Obesity Index That Better Predict Ovarian Response: Body Mass Index, Waist Circumference, Waist Hip Ratio, or Waist Height Ratio in Women Undergoing ICSI : A Pilot Study

Original Article

*Aly Elyan Khalaf Allah, Sherif Fathy Elmekkawi, Ahmed Mohammed ElKotb, Ahmed Hamed Elmetwalli Megahed**

Department of Obstetrics and Gynecology, Faculty of Medicine, Ain-Shams University, Cairo, Egypt

ABSTRACT

Objective: This study is designed to assess the accuracy of Body Mass Index, waist circumference, waist Hip Ratio or Waist Height Ratio as a predictor of ovarian response in women undergoing ICSI.

Patients and Methods: This Pilot study was done at Clinical IVF and ART unit at Faculty of Medicine, Ain-Shams University Hospital, Number of Participant women 150.

Results and Conclusion: The anthropometric measures, only the waist circumference, waist/hip ratio and waist/height ratio were related to ovarian response (*p-value* = 0.014, 0.004 and 0.020, respectively) and to the occurrence of clinical pregnancy (*p-value* = 0.017, 0.030 and 0.010, respectively). The measures, however, were modest predictors for either outcome. A waist circumference ≤ 0.81 cm could predict good ovarian response with a sensitivity of 35% and specificity of 100% (AUC = 0.656) and a waist circumference >98 cm could predict clinical pregnancy with a sensitivity of 61% and specificity of 80% (AUC = 0.609). A waist/hip ratio ≤0.82 could predict good ovarian response with a sensitivity of 62.4% and specificity of 68% (AUC = 0.652) and a ratio >0.84 could predict clinical pregnancy with a sensitivity of 56.3% and specificity of 70.9% (AUC = 0.612).On the other hand, a waist/height ratio ≤0.54 could predict good ovarian response with a sensitivity of 48% and specificity of 92% (AUC = 0.651), while a waist/height ratio >0.62 cm could predict clinical pregnancy with a sensitivity of 61% and specificity of 80% (AUC = 0.609).

Key Words: Body mass index, waist circumference,waist hip ratio, waist height ratio, ICSI

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Corresponding Author: Ahmed Hamed Elmetwalli Megahed, Department of Obstetrics and Gynecology, Faculty of Medicine, Ain-Shams University, Cairo, Egypt,**Tel.:** 01012476666, **E-mail:** megahedahmed741@gmail.com

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INTRODUCTION

Obesity is an increasingly serious health concern worldwide and its association with many diseases has been demonstrated. Obesity as it relates to infertility is also being studied. The effects of obesity on ovarian reserves are being debated. While some studies reveal negative effects of obesity on ovarian reserves[1,2], others reveal conflicting results[3].

All these studies used body mass index (BMI) to determine obesity. Although it is the most commonly used parameter to measure obesity, BMI does not provide an accurate measure of a person's body composition, including body fat[4]. There seems to be an obesity paradox as some studies have shown unexpected beneficial effects of obesity on cardiovascular diseases. Some researchers later showed that WHR (Waist Hip Ratio) and wrist circumference are better predictors of cardiovascular events[5]. It was concluded that some obese people are metabolically healthy, other normal weight people might be metabolically obese[6]. This might be either because of the body fat content or the body fat distribution of individuals.

In a study of menopausal women, it was demonstrated that central adiposity is a stronger cardiac risk factor compared to peripheral adiposity[7].

These conflicting findings result in our hypothesis that the content and distribution of body fat might affect ovarian response more than BMI, Bioelectrical impedance analysis (BIA) is noninvasive, easy and radiation-free compared to the dual energy X-ray absorptiometry (DEXA) technique used to measure fat distribution in the body. BIA has been demonstrated to be an effective method to estimate total abdominal fat[8].

Previously, it was demonstrated that BIA can be used to accurately estimate body fat distribution, and the results correlate well with DEXA results, except for very obese women (BMI > 35)[9].

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Only morbid obesity was shown to have an effect on clinical pregnancy outcomes and IVF success in obese and overweight women was comparable to that of normal weight women[10].

AIM OF THE WORK

This study is designed to assess the accuracy of Body Mass Index, waist circumference, waist Hip Ratio or Waist Height Ratio as a predictor of ovarian response in women undergoing ICSI.

