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Effect of Obesity on Oocyte and Embryo Quality in Women Undergoing in Vitro Fertilization: A Retrospective Study

Thesis
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Noha Saad

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List of Abbreviations

ART	**:**	Assisted Reproductive Technology
BMI	**:**	body mass index
COH	**:**	Controlled ovarian hyperstimulation
DIC	**:**	Difference Interference Contrast
DIC	**:**	Difference-Interference Contrast
FP	**:**	Fragmentation Pattern
FSH	**:**	Follicle Stimulating Hormone
GIFT	**:**	Gamete Intrafallopian Transfer
GnRH	**:**	Gonadotrophin-releasing hormone
HCG	**:**	Human Chorionic Gonadotrophin
HMC	**:**	Hoffmann Interference Contrast
HMC	**:**	Hoffmann Modulation Contrast
HPO	**:**	Hypothalamic–Pituitary–Ovarian
ICSI	**:**	Intra Cytoplasmic Sperm Injection
IGF1	**:**	Insulin like Growth Factor 1
IVF	**:**	In Vitro Fertilization
LH	**:**	Luteinizing Hormone
MESA	**:**	Microsurgical epididmal sperm extraction
OHSS	**:**	ovarian hyperstimulation syndrome
PCOS	**:**	Poly Cystic Ovary Syndrome
PCT	**:**	post coital test
PGD	**:**	Pre-implantation Genetic Diagnosis

SHBG	**:**	Sex Hormone-Binding Globulin
TESE	**:**	Testicular sperm extraction
TNF	**:**	Tumour Necrosis Factor
WHO	**:**	World Health Organization
WHR	**:**	Waist Hip Ratio
ZIFT	**:**	Zygote Intrafallopian Transfer

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Introduction

Obesity is a medical condition in which excess body fat accumulated to the extent that it may have an adverse effect on body health leading to reduced life expectancy and/or increased health problems ***(WHO, 2000).***

The Calculation of body mass index (BMI) has been also used in the definition of obesity, BMI equals a person's weight in kilograms (kg) divided by his height in meters squared (m^2) ***(WHO, 2000).***

The commonly used definition is established by WHO in 1997 and published in 2000 providing the values listed in the following table for the cutoff points of every group of BMI.

BMI	Classification
<18.5	Underweight
18.5 – 24.9	Normal weight
25 – 29.9	Over weight or pre obese
30 – 34.9	Class I obesity
35 – 39.9	Class Π obesity
≥ 40	Class ΙΙΙ obesity

Then class ΙΙΙ obesity breaks down in to:

- A BMI of 40 – 44.9 is morbid obesity.
- A BMI of ≥ 45 is supper obesity.

Together with other medical complications such as diabetes mellitus, hypertension and cardiovascular diseases, obese women are most likely to experience reproductive problems including menstrual irregularities, anovulation, hirsutism, infertility and miscarriage ***(Pasqual et al., 2003).***

Little is known regarding the mechanism by which obesity exerts its negative effect on reproductive outcome. Prior studies suggested that it may impair the human reproduction through different ways such as it alters secretion of pulsating gonadotrophin releasing hormones (GnRH), reduces sex hormone binding globulin (SHBG) leading to an alteration of androgen and estrogen delivery to the target tissues, insulin resistance and hyperandrogenism and elevated leptin levels in the blood and follicular fluid ***(Urbancsek et al., 2002).***

The deleterious effects of obesity on spontaneous reproduction are well recognized including higher preclinical and clinical miscarriage rates and increased complications during pregnancy for both mother and fetus ***(Fedorcsak et al., 2004).***

Most of these complications between conception and the end of first trimester seems to be due to the abnormal dialogue between the oocyte (and, thus, the resulting embryo) and the endometrium while complications in the second and third trimester of pregnancy are due to maternal manifestations of metabolic syndrome of obesity ***(Zaadstra et al., 1993).***

On the other hand, obese women are almost three times as likely as non obese women to be at risk of infertility ***(Edward et al., 1994)*** and to fail to become pregnant in both natural and assisted conception cycles ***(Crosignani et al., 1994).***

Most reports show lower live birth rates in obese than in non obese women particularly when this parameters is calculated per (IVF – ICSI) cycles ***(Fedorcsak et al., 2000).***

The lower probability of a healthy live born seems to be the result of a combination of lower implantation rates and pregnancy rates, higher preclinical and clinical miscarriage rates, and increased complications during pregnancy for both mother and fetus ***(Maheshwri et al., 2007).***

