The impact of BMI on response to controlled ovarian hyperstimulation in in vitro fertilization/intracytoplasmic sperm injection cycles, a retrospective cohort study.

Version 3

Author: Charlotte Berglund
Supervisor: Mikael Lood, MD
 Supervisor: Karin Franzén MD, PhD
Örebro, Sweden
Abstract

Introduction: Today, IVF/ICSI (in vitro fertilization/intracytoplasmic sperm injection) is a valuable procedure for people suffering from infertility. Controlled ovarian hyperstimulation, whose purpose is to stimulate production of mature oocytes for fertilization, is one of the crucial parts. BMI’s (body mass index) impact on the number of received oocytes is disputed and suspicion towards reduced number of oocytes in women with higher BMI has been suggested.

Objective: This study investigates if there is a significant correlation between high BMI and fewer oocytes collected from controlled ovarian hyperstimulation in IVF/ICSI cycles.

Method: Retrospective data of 399 IVF/ICSI cycles between 2011-2015 were analyzed. The sample was divided in three BMI categories, normal: BMI 18.5-24.9 kg/m², overweight: BMI 25.0-29.9 kg/m² and obese: BMI 30.0 ≤ kg/m². Variables analyzed included AMH-value (anti-Müllerian hormone), total FSH (follicle stimulation hormone) dose, age and number of collected oocytes.

Result: Obese women had significantly fewer oocytes collected compared to women with normal BMI, with a mean difference of 2.0 oocytes, (p=0.037). There was also a significant difference in total FSH dose given between obese women and women with normal BMI, i.e. obese women received a higher total FSH dose, (p=0.007).

Conclusion: Obese women received higher total doses of FSH but still collected fewer oocytes. This suggests that high BMI has a negative impact on controlled ovarian stimulation and the ability to produce mature oocytes. However heterogeneity of the sample and other confounding factors makes the results less convincing, larger sample size and more controlled studies are suggested in the future.

Key words: IVF, ICSI, BMI, COH, oocytes, FSH
**Abbreviations**

AFC - antral follicle count

AMH - anti-Müllerianhormone

BMI - body mass index

COH - controlled ovarian hyper stimulation

ELISA - enzyme-linked immunosorbent assays

ET - embryo transfer

FSH - follicle stimulation hormone

rFSH - recombinant FSH

GnRH - gonadotrophin-releasing hormone

hCG - human chorionic gonadotropin

hMG - human menopausal gonadotropin

ICSI - intracytoplasmic sperm injection

IVF - in vitro fertilization

LH - luteinizing hormone

OHSS - ovarian hyperstimulation syndrome

OPU - ovarian pick-up

ORTs - ovarian reserve tests

PCOS - polycystic ovarian syndrome
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1. Introduction

1.1 IVF (in vitro fertilization)
Today, IVF is a worldwide treatment and thanks to this method over four million infants have been born. IVF is considered to be a reliable and efficient treatment for people that are facing infertility [1].

The purpose of IVF is to create healthy embryos in vitro to be transferred to the uterine cavity. The ovaries are stimulated to produce numerous mature oocytes to be fertilized by sperms in the laboratory. The stimulation allows for selection of embryos to be transferred or cryopreserved (frozen) [1,2].

