Impact of Women's Body Mass Index (BMI) on the Outcomes of Intra-Cytoplasmic Sperms Injection (ICSI)

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الخلاصة:

تعد السمنة واحدة من المشاكل الصحية الكبرى على مستوى دول العالم فهي تؤثر سلبيا على صحة أجهزة وأعضاء الجسم ومن ضمنها الجهاز التناسلي. هدفت الدراسة لمعرفة مدى تأثير مؤشر كتلة الجسم (BMI) على نتائج عمليات الحقن المجهري (ICSI). درست حالات خمسة وثمانون من النساء اللواتي ادخلن برنامج الحقن المجهري في مركز الخصوبة في مدينة الصدر الطبية – النجف الاشرف. امتدت فترة الدراسة من كانون الثاني الى نيسان لسنة 2015. قسمت النساء قيد الدراسة الى ثلاث مجاميع اعتمادا على مؤشر كتلة الجسم هي مجموعة الوزن الطبيعي (BMI 18.5-24.9 kg/m^2) عددها 22، ومجموعة زيادة الوزن (BMI 25-29.9 kg/m^2) وعددها 43، ومجموعة السمنة (BMI≥30 kg/m^2) وعددها 20. عرضت جميع المريضات الى تحفيز المبايض المضاعف المسيطر عليه واجريت عملية الحقن المجهري. وقد اعتمدت معايير عدة للمقارنة بين نتائج المجاميع وهي معايير النتائج الجنينية ونسبة حصول الحمل السريري. أظهرت النتائج تأثيرا سلبيا ذا معيار احصائي مؤثر للسمنة -عند مقارنتها بمجموعتي زيادة الوزن والوزن الطبيعي- فيما يخص عدد البيوض التي سحبت من المبايض (p value 0.021) و عدد البيوض الناضجة (p value 0.003) وعدد البيوض ذات النوعية الجيدة (p value 0.005) وعدد الأجنة من الدرجة الأولى (p value 0.040) ونسبة حصول الحمل السريري (p value 0.001). عند الأخذ بنظر الأعتبار هذه النتائج فأن من المهم تشجيع النساء ذوات مؤشر كتلة الجسم العالي (السمنة) على تقليل الوزن قبل دخول برنامج الحقن المجهري لتحسين نتائج هذه العملية.

Abstract:

Obesity is one of major health problems across the world that negatively impact many body systems and organs including reproductive system. The objective of this study was to examine the effect of body-mass index (BMI) on the outcomes of intra-cytoplasmic sperms injection (ICSI). Eighty five women entering an ICSI program in the fertility center of Al-Sadr medical city / Al-Najaf Al-Ashraf, from January till April 2015, were enrolled in this study and divided according to BMI to normal weight group [(BMI 18.5-24.9 kg/m^2) (n=22)], overweight group [(BMI 25-29.9 kg/m^2) (n=43)] and obese group [(BMI≥30 kg/m^2) (n=20)]. The patients underwent standard controlled ovarian hyperstimulation protocols and ICSI procedures. The outcome measures in the form of embryological outcomes and most importantly pregnancy rates were studied. The results revealed a significantly negative impact of high BMI in obese women group on total oocytes number retrieved (p value 0.021), mature oocytes number [oocytes in meiosis II (M II)] (p value 0.003), good quality oocytes number (p value 0.005), grade I embryos number (p value 0.040) and clinical pregnancy rate (p value 0.001). On behalf of these results, it is worthy to encourage women with high BMI to lower their body weight before entering an ICSI program.

Introduction:

Overall the world, obesity hits the bell of danger and considered as an international problem not only regarding population health, but also burden economic and social issues. It is becoming a rapidly growing health problem that negatively impact on ,or even as a causative factor in, many diseases like cardiovascular diseases, diabetes, sleep apnea, osteoarthritis, breast and uterine cancers and other reproductive disorders in women (1-4). Body mass index has been broadly used to assess the extent of obesity and overweight objectively and used as an indicator in a lot of studies (5).

On the other hand, infertility is regarded as a one of most prevalence diseases that increasingly necessitate the need for assisted reproductive technologies (6).