A systemic review in the year 2007 concluded that over weigh and obese women with BMI > 25 have lower pregnancy rates after IVF cycles, require higher doses of gonadotrophins to achieve sufficient ovarian response, lower number of mature oocyets, reduced number of oocyte retrieval, poor oocyte and embryo quality with subsequent lower fertilization and implantation rates ***(Maheshwari et al., 2007).***

However the impact of obesity on IVF is still conflicting, some studies have revealed that these patients have an increased cycle cancellation rates and less oocytes retrieval ***(Mc cormick et al., 2008).***

In contrast other studies found no significant effect of obesity in response to ovarian stimulation ***(Thum et al., 2007).***

The controversy over assisted reproductive technology (ART) outcome in obese patients may be due to different cutoff value used to define obesity, inclusion of over weight and obese patient in the same study, the different types of obesity, inclusion of patient with different infertility etiologies, the different individual endocrine and metabolic patterns of each woman and\ or varying focus of outcome measures.

In addition to that some confounding factors such as age and polycystic ovary syndrome (PCOS), which may specifically affect the duration of ovarian stimulation, gonadotrophin dose, peak serum estradiol level, cancellation rate and the number of mature follicles have not been taken into consideration ***Dokras et al. (2006),***.

PCOS is an important issue in obese women**,** a previous study has emphasized that the obese women (with BMI>40kg/m^2) with PCOS had a lower ART cycle cancellation rate and fewer days of gonadotrophin stimulation than those without PCOS ***Dokras et al. (2006)***.

Another study showed that although total gonadotrophin dose was similar among all BMI groups, starting gonadotrophin dose was significantly lower in PCOS patien ***Martinuzi et al. (2008)***.

In contrast, some authors have claimed that the presence of PCOS did not positively affect the duration of ovulation induction cancellation rate and gonadotrophin dose ***(Fedorcsak et al., 2004).***

(Matalliotakis et al., 2008) have excluded PCOS patients from their study and found a lower stimulation response in women with elevated BMI.

Most of the study exploring the effect of obesity on infertility and IVF cycles have focused exclusively on clinical out comes such as pregnancy rate or implantation rate rather than oocyte or embryo quality, aspects of reproductive biology that are uniquely observable in the IVF population.

We assume that women with higher BMI are less responsive to gonadotrophines and hence will have poorer quality of oocytes and embryos. Consequently lower implantation and pregnancy rate is expected in them.

Research Hypothesis

Research Question:

Is there a significant effect of obesity on oocyte and embryo quality and cycle outcome in women undergoing IVF with intra cytoplasmic sperm injection?

Research Hypothesis:

We suspected that obesity has a negative effect on embryo quality and cycle outcome in women undergoing IVF with intra cytoplasmic sperm injection.

Participants

The retrospective study will include all infertile women who underwent their first ICSI cycle between 2006-2010 based on the following eligibility criteria:

Inclusion criteria:

Patient who underwent their first ICSI cycles because of tubal factor, male factor, PCOS, pelvic adhesion or unexplained infertility with age < 40 years old and basal FSH < 12 IU/L.

Exclusion criteria:

1- Patient with severe endometriosis diagnosed by laparoscopy.
2- Patient who received frozen thawed embryo transplantation.
3- Patient > 40 years old.
4- Patient with accompanying medical problem which may lead to abnormal BMI such as diabetes mellitus, hyper or hypothyroidism.
5- Patient with basal FSH > 12 IU/L.

Outcome measures:

Main outcome measures included, number of mature and normally fertilized oocytes, embryo morphology, estradiol level on the day of human chorionic gonadotropin administration, clinical pregnancy, spontaneous abortion and live birth.

Data to be collected:

1- Age of the woman at the start of the cycle and categorized as younger than 35, 35-37, 38-40, 41-42 and older than 42 years old according to Centers for Disease Control and Prevention and Society for Assisted Reproductive Technology cut points.

2- BMI of the woman and categorized as under weight, normal weight, over weight or obese which was further classified into class I, class II and class III obesity according to WHO cut points.

(Normal weight women were used as reference population for all comparisons).

3- Infertility history of the woman will be retrieved including duration of in fertility, menstrual history and causes of infertility (male factor infertility, anovulatory factor, tubal factor, pelvic factor, endometriosis, unexplained infertility or combined male and female factor of infertility).

4- Diagnosis of PCOS is justified if the woman met any two of the following three criteria (using the 2003 Rotterdam criteria): 1- oligo– or an ovulation; 2- clinical or biochemical signs of hyperandrogenism and 3-polycystic ovaries by ultrasound.

5- Routine infertility investigations will be registered in all couples including semen analysis and evaluated according to WHO criteria ***(WHO, 1992).***

6- Hormonal profile of all women including FSH, LH, prolactin and estradiol level on the third day of menstrual bleeding will be registered.