PATIENTS AND METHODS

Study Setting was done at Clinical IVF and ART unit at Faculty of Medicine, Ain-Shams University Hospital.

Type of the study:

- A Pilot study.
- Number of Participant women: 150

Recruitment and randomization:

During the pre-selection phase (after admission into the IVF Unit at Ain-Shams University hospital) inclusion and exclusion criteria were applied.

Suitable women invited to participate in the study then a signed and informed consent will be obtained from them. When the patient's consent is obtained, they are included into the study.

Patients:

- After obtaining the consent of patients, their sociodemographic information and medical histories were recorded.
- The anthropometric measurements of all women were taken when they were in the early follicular phase of menstruation. The measurements were taken in the morning when the patients were in a fasting state, according to the International Standards for Anthropometric Assessment [11].
- A gynecologist examined the patients when they were in the early follicular phase of their menstrual cycle using transvaginal ultrasonography. Their AFC will be noted.
- The patients' height, weight, waist and hip circumferences, were measured. Next, their BMIs and WHRs calculated.
- BMI was calculated as weight in kilograms divided by height in square meters. According to the World Health Organization (WHO), overweightness is defined as a BMI > 25 kg/m2, and obesity is defined as a BMI > 30 kg/m2 [12].
- Waist circumference was measured at the level of the umbilicus while patients were standing, and hip circumference was measured at the broadest part of the hip and height will be measured[13].
- WHR was calculated by dividing waist circumference by hip circumference. A WHR = 0.85 will be accepted as normal and a WHR > 0.85 will be accepted as high.
- Waist height ratio is defined as their waist circumference divided by their height, both measured in the same units[14].
- All women were exposed to agonist ovarian stimulation protocol (long protocol).
- Then oocytes retrieved 36 hours after triggering by BHCG.
- This Pilot study consists of 150 participant women were preparing to do ICSI.

Data collection, management and analysis:

Data Collection Enrollment (recruitment) Data (Patient Characteristics) [Case Record Form (CRF)]:

During visit 1, all patients were undergoing complete clinical examination and detailed medical history will be obtained. Each patient had a Case Record Form (CRF) in which the following data will be recorded.

- Patient number (according to the randomization schedule).
- Age, BMI, waist hip ratio, waist circumference and waist height ratio.
- Past medical and surgical history.

Ethical approval and written informed consent:

An approval of the study was obtained from Ain-Shams University academic and ethical committee. Every patient signed an informed written consent for acceptance of the study.

Subject confidentiality:

All evaluation forms, reports and other records did not include unique personal data to maintain subject confidentially.

Sample Size Calculation:

The required sample size has been calculated using the Power Analysis and Sample Size Software (PASS©) version 11.0.10 (NCSS©, LLC. Kaysville, Utah, USA).

Since there is currently no adequate information regarding the expected strength of correlation among BMI, waist/hip ratio, waist circumference, waist height ratio and the number of oocytes retrieved, the current pilot study targeted an effect size that could be clinically relevant.

So, it is estimated that a sample of 150 patients achieved a power of 90% (type II error, 0.1) to detect statistical significance for a correlation coefficient of 0.5 with a confidence of 99% (type 1 error, 0.01) using a two-sided Pearson product-moment correlation test.

The null hypothesis is that there is no correlation between the waist/hip ratio and the number of oocytes retrieved (i.e., correlation coefficient equals zero). The alternative hypothesis is that there is moderate correlation between the waist/hip ratio and the number of oocytes retrieved, and the correlation coefficient equals 0.5.

A correlation coefficient of 0.5 has been chosen as it could be regarded as a clinically relevant effect size to seek in this pilot study.

Statistical Methods:

Data were collected, tabulated, then analyzed using IBM© SPSS© Statistics version 22 (IBM© Corp., Armonk, NY).

Normally distributed numerical data were presented as mean and SD, and skewed data as median and inter quartile range. Qualitative data will be presented as number and percentage.

Comparison of normally distributed numerical data was done using the unpaired Student t test. Skewed data were compared using the Mann-Whitney U test. Categorical data will be compared using the chi-squared test or Fisher's exact test, when appropriate.

Correlations between numerical variables were tested parametrically using the Pearson product-moment correlation, or non-parametrically using the Spearman rank correlation, as appropriate.