Although the development of assisted reproductive technologies is rapidly growing field that reaching a high levels of control regarding ovarian stimulation and culture systems, yet the success rate remain relatively not satisfying and this could be due

to that numerous factors could impact the results. So that, researchers continuously studying many factors that possibly affect the results.

Obesity of women is one of these factors that showed controversial and conflicting results giving us a motive to study its possible effect on intra-cytoplasmic sperm injection (ICSI) outcomes in our fertility center. It is important to state that obesity has a well kwon negative impact on reproductive systems as in cases of anovulation and menstrual abnormalities in addition to obstetrical negative impact as in cases of preeclampsia, gestational diabetes, miscarriages, caesarean section indications, and live birth (7-11).

Patients and Methods:

Eighty five women entering an ICSI program in the fertility center of Al-Sadr medical city / Al-Najaf Al-Ashraf, from January till April 2015, were enrolled in this study and divided according to BMI (calculated as body weight in kg divided by height squared in meters) into normal weight group [(BMI 18.5-24.9 kg/m^2) (n=22)], overweight group [(BMI 25-29.9 kg/m^2) (n=43)] and obese group [(BMI≥30 kg/m^2) (n=20)]. The patients underwent standard controlled ovarian hyperstimulation protocols. The outcome measures in the form of embryological outcomes and most importantly pregnancy rates were studied. Potential confounding factors, especially women's ages and infertility periods were noted when compared among studied groups minimizing bias in classifying women among the various BMI categories (**Table 1**).

The embryological parameters that studied as an outcome measures are (**Table 2**):

1. Total oocytes number retrieved: for each patient, the total number of oocytes that retrieved at the oocytes pick-up day (36 hours after human chorionic gonadotropin (hCG) injection) were counted after searching and collecting them from aspirated follicular fluid.
2. Oocytes maturity: after oocytes collection, they were denuded (both chemically by hyaluronidase enzyme and mechanically by a series of smaller diameter denudation pipettes) to remove cumulus cells around them to assess their maturity clearly. According to maturity they were divided into 3 types; first are germinal vesicle (GV) oocytes (not completed meiosis I) where the genetic material was noticed like a nucleus in the cytoplasm, second are M I oocytes (completed meiosis I, but not entering meiosis II) where they have clear cytoplasm with no polar body, and third are mature oocytes (entered meiosis II) where they have clear cytoplasm and contain first polar body in perivitelline space. Only M II oocytes considered mature and could be injected during ICSI.
3. Good quality oocytes: the M II oocytes where subdivided into good quality and poor quality according to the following morphological factors: shape (good quality: round shape); cytoplasm (good quality: no darkness, no vacuoles or inclusion bodies and no granulation); perivitelline space (good quality: not wide and contain no debris or cytoplasmic fragments); polar body (good quality: not fragmented); and zona pellucid (good quality: not thick nor irregular).
4. Fertilization rate: on the day after injection day (16-18 hour after injection i.e. day 1 after injection), the fertilization was assisted where the oocyte considered fertilized if it contain a second polar body and two pronclei. The fertilization rate obtained by dividing fertilized oocytes number on the number of injected oocytes.
5. Total embryos: on the day after fertilization day (day 2 after injection and the day of embryo transfer in our study), the fertilized oocytes that developed to embryos were counted.
6. Grade I embryos: the embryos were considered grade I if they mach the

following criteria (the blastomeres are even in number, equal in size and the embryo contain less than 20% fragmentation) (12).

In addition to embryological parameters, pregnancy rates were assessed for each group. Clinical pregnancy for each patient was diagnosed when fetal cardiac activity was confirmed by ultrasonography at about 4 weeks after embryo transfer. Pregnancy rate for each group was assessed by dividing the pregnant women number on the total number of women of that group.

Statistical analysis was done by using SPSS (statistical package for social sciences) version 20 in which analysis of variance (ANOVA) with LSD for numerical data and *chi*-square test for categorical data were used. The *P value* ≤0.05 was set as significant.

