Effect of obesity on ovarian reserve parameters in mid-reproductive age women [version 1; referees: 1 approved, 1 approved with reservations]

Hanan Altaee¹, Zaid Abdul Majeed Al-Madfai², Zainab Hassan Alkhafaji³

¹Physiology Department, College of Medicine, Babylon University, Babylon, Iraq
²Physiology Department, College of Medicine, Baghdad University, Baghdad, Iraq
³Department of Gynecology, College of Medicine, Kufa University, Kufa, Iraq

Abstract
Background: The initiation and maintenance of reproductive functions are related to an optimal body weight in women. Body weight affects the ovarian reserve, which is basically an estimate of how many oocytes (eggs) are left in the ovaries.

Objective: To study the relationship between obesity and serum and ultrasound markers of ovarian reserve in mid-reproductive age women (21–35 years old).

Patients and methods: Twenty participants (“obese”) had a body mass index (BMI) of 30 to 35 kg/m² and another 20 participants (“non-obese”) had a BMI 20–29 kg/m². The obese women had a mean age of 27.9 years and the non-obese women had a mean age of 29.5 years. Blood samples were collected from all participants, anthropometric measurements were calculated, and transvaginal ultrasonography was performed to measure the antral follicle count (AFC) during the early follicular phase. The blood samples were assayed for antimüllerian hormone (AMH), follicle-stimulating hormone (FSH) and estradiol (E2).

Results: There was no significant difference between the two groups regarding ovarian reserve markers and there is no significant correlation between these markers and BMI, except for serum E2 in the obese group.

Conclusion: Obesity has no effect on the levels of serum FSH, AMH, or AFC indicating that obesity is unlikely to affect ovarian reserve in the mid-reproductive age group.

Corresponding author: Hanan Altaee (hanantaee@yahoo.com)

How to cite this article: Altaee H, Al-Madfai ZAM and Alkhafaji ZH. Effect of obesity on ovarian reserve parameters in mid-reproductive age women [version 1; referees: 1 approved, 1 approved with reservations] F1000Research 2012, 1:43 (doi: 10.12688/f1000research.1-43.v1)

Copyright: © 2012 Altaee H et al. This is an open access article distributed under the terms of the Creative Commons Attribution Licence, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Grant information: This work had been funded by the Iraqi Ministry of Higher Education and Scientific Research. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing interests: No competing interests were disclosed.

Introduction

The initiation and maintenance of reproductive functions are related to an optimal body weight in women. Underweight (BMI under 19 kg/m²), as well as overweight (BMI over 25 kg/m²) and obesity (BMI over 30 kg/m²) are associated with an increased risk of certain disorders. In addition to conditions such as diabetes mellitus, hypertension, cardiovascular disease, pancreatitis, and musculoskeletal diseases, obese women are more likely to experience reproductive problems, which include menstrual disorders, infertility, and maternal complications during pregnancy. Overweight women, as distinct from obese women, are known to be at higher risk of menstrual dysfunction and anovulation. The mechanisms by which obesity causes or exacerbates subfertility are manifold, one suggested theory that Hyperandrogenemia results in granulosa cell apoptosis, while peripheral conversion of androgens to estrogen in adipose tissue inhibits gonadotrophin secretion, or possibly due to altered secretion of pulsatile GnRH. Obesity is also associated with polycystic ovary syndrome (PCOS), which is a heterogeneous condition characterized by oligo or anovulation, hyperandrogenism, menstrual irregularities and subfertility. Overweight and obese subfertile women have a reduced probability of successful fertility treatment and their pregnancies are associated with more complications and higher costs. Weight loss regularizes menstrual cycles and increases the chance of spontaneous ovulation and conception in anovulatory overweight and obese women. In women undergoing assisted reproductive technology, being obese or overweight has been associated with a need for higher doses of gonadotropins, increased cycle cancellation rates, and oocytes retrieved than in women of normal weight. Lower rates of embryo transfer, pregnancy, and live birth have also been reported in these women, as well as higher miscarriage rates.