The first stage in IVF therapy is to subcutaneously inject the woman with FSH (follicle stimulation hormone) either as hMG (human menopausal gonadotropin) or recombinant FSH and then administer hCG (human chorionic gonadotropin) that will induce final maturation of the oocytes before collecting them. These are ovary-stimulating drugs whose purposes is to hyper stimulate the ovary to produce multiple mature oocytes [3]. The optimal number of mature oocytes is between 8 and 15 [4], as this will give a higher chance of receiving a high quality embryo and increase the possibility of a successful treatment. This becomes less likely if only one oocyte is able to be collected after stimulation [1]. After achieving mature oocytes the next step is ovum pick-up, a procedure that collects the mature eggs from the ovary. An ovum pick-up is guided by a vaginal ultrasound that will give an image of the ovaries on a screen. On the vaginal ultrasounds probe there is a needle that will pierce the vaginal wall and reach in to the ovary and aspirate follicle fluid and the mature oocytes [1,2]. The collected oocytes will then be fertilized with the sperms, either through conventional IVF where the oocytes and the sperms are mixed together [2]. Or if the amount and/or the mobility of the sperm are low, a sperm will be directly injected into each one of the oocytes for fertilization, a method called ICSI (intra-cytoplasmic sperm injection). After this the oocytes will be placed in a beneficial environment to grow and after 16-18 hours they will be examined to see if the fertilization was successful [2]. The fertilized oocyte now called a zygote will become an embryo after cell cleavage. The embryo will be cultivated in an incubator between two and five days [1] after which it will be evaluated according to morphological criteria and the finest will pass on to ET (embryo transfer) or cryopreservation. The ET is executed via a thin catheter containing the embryo, which penetrates the cervix uteri and injects the embryo into the uterine cavity [2].
1.2 Controlled ovarian hyper stimulation (COH)

The purpose of COH is to stimulate production of mature oocyte from the ovaries by inducing follicular growth by giving a subcutaneous injection of exogenous FSH. The exogenous FSH is either a recombinant product (rFSH) or urinary-derived gonadotropin (hMG, human menopausal gonadotropin) and these doses of FSH are given as daily injection for 10±2 days [1].

The theory behind hormone stimulation with FSH is to enhance the already existing cycle of oocyte development in the female body [2]. The natural secretion of FSH is controlled by pulsatile secretion of GnRH (gonadotrophin-releasing hormone), from the hypothalamus that influences the secretion of FSH from the anterior pituitary gland. The function of FSH is to work as a main regulator for follicular growth [1]. In the natural ovulatory cycle there is usually only one oocyte that will reach full maturation and ovulate. In response to increased levels of FSH in late luteal phase antral follicles with FSH receptors start to grow [2,3]. The follicles that are recruited to growth become sensitive to FSH and granulosa cells and theca cells within the follicles starts to proliferate. Proliferation of the follicular cells that caused by FSH stimulation will enable oestogens synthesis by aromatizing androgens. The oestrogens and FSH will then act synergistically on granulosa cells and enhance the proliferation even more, while also increasing the number of FSH receptors in the follicles. This in turn will further benefit the development of the follicles [1,3]. The follicle that becomes most sensitive to FSH is the one to be selected to become the dominant follicle and receives an advantage against the other growing follicles. The dominant follicle will develop and produce more oestrogen and soon adopt an estrogen environment. This will give the dominant follicle more FSH receptors, which in turn increases its sensitivity to FSH. The increasing level of oestogen and inhibin will decrease the secretion of FSH via a negative feed back system from the pituitary, leading the follicles with fewer FSH receptors than the dominant follicle to atresia (apoptosis) [3]. The dominant follicle will be protected from atresia due to its high amount of FSH receptors and therefore higher ability to aromatize androgens to oestorgens.

The theory of COH with FSH is to disturb the natural recruitment cycle of the dominant follicle by giving high dose of exogenous FSH. By doing this, the FSH levels in the blood and in the ovaries will reach higher than normal levels, with the intention of saving more follicles with dominant follicle quality from atresia [2].

The treatment with high dose exogenous FSH during COH will induce the growth of follicles to produce high levels of estradiol, far beyond normal levels. This in turn will trigger a premature LH (luteinizing hormone) surge because of the positive feedback system that
estradiol has with the pituitary gland. In the COH for IVF it is important to prevent this LH surge, as it may induce ovulation of the not yet mature oocyte. There are two ways of blocking the LH surge: either by administrating a GnRH agonist or a GnRH antagonist. These GnRH analogues have the same main effect, to prevent ovulation, but differ in their mechanisms of action [1]. The GnRH agonist is a long acting down regulator of the pituitary gland which acts by exhausting it after a short period of hypersecretion of gonadotropins [5] that later will down regulate GnRH receptors in the pituitary gland and desensitize the gonadotrotophic cells [6] and obstructing the secretion of LH [1]. The GnRH antagonist binds and blocks the receptor, which prevents the endogenous GnRH from stimulating the pituitary gland cells. This blockage induces a immediate and quick suppression of gonadotropin [5,6]. Previously, COH treatment for IVF patients was initiated with GnRH agonist but lately it has become more and more common to choose GnRH antagonist for ovarian stimulation [7,8]. The reason for the change from GnRH agonist to GnRH antagonist is the to long treatment cycles, high cost, intensive monitoring and discomfort to the woman created by the temporary irregular hormone environment with climacteric symptoms of the GnRH agonist treatment. The GnRH antagonist on the other hand is believed to give a more gentle ovarian stimulation [6].

