The possible influence of increased body mass index on the clinical efficacy of standard human chorionic gonadotropin dosage

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Summary

Objectives: To evaluate whether the efficacy of standard (10,000 IU) hCG dosage is BMI dependent. P*atients & Methods:* During the study period, body mass index (BMI) was recorded in 261 consecutive women enrolled in our ICSI program. Women in the 90th BMI percentile were compared with those in the 10th percentile. The number and percent of mature metaphase-II (M-II) oocytes were considered as the outcome measure. *Results:* Mean BMI of the 10th and 90th percentile groups were 18.2 ± 0.7 kg/m^2 (n = 26) and 32.8 ± 2.2 kg/m^2 (n = 27), respectively. There were no differences between the groups in mean patients age, number of gonadotropin ampoules used, mean number of oocytes retrieved or the number and percentage of mature M-II oocytes. *Conclusions:* Standard (10,000 IU) hCG dosage is adequate to induce final oocyte maturation in IVF patients regardless of their BMI. This may imply that this hCG dosage is much higher than the dosage that is actually required.

Key words: BMI; ART; ICSI; hCG; M-II oocyte.

Introduction

Obesity is an increasing major health problem [1]. The magnitude of its associated health detriments increases with increasing body mass index (BMI). While being overweight or obese (BMI > 30 kg/m^2) may reduce a woman's fertility and increases pregnancy loss [2] and late pregnancy complications (preeclampsia, gestational diabetes, etc.) [3], data regarding the impact of obesity on IVF cycle outcomes are controversial.

Moreover, while several reports have shown no effect of increasing BMI on in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI) success rates, except for higher cancellation rates [4-7], others have demonstrated that excess weight is associated with lower cumulative live birth rates, lower implantation rates, increased gonadotropin requirement, and the possibility of decreased follicle development and oocyte numbers [8-14].

Controlled ovarian hyperstimulation (COH) is apparently a key factor in the success of in vitro fertilization-embryo transfer (IVF-ET). During IVF treatment, human chorionic gonadotropin (hCG) is usually used as a surrogate LH surge to induce final oocyte maturation and resumption of meiosis. The presence of metaphase-II (MII) oocytes reflects the resumption of meiosis of the oocyte and can be objectively assessed after the oocytes have been denuded before ICSI. The number and the percentage of MII oocytes are therefore better indicators of final maturation of the oocyte than the total number of oocytes retrieved.

Recently, in an attempt to explore whether the mechanism is ovarian or extraovarian, Bellver and colleagues [15] studied the effect of BMI on the reproductive outcome in the oocyte donation model, thus excluding potentially confounding ovarian hormonal environment. Their results showed similar implantation, pregnancy, and ongoing pregnancy rates among the four studied BMI groups (< 20 kg/m^2, 20-24.9 kg/m^2, 25-29.9 kg/m^2, and > 30 kg/m^2), with negative trends as BMI increased. They therefore concluded that the ovary is not the only factor responsible for the poor reproductive outcome in obese patients; the endometrium or its environment also contributes to this discouraging prognosis, but in a more subtle manner.

Carrell *et al.* [16] evaluated the relationship between intra-follicular hCG concentration and BMI. They observed a significant inverse correlation between the BMI and intra-follicular hCG concentration, which could be attributed to the concurrent decrease in embryo quality and pregnancy rates. Salha *et al.* [17] while examining the effect of adiposity on serum concentrations of hCG found that patients with high BMI had a significantly lower mean serum hCG concentration, required a higher dosage of gonadotrophin and had significantly fewer oocytes aspirated.

Prompted by these findings, and in a further attempt to clarify the mechanisms by which BMI affects the reproductive outcome, we decided to evaluate whether the effect of standard (10,000 IU) hCG dosage on resumption

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of meiosis and final maturation of the oocytes are BMI dependent.

Patients and Methods

We reviewed the computerized files of all consecutive women admitted to our IVF unit during a one-year period, who had reached the ovum pick-up (OPU) stage. Exclusion criteria included use of donor oocytes or transfer of frozen-thawed embryos, and use of any other procedure which does not include ICSI. All the usual indications for ICSI and accepted protocols for ovarian stimulations were included.

All patients received 10,000 IU to induce final oocyte maturation. The criteria for hCG administration were identical in all of these patients, namely, at least three follicles with the diameter of 18 mm with appropriate peripheral estradiol levels. Oocytes were retrieved 35 to 38 hours after hCG administration. Following OPU, and before the ICSI procedure, oocytes were denuded and classified according to their intactness and nuclear maturational stages, e.g., germinal vesicle, metaphase-I and mature metaphase II (M-II) oocytes.

Data on patient age and infertility-treatment-related variables, with emphasis on the patients' BMI, ovarian stimulation characteristics, number of oocytes retrieved and the number of M-II oocytes, were collected from the files.

Results are presented as means ± standard deviations. Differences in variables were statistically analyzed with the nonparametric Wilcoxon signed rank test, Student's t-test and chi-square test, as appropriate. A p value of less than 0.05 was considered significant.