The term “ovarian reserve” refers to the quantity and quality of a woman’s current reservoir of oocytes, and is closely associated with reproductive potential. It is an indirect measure of a woman’s reproductive age. Over the past two decades, a number of tests of ovarian reserve have been used to determine follicle number and quality and to predict the outcome of assisted reproduction procedures. The woman’s age and assays of serum FSH in the early follicular phase were among the earliest and most useful parameters used for evaluation of ovarian reserve. Several ultrasound parameters have been used for evaluation of ovarian reserve, including ovarian volume and the antral follicle count (AFC), with varying degrees of reliability. Recently, serum antimullerian hormone (AMH) levels have been introduced as a novel measure of ovarian reserve. AMH is a product of the granulosa cells in preantral and antral follicles. Serum AMH levels decline with age and are correlated with the number of antral follicles and the ovarian response to hyperstimulation.

Few studies have evaluated the effect of obesity on ovarian reserve. The present study was conducted to examine the effect of obesity on ovarian reserve in women in the mid-reproductive age group. We assessed the effect of obesity on accepted markers of ovarian reserve, specifically levels of basal FSH, E2 and AMH, as well as the ultrasound marker of AFC.

Patients and methods

This study was conducted in the fertility center of Al-Sader Medical City, in Al Najaf province/Iraq, from December 2010 to March 2011. All participating women gave written informed consent before beginning the study. We performed a cross-sectional comparative study of two age-matched groups of 20 participants (group A, obese women) and 20 participants (group B, non-obese women) BMI of 20–29 kg/m² with mean age 27.9 years, and the other 20 participants (group B, non-obese women) BMI of 20–29 kg/m² with mean age of 29.5 years, these serve as a control group. Blood samples were collected from all participants, and transvaginal ultrasonography was performed to measure the AFC during the early follicular phase. The blood samples were assayed for AMH, follicle-stimulating hormone (FSH) and estradiol (E2). Thyroid function test and serum testosterone as well as dehydroepiandrosterone serum levels were assayed. The women were seeking treatment for infertility because of tubal factor proved by hysterosalpingography or laparoscopy.

To meet the inclusion criteria, women had to be in the mid-reproductive age (20–35 years) according to Stages of Reproductive Aging Workshop (STRAW), with an intact uterus and ovaries and to have a regular menstrual cycles for the previous three months, normal thyroid function and no evidence of hyperandrogenism by examination or hormonal assessment. Exclusion criteria were: current use of hormones or drugs that may affect ovarian function, smoking, pregnancy, lactation, previous ovarian surgery, clinical or ultrasound criteria suggesting polycystic ovarian syndrome or endometriosis, or any medical condition that might affect ovarian function. All participating women underwent a comprehensive history and thorough physical examination, calculation of BMI, assays of serum FSH, E2 and AMH, and had a transvaginal ultrasound examination for assessment of AFC. For calculation of BMI, height and weight were measured using the same scale for all participants. BMI was determined by the ratio of weight in kg divided by the height squared in metric units. Blood samples were withdrawn from the antecubital vein on cycle day 2, 3 of the menstrual cycle in all women. All samples were centrifuged at 2000 g for 15 minutes. Serum was separated and stored at -20°C until assayed. Measurement of serum FSH was performed using Mini VIDAS method (bioMérieux France). Inter-assay Coefficient of Variance% (CV%) 4.7; Intra-assay CV% 5.9, lower limit of detection ≤ 0.1 mIU/ml within

Editorial note:

Please note that the refereeing status of this article was changed from “indexed” to “[v1; ref status: approved 1, approved with reservations 1]”.

When this article was first published, F1000Research was still in its beta phase; during this period articles that received any two of “Approved” or “Approved with Reservations” statuses from the reviewers were labelled as “indexed”. When the journal was formally launched in January 2013, the requirements for indexing were tightened, and only articles that are given either two “Approved” or one “Approved” plus two “Approved with Reservations” statuses by the reviewers are labelled “indexed”. The new criteria for “indexing” can still be met in the future if a new revised version receives the necessary approval status from the reviewers.
Transvaginal ultrasound was performed during the early follicular phase (cycle day 2 or 3), by means of a transvaginal ultrasound scanner (Philips 11®E), with a 5 MHz probe. In each ovary, the total number of small follicles (2–8 mm) was counted. The total follicle count was the sum of the follicle counts in each ovary.