There have been studies comparing the two options to explore any differences between these GnRH analogues on treatment outcomes. GnRH antagonist could benefit poor responders to COH, due to the lower levels of endogenous gonadotropin suppression than the agonist is able to achieve [6,9]. However, there are also results implying that these two treatments did not vary in outcomes when it comes to women who respond poorly to COH [9]. The findings on GnRH antagonist and agonist effect on COH are inconsistent. In addition, some studies suggest that there is no significant difference between the two groups when it comes to number of oocytes retrieved, and these results included women with both normal and high BMI [10]. Another study implies that the number of retrieved oocytes was in fact more favorable with the GnRH agonist treatment [5].

To predict the patient response to COH is a big challenge [11] and it is of great importance to optimize the response of the oocytes, [7] but this is far from easy [6]. Treatments must be highly individualized according to the patients’ characteristics such as age, menstrual cycle length, BMI, previous results from IVF treatment or some kind of ovarian reserve marker such as basal FSH, antral follicle count or anti-Müllerian hormone level [8]. Some of the difficulties of COH include how much of FSH to administer as well as choice of the GnRH analogue, as one fixed standard dose may not be appropriate for all patients. The goal of COH
is to provide an optimal starting dose of gonadotropins [9] and find a balance between dosing high enough to receive 8-12 good quality follicles but not so high as to cause the critical condition called OHSS, (ovarian hyperstimulation syndrome) [11]. Women that are highly responsive to the COH-drugs have a risk of developing OHSS. It is a serious complication associated with COH treatment and can be life threatening. The condition causes severe cystic ovarian enlargement [9] and increased capillarity permeability that causes a rapid fluid shift from the intravascular space to the extravascular space [12]. OHSS can result in thromboembolism, disturbances in the coagulations system, pulmonary failure, disturbed cardiovascular function, and renal failure [1,12]. To minimize the risk of OHSS it is necessary to try to predict the response of COH; one way to do this is to examine the women’s ovarian reserve [8].

1.3 Ovarian reserve
The ovarian reserve is unique for every woman and is defined as the remaining pool of oocytes and their quality. The factors that seem to decide the extent of the ovarian reserves extent are mainly genetic. These genetical variations can affect individual follicle density as well as the amount of oocytes one is born with. The primordial follicles contain oocytes, and while at birth women have about quarter to a half million follicles and only half of those will remain when the woman reaches menarche. The ovarian reserve will decline with increasing age, as the oocytes decrease in both number and quality. When the ovarian reserve is used up menopause occurs.

To minimize the risks and increase the chances for a successful IVF, it is very important to evaluate the ovarian reserve. To do this there are a several of different ORTs (ovarian reserve tests) [1]. It has been shown that ORTs with AFC (antral follicle count) and AMH (anti-Müllerianhormone) are preferable due to their favorable analytical methods and performance [9,13,14].

The ORTs with AFC is performed via a vaginal ultrasound, in which the performer subjectively counts the antral follicles. Only follicles that are 2-10 mm in size and are mature enough to contain fluid in the antrum will be counted [1,9]. AMH on the other hand is a glycoprotein that is produced from growing pre-antral and small antral follicles and secreted from the granulosa cells. The serum level of AMH increases up to age 25 and then decreases with increasing age. AMH is considered to be a reliable measurement for the adult woman when it comes to the ovarian reserve. The AMH levels are usually analyzed with an ELISAs (enzyme-linked immunosorbent assays) [1,15].
There have been several studies to see if there are any differences between these two tests and their significance in clinical practice. There are several studies comparing the two methods; a review from 2014 suggests that AMH is the better of the OTRs. ACF was believed to be a weaker test due to observer and equipment bias [13]. Results of a prospective cohort study show results that suggest that both AMH as OTRs exhibit a reasonable accuracy when it comes to predicting ovarian response when using GnRH antagonist. However the study also indicates that AMH is a better predictor for high compared to low ovarian responses [8].