Results

Two hundred and sixty one patients with a mean age of 32.8 ± 5.9 years and mean BMI of 23.7 ± 4.4 kg/m2 (range: 16.6-38.1 kg/m^2), were evaluated. Patients were divided into three groups according to their BMI. Underweight, BMI ≤ 10th percentile (10th percentile group); normal; at risk of overweight, BMI > 10th and < 90th percentile (10-90th percentile group); obese, BMI ≥ 90th percentile (90th percentile group). The clinical characteristics of their ICSI cycles are shown in Table 1.

Mean BMI of the 10th and 90th percentile groups were 18.2 ± 0.7 kg/m^2 (n = 26) and 32.8 ± 2.2 kg/m^2 (n = 27), respectively ($p < 0.0001$). Patients in the 90th percentile group required significantly longer stimulation compared to the two other groups, and had significantly lower peak E2 levels as compared to the 10th percentile group. Moreover, we observed non-significant trends toward increase in the length of stimulation and the number of gonadotropin ampoules used, with increasing BMI. There were no differences between the groups in mean patient age, number of gonadotropin ampoules used or mean number of oocytes retrieved. Moreover, the number and percentage of mature M-II oocytes were similar among the three groups (Table 1).

Table 1. — *Comparison between IVF cycles according to the different BMI percentile groups.*

	BMI - 10th percentile	BMI - 10th to 90th percentile	BMI-90th percentile
Number of cycles	26	208	27
Patient age (yrs)	31.3 ± 5.9	33.1 ± 6.0	31.9 ± 4.8
BMI (kg/m^2)	18.2 ± 0.7^a	23.2 ± 2.9^b	32.8 ± 2.2^c
Day 3 FSH (IU/l)	6.5 ± 2.3	6.5 ± 3.1	5.9 ± 2.5
Length of stimulation (days)	10.1 ± 2.0^d	10.5 ± 2.0^e	11.0 ± 2.7^f
Number of gonadotropin ampoules used	43 ± 25	46 ± 26	50 ± 25
Peak E2 levels on day of hCG administration (pg/ml)	2480 ± 1428^g	2093 ± 1171	1666 ± 1065^h
Progesterone levels on day of hCG administration (ng/ml)	0.8 ± 0.4	1.0 ± 0.9	0.5 ± 0.3
Number of oocytes retrieved	11.6 ± 7.4	10.6 ± 6.6	12.3 ± 8.8
Number of oocytes stripped for ICSI	10.4 ± 7.1	8.9 ± 6.2	10.6 ± 7.6
Ratio of M-II oocytes per oocytes stripped for ICSI (%)	72 ± 23	78 ± 21	77 ± 21

BMI - body mass index.
$p < 0.05$ between ^{a}and ^{b}and ^{c}, between ^{d} ^{e}and ^{f}, between ^{g} and ^{h}.
Standard (10,000 IU) hCG dosage is adequate to induce final oocytes maturation in IVF patients regardless of their BMI.

Discussion

In the present study of patients undergoing ICSI, standard (10,000 IU) hCG dosage was adequate to induce final oocyte maturation regardless of their BMI. This probably implies that the current hCG dosage is much higher than the dosage actually required for the resumption of meiosis of the oocyte. This observation is in agreement with previous studies demonstrating that oocyte maturation can be achieved with hCG doses of lesser amplitude than those required for follicular rupture [18]. Moreover, a low serum hCG level before oocyte recovery was shown to be as equally potent as the higher levels at initiating oocyte maturity and as reflected by a similar percentage of MII oocytes recovered [19].

We also observed a trend toward increase in the length of stimulation and the number of gonadotropin ampoules used and a decrease in peak E2 levels, with increasing BMI. These later observations are in accordance with other studies showing an association between an increased BMI and an increased gonadotrophin requirement during COH [8, 12] or decreased serum estradiol concentrations [5, 7].

Recently, several editorials have addressed the role of BMI in IVF outcome [20, 22]; all of which referred to the study by Bellver and colleagues [15], who attempted to delineate the mechanism for the observed decrease in the reproductive outcome of obese patients, by the oocyte donation model. In the later study, an extraovarian mechanism was shown to contribute to the poor reproductive outcome in obese patients. Exploring the effect of obesity on folliculogenesis will therefore complete this puzzle.

In the present study, we added further information to this puzzle by demonstrating no effect of obesity on final oocyte maturation and resumption of meiosis. Further large studies are therefore required to assess the effect of obesity on COH variables and embryo quality and to clarify the pathophysiologic alterations responsible for the associated poor reproductive outcome in obese patients.

These studies may help fertility specialists in individualization and careful tailoring of the COH protocol, for optimizing IVF success in obese patients.

References

[1] Must A., Spadano J., Coakley E.H., Field A.E., Colditz G, Dietz W.H.: "The disease burden associated with overweight and obesity". *JAMA*, 1999, *282*, 1523.

[2] Froen J.F., Arnestad M., Frey K., Vege A., Saugstad O.D., Stray-Pedersen B.: "Risk factors for sudden intrauterine unexplained death: epidemiologic characteristics of singleton cases in Oslo, Norway, 1986-1995". *Am. J. Obstet. Gynecol.*, 2001, *184*, 694.