Statistical analysis: descriptive statistics were expressed as mean and standard deviation. Student’s t-test was used to compare groups. Significant relationships between study parameters were evaluated by Pearson’s correlation coefficient. P-values < 0.05 were considered to be significant. Statistical analysis was performed using SPSS version 17.

Results
The 20 women in group A (obese women) had a mean BMI of 32.45 kg/m², with a range of 30 to 35 kg/m², and the 20 non-obese women (group B) had a mean BMI of 24.9 kg/m², with a range of 20 to 29 kg/m². The mean age in the obese group was 27.9 years; with a range of 22 to 35 years. The mean age in the non-obese group was 29.5 years; with a range of 21 to 35 years. The mean BMI in the obese group (32.45 ± 1.57) was significantly higher than that of the non-obese group (24.9 ± 2.57) (P < 0.05). There was no significant difference between the two groups regarding age, serum levels of AMH or FSH, E2, or AFC. These data are shown in the (Table 1). There was no significant correlation between BMI and serum AMH, serum FSH and AFC in both groups; but significant positive correlation at P < 0.05 level was found between BMI and serum E2 in group A only, these results are shown in (Table 2).

Discussion
Obesity is an increasingly prevalent health hazard and causes many disorders of female reproduction23,24. In fact, overweight women have a higher incidence of menstrual dysfunction, anovulation, and infertility than other women of reproductive age25, even though altered pulsatile gonadotropin secretion is a well-defined mechanism in obese patients26.

This study was performed in obese and non-obese women25 with normal menstrual cycles who were referred to fertility center because of tubal factor infertility. Our aim was to examine the possible effects of body mass on some ovarian reserve markers, namely FSH, E2, AMH plasma levels and the number of ovarian follicles in the early follicular phase. The women included were normally ovulating obese and non-obese, with regular menstrual cycles and with neither clinical nor hormonal signs of hyperandrogenism in their mid-reproductive age.

Several studies have suggested a negative effect of obesity on parameters of ovarian reserve. De Pergola and his coworkers suggested that overweight and obese fertile women, in comparison with women of normal weight, have lower serum levels of FSH, LH, inhibin B, and estradiol in the early follicular phase, with a possible direct inhibitory effect of body mass on gonadotropin and estradiol production, independent of age27. The difference between their study and our findings may be attributed to selection of BMI of the control group which was normal (BMI < 25 kg/m²), compared to our control group which included BMI > 25 kg/m². Other investigators reported lower levels of AMH in obese women compared with normal weight women in the late reproductive age28. However, these studies documented that obesity had no effect on ovarian follicle count. They suggested that lower levels of AMH in obese late-reproductive age women result from physiologic processes other than decreased ovarian reserve27. Our results showed that there are no significant differences in serum levels of FSH, E2, AMH, and AFC between obese and non-obese women. There was no significant correlation between BMI and the serum or ultrasound markers of ovarian reserve. Accordingly, we are suggesting that obesity may have limited effect on ovarian reserve in mid-reproductive age women.

The fact that our results showed no effect of obesity on AMH levels, contrary to other studies, may be related to factors in our study population and limitations in other reports. Our group of obese women was limited to women with a BMI between 30 and 35 kg/m². We did not include morbidly obese patients because we thought that this specific group of women may have a different endocrine profile that may not apply to women with lesser obesity.

In a study of women with polycystic ovary syndrome by Pigny and his team, they found that AMH levels were lower in obese than

### Table 1. The studied parameters in the two groups.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group A (obese women)</th>
<th>Group B (non-obese women)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>27.9 ± 4.29</td>
<td>29.50 ± 4.76</td>
<td>NS</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>32.45 ± 1.57</td>
<td>24.9 ± 2.57</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>AMH (ng/ml)</td>
<td>3.06 ± 1.49</td>
<td>2.83 ± 3.51</td>
<td>NS</td>
</tr>
<tr>
<td>FSH (mIU/ml)</td>
<td>5.56 ± 2.12</td>
<td>5.63 ± 2.53</td>
<td>NS</td>
</tr>
<tr>
<td>E2 (pg/ml)</td>
<td>40.64 ± 16.16</td>
<td>40.11 ± 19.53</td>
<td>NS</td>
</tr>
<tr>
<td>AFC</td>
<td>7.5 ± 1.61</td>
<td>7.3 ± 3.61</td>
<td>NS</td>
</tr>
</tbody>
</table>

The values are expressed as mean ± SD.
non-obese women, but the difference was not statistically significant. Another study suggested no correlation between BMI and AMH in women with polycystic ovary syndrome and control subjects. These data may support our findings. We did not find an effect of obesity on AFC, which has been suggested by others. This supports our impression of a limited effect of obesity on ovarian reserve.