A two-sided *p-value* of <0.05 were considered statistically significant.

The predictive value of obesity indices and other relevant variables was examined using receiver-operating characteristic (ROC) curve analysis was. The area under the ROC curve (AUC) is interpreted as follows: *P-values* <0.05 were considered statistically significant.

RESULTS

The results showed variables as age, height, waist circumference, hip circumference, BMI, hormonal profile, AFC, duration of HMG, number of ampoules, number of follicles, E2 at day of HCG and number of M2 oocytes retrieved impact on ovarian response (Table 1).

The study also showed comparison of patients with poor or good ovarian response (Table 2).

The study also revealed correlation between obesity indices and other numerical variables (Table 3).

Table 1: Characteristics of the study population: Numerical data

					Percentiles		
Variable	Mean	SD	Min.	Max.	25th p.	Median	75th p.
Age (years)	30	4	23	39	28	31	33
Weight (kg)	77	11	48	108	70	75	86
Height (cm)	159	5	150	169	155	159	163
BMI (kg/m2)	33.5	12.0	17.8	85.0	26.9	30.7	37.5
Waist circumference (cm)	91	11	70	119	80	90	101
Hip circumference (cm)	111	10	91	135	103	112	116
Waist/hip ratio	0.81	0.08	0.63	0.96	0.77	0.81	0.87
Waist/height ratio	0.57	0.08	0.42	0.77	0.50	0.56	0.64

Duration of marriage (years)	6	3	1	16	3	5	7
Duration of infertility (years)	5	3	1	14	3	4	6
FSH (IU/l)	6.6	1.7	3.2	13.0	5.5	6.3	7.1
LH (IU/l)	5.7	2.1	2.0	11.9	4.8	5.2	6.0
E2 (ng/dl)	41	22	5	102	28	32	51
PRL (ng/ml)	17.5	6.9	0.8	45.0	13.5	16.0	20.0
TSH (IU/l)	2.5	1.9	0.5	15.0	1.5	2.0	2.6
AFC on right side	7	3	2	15	4	5	8
AFC on left side	6	3	2	15	4	5	7
Total AFC	13	6	5	30	8	11	16
Average AFC	6	3	3	15	4	5	8
Duration of HMG treatment (days)	12	2	9	16	10	11	13
Dose of HMG treatment (ampoules)	42	15	14	72	33	42	50
Number of follicles >14 mm in diameter	7	3	2	14	5	7	10
Number of follicles ≤14 mm in diameter	4	3	0	12	1	3	4
Total number of follicles	11	5	2	21	7	10	15
E2 on hCG day (ng/dl)	1886	741	380	3200	1300	2000	2600
Day of oocyte retrieval	13	2	11	18	12	13	14
Number of retrieved M2 oocytes	7	4	1	20	4	7	10

SD = standard deviation, Min. = minimum, Max. = maximum, 25th p. = 25th percentile, 27th p. = 27th percentile.

Table 2: Comparison of patients with poor or good ovarian response: Numerical variables

	Poor ovarian response (n=25)		Good ovarian response (n=125)				
Variable	Mean	SD	Mean	SD	Difference	95% CI	*p-value**
Age (years)	30.9	1.5	30.4	4.4	-0.5	-2.3 to 1.2	0.557
Weight (kg)	76.0	5.2	77.2	12.3	1.2	-3.8 to 6.2	0.636
Height (cm)	158.5	3.5	158.6	5.2	0.1	-2.0to 2.2	0.917
BMI (kg/m2)	30.3	2.9	34.1	13.0	3.9	-1.3 to 9.1	0.142
Waist circumference (cm)	96.1	8.5	90.0	11.7	-6.1	-11.0 to -1.2	0.014
Hip circumference (cm)	111.9	4.4	111.3	11.2	-0.6	-5.1 to 3.9	0.781
Waist/hip ratio	0.85	0.08	0.80	0.08	0.50	-0.02 to -0.08	0.004
Waist/ height ratio	0.60	0.05	0.56	0.08	-0.04	-0.071 to -0.006	0.020
Duration of marriage (years)	6.0	3.1	5.5	3.1	-0.6	-1.9 to 0.7	0.392
Duration of infertility (years)	6.0	3.1	4.7	2.7	-1.4	-2.6 to -0.2	0.025
FSH (IU/l)	6.9	1.5	6.5	1.7	-0.4	-1.1 to 0.3	0.262
LH (IU/l)	3.7	1.3	6.1	2.0	2.4	1.6 to 3.2	<0.0001
E2 (ng/dl)	51.2	16.8	38.4	21.8	-12.8	-21.9 to -3.7	0.006
PRL (ng/ml)	15.7	2.4	17.8	7.5	2.2	-0.8 to 5.1	0.154
TSH (IU/l)	3.7	1.4	2.2	1.9	-1.5	-2.3 to -0.7	<0.001
AFC on right side	5	2	7	3	2	1 to 4	0.003