1.4 The impact of BMI on COH

It is known today that weight and body mass are important parameters in determining the potential of a woman’s reproductive system [10,16]. Being overweight is well known to be a high risk factor for menstrual dysfunction and anovulation [17]. Obesity has a negative impact on the woman’s reproductive system on several levels including secretion of hypothalamic gonadotropins, steroid production, disturbances in ovulation, lower conceptions rates, longer times until conception, higher rates of miscarriage and pregnancy complications [10,18].

As mentioned earlier in the introduction, BMI can be one of the factors that are taken in consideration when it comes to determining the individualized dose of FSH [8]. However, this topic is still controversial and the results vary regarding whether or not weight and BMI have an influence on ovarian response to exogenous gonadotropins [11,16].

Results of some studies indicate that there is no significant difference between groups with normal BMI and groups with high BMI, when it comes to retrieved oocytes from COH. There is also conflicting results when it comes to whether groups with higher BMI need higher gonadotropin doses: some results show that there are no significant differences between the two groups [19,20] while other studies show that the group with higher BMI needs a significantly higher doses of gonadotropins than the group with normal BMI to get a comparable result of received oocytes [10,16]. It is worth noting that these studies only had one group with high BMI, two of the studies have categorized high BMI as $\geq 25 \text{ kg/m}^2$ [10,20] and the other define high BMI as $\geq 27.9 \text{ kg/m}^2$ [19].

However, there are other results implying the opposite about the impact of BMI of received oocytes and gonadotropin dose. A review from 2007 states that overweight women had reduced number of oocytes retrieved despite the fact that they received higher doses of gonadotropin [17]. Two other retrospective studies have reported the similar results. One of these reported that obese women i.e. BMI 30.0-40.0 $\text{ kg/m}^2$, needed higher doses of gonadotropins and produced lower numbers of medium and/or large follicles for a given total
dose of gonadotropins. However, when the dose was high enough to overcome the weight effect, the total number of received follicles where comparable with normal weigh women [21]. Results of the other study suggest that obese (BMI 30-34.9 kg/m²) and morbidly obese women (BMI 35.0-40.0 kg/m²) need significantly higher start doses of gonadotropins compared to women with normal BMI (18.5-24.9 kg/m²). The obese and morbidly obese women also had significantly fewer oocytes collected [18].

All things considered, the complexity of the treatment and the variety of factors that can influence the ovarian response make the struggle understandable to find good answers between cause and effect. How BMI can influence the number of received oocytes is still debatable. However, clinical experience suggests that overweight and obese need higher doses of stimulating drugs to achieve good results on COH.

2. Objective

2.1 Aim
The aim of this project was to investigate if there is any correlation between high BMI (>25) and decreased number of retrieved oocytes after pick up, compare to women with BMI between 18.5-24.9 when undergoing COH as a part of IVF.

2.2 Hypothesis
There is a significant difference between the groups with BMI 25.0-29.0 kg/m², BMI >30.0 kg/m² and the group with BMI 18.5-24.9 kg/m² when it comes to the number of collected oocytes from COH.

2.3 Null hypothesis
There is no significant difference between any of the groups when it comes to the number of collected oocytes from COH.

3. Method and Materials
This is a retrospective cohort study. The data were collected at The Fertility Unit, Department of Gyn/Ob at University Hospital Örebro. The data are collected from patient files called Linnéfiles (Linnéfiler Fertsoft AB, Sweden), were data from IVF treatment are collected.
3.1 Subjects
The sample included data from 399 women between the ages of 20-41 years. These women were going through IVF treatment for infertility. The sample contained IVF cycles between the years 2011-2015.

