweight and obesity in infertility: cost and consequences. *Hum Reprod Update* 16: 229-230.
9. Pandey S, Maheshwari A, Bhattacharya S (2010) Should access to fertility treatment be determined by female body mass index? *Hum Reprod* 25: 815-820.
10. Zhang XY, Ata B, Son WY, Buckett WM, Tan SL, et al. (2010) Chromosome abnormality rates in human embryos obtained from in-vitro maturation and IVF treatment cycles. *Reprod Biomed Online* 21: 552-559.
11. Son WY, Tan SL (2010) Laboratory and embryological aspects of hCG-primed *in vitro* maturation cycles for patients with polycystic ovaries. *Hum Reprod Update* 16: 675-689.
12. Shalom-Paz E, Marzal A, Wiser A, Almog B, Reinblatt S, et al. (2011) Effects of different body mass indices on *in vitro* maturation in women with polycystic ovaries. *Fertil Steril* 96: 336-339.
13. World Health Organization (2011) Global Database on Body Mass Index.
14. Reinblatt SL, Ishai L, Shehata F, Son WY, Tulandi T, et al. (2011) Effects of ovarian endometrioma on embryo quality. *Fertil Steril* 95: 2700-2702.
15. Tjepkema M Measured Obesity. Adult obesity in Canada: Measured height and weight. Statistics Canada Catalogue no. 82-620-MWE2005001 2005; Nutrition: Findings from the Canadian Community Health Survey: p. 20.
16. Fedorcák P, Dale PO, Storeng R, Ertzeid G, Bjercke S, et al. (2004) Impact of overweight and underweight on assisted reproduction treatment. *Hum Reprod* 19: 2523-2528.
17. van Swieten EC, van der Leeuw-Harmsen L, Badings EA, van der Linden PJ (2005) Obesity and Clomiphene Challenge Test as predictors of outcome of *in vitro* fertilization and intracytoplasmic sperm injection. *Gynecol Obstet Invest* 59: 220-224.
18. Dokras A, Baredziak L, Blaine J, Syrop C, VanVoorhis BJ, et al. (2006) Obstetric outcomes after *in vitro* fertilization in obese and morbidly obese women. *Obstet Gynecol* 108: 61-69.
19. Wittemer C, Ohl J, Bailly M, Bettahar-Lebugle K, Nisand I (2000) Does body mass index of infertile women have an impact on IVF procedure and outcome? *J Assist Reprod Genet* 17: 547-552.
20. Moragianni VA, Jones SM, Ryley DA (2012) The effect of body mass index on the outcomes of first assisted reproductive technology cycles. *Fertil Steril* 98: 102-108.
21. Chavarro JE, Ehrlich S, Colaci DS, Wright DL, Toth TL, et al. (2012) Body mass index and short-term weight change in relation to treatment outcomes in women undergoing assisted reproduction. *Fertil Steril* 98: 109-116.