Table (1): age, duration of infertility, and BMI of females involved in the study; showing the significant difference in BMI (<0.001).

Parameter	Patients' Groups According to BMI			*P value*
	Normal weight (BMI 18.5-24.9) (n=22)	Over weight (BMI 25-29.9) (n=43)	Obese (BMI≥30) (n=20)	
Age/years	27.81±6.842	29.95±6.098	31.15±6.953	0.240
Duration of Infertility/years	6.70±3.875	7.53±4.458	8.70±4.856	0.345
BMI kg/m2	23.27±1.273	26.80±1.394	34.22±3.145	<0.001

Results:

There was a significantly negative impact of obesity (BMI ≥ 30) on total number of retrieved oocytes (*p value* 0.021), mature oocytes number (*p value* 0.003), good quality oocytes number (*p value* 0.005), and clinical pregnancy rate (*p value* 0.001) when compared with overweight (BMI 25-29.9) and normal weight (BMI 18.5-24.9) groups (**Table 2** and **Figure 1**).

The pregnancy rate was 59.1% in normal weight group (13 from 22), 34.9% in overweight group (15 from 43) and 5% in obese group (1 from 20) (**Figure 1**). Although, the pregnancy rate was higher in normal weight group as compared with overweight group, there was no statistical significant difference. The negative impact of increased BMI on pregnancy rate was statistically significant in obese group.

In addition, there was a negative impact of obesity on grade I embryos number (*p value* 0.040) when compared with normal weight, but not overweight groups (**Table 2**).

However, there was no significant difference between the three groups regarding GV oocytes number (*p value* 0.128), M I oocytes number (*p value* 0.625), fertilization rates (*p value* 0.410) and total number of embryos (*p value* 0.058) (**Table 2**).

Table (2): Parameters Studied as Outcomes of ICSI According to BMI [*significant against normal weight group (P≤0.05); #significant against overweight group (P≤0.05)].

Parameter	Normal weight (BMI 18.5-24.9) (n=22)	Over weight (BMI 25-29.9) (n=43)	Obese (BMI≥30) (n=20)	P *value*
Total Oocytes no.	12.90±6.225	11.46±6.295	7.65±6.054*#	0.021
GV Oocytes	0.27±0.455	1.16±2.369	0.55±0.825	0.128
M1 Oocytes	1.13±1.753	1.37±1.647	0.95±1.571	0.625
M2 Oocytes	11.36±5.593	8.93±4.295	6.15±4.782*#	0.003
Good quality oocytes	10.27±5.504	8.23±4.093	5.60±4.185*#	0.005
Fertilization Rate	69.5%	69.3%	76.9%	0.410
Total Embryos	6.04±3.03	5.23±2.732	3.90±3.059	0.058
Grade I Embryos	3.74±2.42	2.7±1.7	2.9±0.9*	0.040