3.2 Sample
We choose to study women who received their first cycle treatment for IVF during the defined time period, to exclude prior treatment bias. They were treated with recombinant FSH or hMG. 37 of the women received a GnRH agonist and 362 of them received a GnRH antagonist.

The sample only includes the patients that after COH produced enough oocytes, at least 3, to go on to and complete an oocyte pick-up. The patients that interrupted their treatment cycle due to poor follicle response or other reasons are not included in the sample.

Patients that did not have an AMH-value or had an AMH-value that was collected more than a year before start of treatment were excluded from the sample.
The ELISA analysis for the AMH-values were 20130808 exchanged to another, from Beckmans coulter ELISA to Amshlab Ultrasens AMH ELISA, which means that both ELISA methods have been used in this data.

3.3 BMI classification
The patients were divided into three groups according to the WHO’s (World Health Organization) BMI scale, BMI was calculated by the formula weight/height$^2$, (kg/m$^2$). One normal BMI group with values between 18.5-24.9 kg/m$^2$ and the other two groups with above normal BMI, were classified as overweight with a BMI criteria of 25.0-29.9 kg/m$^2$ and obese with a BMI of 30.0 ≤ kg/m$^2$

3.4 Statistics
All the patients data from the Linnéfiles were transferred into excel there all the initial data handling was made before transferred to the statistical program SPSS, that was for the statistical analyses of the data. ANOVA, an one-way analysis of variance was the test that was applied to analyze the mean value outcome in the three BMI categories for variable such as, AMH-level, total dose of stimulating FSH, age at pick up and collected oocytes at pick up.

The Dunnett t-test was applied to analyze if there were any significant relationships between the BMI categories and variables such as AMH-value, total dose of stimulating FSH,
age at pick up and total oocytes collected at pick up. Statistical significance was considered to be \( p < 0.05 \)

3.5 Ethical considerations

All the data were collected from the clinic’s Linné files in which the patient’s file is marked with an id number and only data values from the IVF treatment were available. Therefore none of the patients identifying data have been revealed.

4. Results

The patients were divided into three groups depending on their BMI. The control group consisted of the patients with normal BMI (18.5-24.9 kg/m\(^2\)) and was comprised of 245 patients, which represented 61.4 % of the sample. The other two groups were compared to the control group and were BMI classified as overweight or obese. The overweight (BMI 25.0-29.9 kg/m\(^2\)) group was made up of 101 patients and represented 25.3 % of the sample while the obese group (BMI 30.0 ≤ kg/m\(^2\)) consisted of 53 patients and represented 13.3 % of the sample.

The overweight and obese groups were compared to the group with normal BMI in variable such as AMH-value, total FHS-dose during the treatment, age and total amount of oocytes collected during the pick-up procedure. The mean values of these variables within each group are presented in table 1.

Table 1: Result of mean value from chosen variables within the three different BMI groups.