Zaidi and his colleagues showed that ovarian volume decreases with an increase in the BMI, indicating the possible decrease in fertility with an increase in a woman’s weight; their study group included normal weight and overweight, and includes a higher-age study group than ours. This decrease may be due to age effect rather than BMI. They didn’t find any correlation between BMI and AFC, which is in consistent with our study results. In a study conducted in Tehran where 115 fertile women were included of a different age group (25–45 years old), they found that BMI had moderate positive correlation with FSH and a moderate negative correlation with estradiol and AFC, but after adjustment of age, BMI as an independent factor had no effect on ovarian reserve markers, a finding which supports our results.

The significant positive correlation of BMI with estrogen in obese women may be attributed to the contribution for estrogen from the conversion of androgens to estrogens by aromatase in adipose tissue, or may be due to subtle undetected lack of insulin that increases the blood cholesterol concentration. These effects are probably caused mainly by changes in the degree of activation of specific enzymes responsible for the metabolism of lipid substances including cholesterol, which is the precursor of estrogen. The difference between our finding and that found by other researchers may be attributed to ethnic difference or life style factors. The negative correlation between BMI and AMH have been confirmed by Pingy et al. but it doesn’t prove to be significant.

Conclusion
Obesity doesn’t have an effect on the selected parameters of ovarian reserve among our cohort of mid-reproductive age women. However, this should be verified by larger studies with clear distinctions between normal, overweight, obese, and morbidly obese women, and between groups of different age groups.

Author contributions
Hanan Altaee is the principal author who designed and implemented the study, and conducted the bulk of the research. Zeid Almadfa supervised the work and aided with the statistical analysis. Zainab Alkhafaji provided assistance with participant selection and conducted any vaginal ultrasound examinations.

Competing interests
No competing interests were disclosed.

Grant information
This work had been funded by the Iraqi Ministry of Higher Education and Scientific Research.

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Acknowledgments
We would like to thank all the staff of fertility centre in Al-Sader teaching medical city/Al-najaf/Iraq, in particular, the hormonal analysis lab.

References


Open Peer Review

Current Referee Status: ✔️ ❓

Version 1

Referee Report 29 January 2013

doi:10.5256/f1000research.219.r741

Angelique Goverde
Department of Reproductive Medicine and Gynaecology, University Medical Centre Utrecht, Utrecht, Netherlands

This is a cross-sectional comparative study of two age-matched groups, each of 20 participants, the first being obese (BMI 30-35 kg/m²), the second (control) group with BMI 20-29 kg/m², in which the effect of obesity on markers of ovarian reserve in the early follicular phase was investigated. Cases and controls were attending the fertility clinic for tubal infertility and had regular menstrual cycles. Student’s t test was used to compare groups and Pearson’s correlation coefficient was used to evaluate relationships between study parameters.

No differences between groups were found for AMH, FSH, E2 and antral follicle count (AFC); no correlation was found between BMI and AMH, FSH and AFC, but a significant positive correlation was found between BMI and E2.

My main concern is that the design and the study size of the work was insufficient to draw any conclusion whatsoever. No sample size calculations were reported, neither was type B error. Although BMI in the study cases was significantly higher than in control cases, the BMI range of the control group included overweight women as well, thus limiting the contrast between groups in this regard.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Competing Interests: No competing interests were disclosed.

Referee Report 07 November 2012

doi:10.5256/f1000research.219.r355

Richard A. Anderson
MRC Human Reproductive Sciences Unit, The Queen's Medical Research Institute, Edinburgh, UK

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Competing Interests: No competing interests were disclosed.