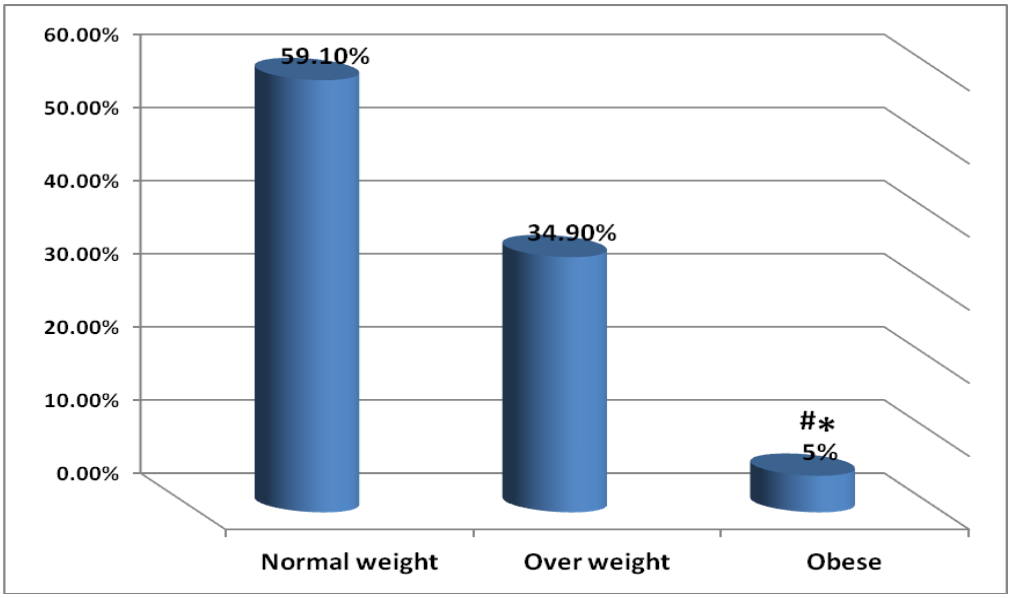

Figure (1): Clinical Pregnancy According to BMI groups (*p value* 0.001).
*significant against normal weight group (P≤0.05)
#significant against overweight group (P≤0.05)

Discussion:

Obesity is known to affect women's fertility. Several studies have been shown that it led to anovulatory infertility, associated with high miscarriage rate and high prevalence of gestational diabetes and pregnancy induced hypertension (7-11). On the other hand, weight reduction has been well recognized to improve the outcomes of reproduction in overweight and obese women where even modest weight loss about 5-10% of preliminary body weight can efficiently improve regularity of menstrual cycle, ovulation, and pregnancy rate (7). However, in assisted reproductive technologies, there are conflicting reports concerning the effect of obesity on the outcomes (10, 13-16).

Our study revealed that obesity has a significantly negative impact on the outcomes of ICSI in the form of lower total number of retrieved oocytes, number of mature oocytes, number of good quality oocytes, number of grade I embryos and most importantly clinical pregnancy rate.
This study goes with the agreement of many studies (16-19).

The exact pathophysiological mechanism explaining the effect of BMI on the ICSI outcomes is uncertain yet. However, there are many postulations. One of them was that BMI inversely affect the intrafollicular hCG levels affecting the final maturation steps of oocytes (20). Others linked the bad ICSI outcomes to a negative effect of high BMI on the folliculogenesis in ovaries and, as a consequence, embryos quality (16). This result was strengthen from oocytes donation models where it was reported that there was no difference in the endometrial thickness among women with different BMI concluding that folliculogenesis and embryos quality rather than uterine receptivity affect the results (21 and 22). Some researchers suggested that elevated levels of intrafollicular leptin were associated with relative resistance to exogenous gonadotropin and inhibited estradiol (E2) synthesis by granulasa cells resulting in low E2 levels and necessitating a higher doses of gonadotropin for controlled ovarian hyperstimulation, so that negatively affect oocytes and embryos development and quality and also negatively affect the endometrial development and receptivity (23-25).

Moreover, researchers found that the cancellation rate in morbidly obese women was higher than that in normal weight women (11). Also it had been found that high BMI was negatively affect blastocyst formation rate (26).

On the other hand, some researchers didn’t found such a negative effect of high BMI or obesity on the ICSI outcomes; however, they state that overweight and obese women must be counseled on weight reduction to reduce pregnancy related complications (27).

These conflicting results could be explained by many aspects. There are many factors could adversely affect the outcomes and some factors could be with more impact than the others or have synergistic effects between them. The choice of appropriate controlled hyperstimulation protocol had been found to affect the outcomes of ICSI in women with high BMI (28). An ethnic difference in the outcomes was reported where a difference in BMI was also reported. For that reason, it should be differentiated whether the effect of BMI is confounded by a racial difference (29). A novel study demonstrated that the effect of BMI on the outcomes appeared to be age related, where at younger age, a higher BMI had an obvious negative influence on pregnancy rate, but this effect was attenuated as age increased (30). Also the reason underling infertility could impact the outcomes in cases of high BMI as in cases of polycystic ovary syndrome (31).

In conclusion, obesity appeared to be negatively impact the outcomes of ICSI especially regarding the occurrence of pregnancy. Accordingly, it is worthy to encourage women with obesity to reduce their weight to a reasonable level before attempting an ICSI program.

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