<table>
<thead>
<tr>
<th>Descriptives</th>
<th>BMI Classes</th>
<th>N</th>
<th>Mean</th>
<th>Standard Deviation</th>
<th>95% Confidence Interval for Mean</th>
<th>95 % Confidence Interval for Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>kg/m(^2)</td>
<td></td>
<td></td>
<td></td>
<td>Lower Bound</td>
<td>Upper Bound</td>
</tr>
<tr>
<td>AMH Value (ng/mL)</td>
<td>18.5-24.9</td>
<td>245</td>
<td>3.0</td>
<td>4.1</td>
<td>2.4</td>
<td>3.4</td>
</tr>
<tr>
<td></td>
<td>25.0-29.9</td>
<td>101</td>
<td>4.4</td>
<td>14.9</td>
<td>1.5</td>
<td>7.4</td>
</tr>
<tr>
<td></td>
<td>30.0≤</td>
<td>53</td>
<td>2.8</td>
<td>2.7</td>
<td>2.0</td>
<td>3.5</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>399</td>
<td>3.3</td>
<td>8.2</td>
<td>2.4</td>
<td>4.1</td>
</tr>
<tr>
<td>Total stimulating FSH dose (IU)</td>
<td>18.5-24.9</td>
<td>245</td>
<td>1849.3</td>
<td>963.4</td>
<td>1728.0</td>
<td>1971.0</td>
</tr>
<tr>
<td></td>
<td>25.0-29.9</td>
<td>101</td>
<td>1932.1</td>
<td>809.2</td>
<td>1772.3</td>
<td>2091.8</td>
</tr>
<tr>
<td></td>
<td>30.0≤</td>
<td>53</td>
<td>2263.6</td>
<td>964.4</td>
<td>1997.8</td>
<td>2529.4</td>
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<td></td>
<td>Total</td>
<td>399</td>
<td>1925.3</td>
<td>934.8</td>
<td>1833.3</td>
<td>2017.3</td>
</tr>
<tr>
<td>Age (OPU**)</td>
<td>18.5-24.9</td>
<td>245</td>
<td>31.9</td>
<td>4.7</td>
<td>31.2</td>
<td>32.4</td>
</tr>
<tr>
<td></td>
<td>25.0-29.9</td>
<td>101</td>
<td>32.0</td>
<td>4.8</td>
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<tr>
<td></td>
<td>30.0≤</td>
<td>53</td>
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<td>4.5</td>
<td>30.2</td>
<td>32.7</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>399</td>
<td>31.8</td>
<td>4.7</td>
<td>31.3</td>
<td>32.3</td>
</tr>
<tr>
<td>Total oocytes (OPU**)</td>
<td>18.5-24.9</td>
<td>245</td>
<td>10.1</td>
<td>5.7</td>
<td>9.4</td>
<td>10.9</td>
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<td>25.0-29.9</td>
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<td>5.7</td>
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<tr>
<td></td>
<td>30.0≤</td>
<td>53</td>
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<td>4.5</td>
<td>6.9</td>
<td>9.4</td>
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<tr>
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<td>9.6</td>
<td>5.6</td>
<td>9.1</td>
<td>10.2</td>
</tr>
</tbody>
</table>

**OPU= The value is taken from the day of ovarian pick-up.**
As the results from table 1 demonstrate, mean values for total oocyte pick up showed little difference in the three different BMI groups. The group with normal BMI (18.5-24.9 kg/m\(^2\)) showed higher mean value, 10.1 ±5.7 for total oocytes. The groups with higher BMI had a lower mean values for total oocytes collected: the overweight group (BMI 25.0-29.9 kg/m\(^2\)) had 9.1 ±5.7 oocytes and the obese group (BMI 30.0 ≤ kg/m\(^2\)) had 8.2 ±4.5 oocytes.

There was a marginal difference between the groups mean value then it came to age. The mean ages in the normal, overweight and obese BMI groups were 31.8 years, 32.0 years and 31.4 years respectively.

As table 1 also shows, the mean AMH-value for the overweight BMI category is higher, 4.4 ±14.9, than it is for the normal BMI category, 3.0 ±4.1 and for the obese BMI category, 2.8 ±2.7.

Using the Dunnett t-test the group with normal BMI served as a control group for comparison with the other two groups, overweight and obese. This is presented in table 2. The results from the test showed that the obesity group (BMI 30.0 ≤ kg/m\(^2\)) had a significant fewer oocytes collected compared to the group with normal BMI (18.5-24.9 kg/m\(^2\)), with a mean difference at 2.0 oocytes fewer for the obesity group than for the group with normal BMI, (95 % CI -3.9 - (-0.1) p=0.037).

The Dunnett t-test also revealed a significant difference of the total dose of stimulating FSH between the control group, with normal BMI (18.5-24.9 kg/m\(^2\)) and the BMI group rated as obese (30.0 ≤ kg/m\(^2\)). The obese BMI group received a significant higher dose (95% CI 99.7 - 728.9, p=0.007). This is presented in table 2.
Table 2: Results of significance of the variables in comparison between the BMI groups.