[3] Boomsma C.M., Eijkemans M.J., Hughes E.G., Visser G.H., Fauser B.C., Macklon N.S.: "A meta-analysis of pregnancy outcomes in women with polycystic ovary syndrome". *Hum. Reprod. Update*, 2006, *12*, 673.

[4] Spandorfer S.D., Kump L., Goldschlag D., Brodkin T., Davis O.K., Rosenwaks Z.: "Obesity and in vitro fertilization: negative influences on outcome". *J. Reprod. Med.*, 2004, *49*, 973.

[5] Dokras A., Baredziak L., Blaine J., Syrop C., VanVoorhis B.J., Sparks A.: "Obstetric outcomes after in vitro fertilization in obese and morbidly obese women". *Obstet. Gynecol*., 2006, *108*, 61.

[6] Dechaud H., Anahory T., Reyftmann L., Loup V., Hamamah S., Hedon B.: "Obesity does not adversely affect results in patients who are undergoing in vitro fertilization and embryo transfer". *Eur. J. Obstet. Gynecol. Reprod. Biol.*, 2006, *127*, 88.

[7] Lashen H., Ledger W., Bernal A.L., Barlow D.: "Extremes of body mass do not adversely affect the outcome of superovulation and in-vitro fertilization". *Hum. Reprod.*, 1999, *14*, 712.

[8] Fedorcsak P., Dale P.O., Storeng R., Ertzeid G., Bjercke S., Oldereid N. *et al.*: "Impact of overweight and underweight on assisted reproduction treatment". *Hum. Reprod.*, 2004, *19*, 2523.

[9] Lintsen A.M.E., Pasker-de Jong P.C.M., de Boer E.J., Burger C.W., Jansen C.A.M., Braat D.D.M. *et al.*: "Effects of subfertility cause, smoking and body weight on the success rate of IVF". *Hum. Reprod.*, 2005, *20*, 1867.

[10] Ku S.Y., Kim S.D., Jee B.C., Suh C.S., Choi Y.M., Kim J.G. *et al.*: "Clinical efficacy of body mass index as predictor of in vitro fertilization and embryo transfer outcomes". *J. Korean Med. Sci.*, 2006, *21*, 300.

[11] Nichols J.E., Crane M.M., Higdon H.L., Miller P.B., Boone W.R.: "Extremes of body mass index reduce in vitro fertilization pregnancy rates". *Fertil. Steril.*, 2003, *79*, 645.

[12] Wittemer C., Ohl J., Bailly M., Bettahar-Lebugle K., Nisand I.: "Does body mass index of infertile women have an impact on IVF procedure and outcome?". *J. Assist. Reprod. Genet.,* 2000, *17*, 547.

[13] Loveland J.B., McClamrock H., Malinow A., Sharara F.: "Increased body mass index has a deleterious effect on in vitro fertilization outcome". *J. Assist. Reprod. Genet.*, 2001, *18*, 382.

[14] Mulders A.G., Laven J.S., Eijkemans M.J., Hughes E.G., Fauser B.C.: "Patient predictors for outcome of gonadotropin ovulation induction in women with normogonadotrophic anovulatory infertility: a meta-analysis". *Hum. Reprod. Update*, 2004, *9*, 429.

[15] Bellver J., Melo M.A.B., Bosch E., Serra V., Remohi J., Pellicer A.: "Obesity and poor reproductive outcome: the potential role of the endometrium". *Fertil. Steril.*, 2007, *88*, 446.

[16] Carrell D.T., Jones K.P., Peterson C.M., Aoki V., Emery B.R., Campbell B.R.: "Body mass index is inversely related to intrafollicular HCG concentrations, embryo quality and IVF outcome". *Reprod. Biomed. Online*, 2001, *3*, 109.

[17] Salha O., Dada T., Sharma V.: "Influence of body mass index and self-administration of hCG on the outcome of IVF cycles: a prospective cohort study". *Hum. Fertil.*, 2001, *4*, 37.

[18] Bomsel-Helmreich O., Vu N Huyen L., Durand-Gasselin I.: "Effects of varying doses of HCG on the evolution of preovulatory rabbit follicles and oocytes". *Hum. Reprod.*, 1989, *4*, 636.

[19] al-Hassan S., Fishel S., Fleming S., Thornton S.: "Low plasma levels of hCG after 10,000-IU hCG injection do not reduce the number or maturation of oocytes recovered in patients undergoing assisted reproduction". *J. Assist. Reprod. Genet.*, 1998, *15*, 583.

[20] Howards P.P., Cooney M.A.: "Disentangling causal paths between obesity and in vitro fertilization outcomes: an intractable problem?". *Fertil. Steril.*, 2008, *89*, 1604.

[21] McClamrock H.D.: "The great weight debate: do elevations in body mass index (BMI) exert a negative extraovarian effect on in vitro fertilization outcome?". *Fertil. Steril.*, 2008, *89*, 1609.

[22] Norman R.J., Chura L.R., Robker R.L.: "Effects of obesity on assisted reproductive technology outcome". *Fertil. Steril.*, 2008, *8*9, 1611.

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