J=Control group, normal BMI 18.5-24.9 kg/m², I= Test groups BMI 25.0-29.9 kg/m² or 30.0 ≤ kg/m²

<table>
<thead>
<tr>
<th>Dependent Variable</th>
<th>BMI Classes (I)</th>
<th>BMI Classes (J)</th>
<th>Mean Difference (I-J)</th>
<th>Significans</th>
<th>95% Confidence Interval Lower Bound</th>
<th>95% Confidence Interval Upper Bound</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMH Value (ng/mL)</td>
<td>25.0-29.9 kg/m²</td>
<td>18.5-24.9 kg/m²</td>
<td>1.6</td>
<td>.197</td>
<td>-.6</td>
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<tr>
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<td>30 ≤</td>
<td>18.5-24.9 kg/m²</td>
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<td>.994</td>
<td>-3.0</td>
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<td>Total stimulating FSH dose (UI)</td>
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<td>-162.8</td>
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<tr>
<td></td>
<td>30 ≤</td>
<td>18.5-24.9 kg/m²</td>
<td>414.3*</td>
<td>.007</td>
<td>99.7</td>
<td>728.9</td>
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<td>Age (OPU**)</td>
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<td>.2</td>
<td>.903</td>
<td>-1.0</td>
<td>1.5</td>
</tr>
<tr>
<td></td>
<td>30 ≤</td>
<td>18.5-24.9 kg/m²</td>
<td>-.4</td>
<td>.823</td>
<td>-2.0</td>
<td>1.2</td>
</tr>
<tr>
<td>Total oocytes (OPU**)</td>
<td>25.0-29.9</td>
<td>18.5-24.9</td>
<td>-1.0</td>
<td>.222</td>
<td>-2.5</td>
<td>.5</td>
</tr>
<tr>
<td></td>
<td>30 ≤</td>
<td>18.5-24.9 kg/m²</td>
<td>-2.0*</td>
<td>.037</td>
<td>-3.9</td>
<td>-.1</td>
</tr>
</tbody>
</table>

* The mean difference is significant at the 0.05 level, p<0.05.
**OPU= The value is taken from the day of ovarian pick-up

5. Discussion

The aim of this study was to see whether BMI has an impact on the number of collected oocytes from COH in IVF. The results show that women in the obese BMI category received on average two oocytes fewer than the group with normal BMI. However, there was no significant difference between the overweight group and normal BMI group when it came to number of collected oocytes.

This study also showed a significant result in the total FSH dose. The obese category received a higher total FSH dose than the group with normal BMI. This result could, however, be explained by the fact that fertility clinicians where aware of the patients BMI when they decide the FSH dose, with higher BMI they tend to give higher FSH dose. But despite the fact that women in the obese BMI category received higher doses of FSH and had comparable mean AHM values to the normal BMI category, an indicator of a comparable ovarian reserve, they still produced fewer oocytes. These results increases the suspicions that elevated BMI could negatively impact FSH stimulation of oocytes.

Other studies support the results shown here, one of them reporting that obese and morbidly obese women needed a substantially higher FSH starting dose than the group with normal BMI, but still received significantly fewer oocytes. That study also received results showing no significance in oocyte number between the overweight BMI category and the
normal BMI category [18]. Fedorcsák et al., [22] observed an association between increases in BMI and requests for higher FSH doses but also increased risk of insufficient follicle development during ovarian stimulation and fewer oocytes collected. They suggested that being overweight or obese diminished the response of FSH stimulation.

Souter et al., [21] also found that obese women need higher FSH doses and that they produced fewer follicles per given dose, but they still reported that once the FSH dose was high enough to overcome the effect of the weight, the result of recruited follicles was comparable to that of normal weight women.

Conversely there have been other studies that imply there are no significant differences between the number of oocytes received between the normal BMI group and the group with BMI ≥ 25 kg/m². However, one study showed that BMI category with ≥ 25 kg/m² needed a higher total amount of FSH than the category with normal BMI [10]. Another study showed that there were no significant differences between the normal BMI group and the obese BMI group (>27 kg/m²) in received oocytes after having comparable FSH doses [19]. A similar study that compared one group with BMI <25 kg/m² with an other group with BMI >25 kg/m² retrieved comparable FSH doses and found no significant difference in number of oocytes between the groups, but it is worth noting that most of the patients in this study were considered to be overweight rather than obese [20].

Even if there are inconsistent results between studies as to whether or not BMI has an impact on retrieved oocytes, many studies seems to agree that obese women need higher doses of FSH for effective COH. There are theories that this could be related to an FSH resistance in obese women. This resistance could be caused by increased levels of leptin, which are present in obese women. It has been observed that leptin has an inhibitory effect on the human granulosa cells and that high concentrations of leptin could suppress the dominant follicles ability to produce estradiol [23-25].

There have also been speculations that the decreased response of FSH in obese women could depend on their increased body mass, which enhances the volume of distribution of FSH and also creates differences in absorption and metabolic clearance rate because of excess body fat [26].

One strength of our study was that the mean age were comparable between all the BMI groups. Age is one of the most important factors that influence the success of IVF. Sneed et al., [27] found in their study that high BMI played a more significant role at younger ages.
whereas BMI’s impact became minimal after the age of 36, when it came to number of retrieved oocytes and success in IVF.

Something worth noting is that the mean AMH level for the overweight BMI category was found to differ from the mean AMH value of normal and obese BMI categories, as shown in table 1. The overweight BMI category has a higher AMH mean value on 4.4 (ng/mL) and also a high SD (±14.9), this suggests that in this group there could be patients who respond strongly to COH. It also opens up the speculation that there could be more patients with PCOS (polycystic ovarian syndrome) in this group. PCOS is an endocrine disorder among women, leading to ovulatory dysfunction. Women with PCOS tend to have higher levels of AMH than normal women and are commonly overweight [28,29]. Studies have shown that PCOS increases the possibility that these patients will respond strongly to FSH doses and therefore produce more oocytes [30].

The relatively high AMH mean value seen in the overweight group might compensate for the negative effect elicited by their weight which raises the question of whether this group was really suitable for testing the impact of high BMI on numbers of collected oocytes. Therefore, the results for number of collected oocytes for the overweight group needs to be challenged.

There are several limitations with this study that must be taken in consideration when evaluating the results.

The study had a small sample size and the groups were of unequal sizes. The obese BMI category group contained a low number of patients compared to the control group with normal BMI. Other limitations were that the patients received different doses of FSH at the start of the stimulation, and different IVF protocols i.e. a small amount of the sample received GnRH agonist (37 women) and the other GnRH antagonist. The two different ELISA analyses that have been used to measure the AMH-levels must also be taken into consideration.

In this study BMI was chosen as the marker for body weight and fat tissue, but BMI may not be a suitable marker for all people as it does not differentiate between fat and muscles tissue. There was also no distinction made between patients with PCOS and the non-PCOS patients in this study.

Even if this study got a significant results, which showed that obese women collects fewer oocytes, the question that must be asked is whether this is of clinical significance for the
individual patient. For some women who are poor responders it could be crucial, but for those who respond well this might not be of any clinical importance. However, receiving more oocytes also provides the opportunity to freeze more embryos that could be valuable in the future for the patient. With the possibility that being overweight or obese could impair the IVF process, and bearing in mind all the other damage it can do to fertility, the clinics should continue to encourage women to lose weight to optimize their chances of conception.

This result may be considered to be vague, when taking the study’s limitations into account, but the possibility that BMI could have an impact on received oocytes is still there. Therefore, more studies are required to address these relevant questions in the future. To get more certain results a prospective studies should be performed, with larger sample sizes and with more standardized conditions for the patients, i.e. all the patients have the same FSH doses and IVF protocols.

6. Conclusion
In this study we found that obese women received fewer oocytes in COH, even if they received significantly higher total doses of FSH, compared to the women with normal BMI. There were, however, some limitations in this study making the results uncertain, regarding whether or not overweight and obesity are obstacles in COH. Due to the complexity of this topic, investments in larger and more advanced studies are required to elucidate these important clinical questions.

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8. References