AFC on left side	5	2	7	3	2	0 to 3	0.008
Total AFC	9	3	13	6	4	1.4 to 7	0.003
Average AFC	5	2	7	3	2	1 to 3	0.003
Duration of HMG treatment (days)	12	2	11	2	0	-1 to 0	0.448
Dose of HMG treatment (ampoules)	32	8	44	15	12	6 to 18	<0.001
Number of follicles >14 mm in diameter	5	2	8	3	3	1 to 4	<0.0001
Number of follicles ≤14 mm in diameter	1	1	4	3	3	1 to 4	<0.001
Total number of follicles	6	3	12	5	5	3 to 7	<0.0001
E2 on hCG day (ng/dl)	1105.2	557.0	2042.6	672.5	937.4	653.8 to 1221.1	<0.0001
Day of oocyte retrieval	13	1	13	2	0	-1 to 1	0.679
Number of retrieved M2 oocytes	2	0	8	3	6	5 to 7	<0.0001

Data are mean and standard deviation (SD).
95% CI = 95% confidence interval.
*Unpaired t test.

Table 3: Correlation between obesity indices and other numerical variables

		Weight	Height	BMI	WC	HC	WHR	WHtR
Age	r	.515**	-0.074	0.052	.578**	.473**	0.115	.555**
	p-value	<0.001	0.371	0.524	<0.001	<0.001	0.161	<0.001
Duration of marriage	r	.178*	0.050	-0.131	.260**	0.003	.230**	.239**
	p-value	0.030	0.541	0.110	0.001	0.971	0.005	0.003
Duration of infertility	r	.191*	0.076	-0.089	.322**	0.050	.272**	.295**
	p-value	0.019	0.356	0.279	<0.001	0.547	0.001	<0.001
FSH	r	.334**	0.080	0.056	.278**	.221**	-0.075	.246**
	p-value	<0.001	0.332	0.498	0.001	0.006	0.360	0.002
LH	r	0.008	-0.079	-0.067	-.377**	0.086	0.084	-.343**
	p-value	0.920	0.338	0.417	<0.001	0.296	0.306	<0.001
E2	r	.268**	0.145	-0.056	.264**	.365**	.170*	.208*
	p-value	0.001	0.077	0.499	0.001	<0.001	0.038	0.011
PRL	r	0.115	-0.037	-0.088	0.039	.269**	0.016	0.025
	p-value	0.161	0.653	0.284	0.637	0.001	0.849	0.764
TSH	r	-0.044	0.059	-0.138	0.003	0.134	-0.088	-0.011
	p-value	0.592	0.474	0.093	0.973	0.101	0.282	0.894
Total AFC	r	-.355**	-.215**	-0.043	-.541**	-.169*	-0.042	-.470**
	p-value	<0.001	0.008	0.601	<0.001	0.039	0.608	<0.001
Duration of HMG treatment	r	0.102	0.155	0.107	0.079	-0.111	0.113	0.038
	p-value	0.213	0.058	0.194	0.337	0.178	0.169	0.641
Dose of HMG treatment	r	.476**	0.157	.325**	.457**	.385**	0.082	.387**
	p-value	<0.001	0.055	<0.001	<0.001	<0.001	0.320	<0.001
Number of follicles >14 mm in diameter	r	-0.047	.198*	0.153	-.252**	0.051	0.131	-.288**
	p-value	0.565	0.015	0.061	0.002	0.538	0.109	<0.001

Number of follicles ≤14 mm in diameter	r	-.168*	-0.107	-0.040	-.363**	-0.101	-0.068	-.322**
	p-value	0.039	0.194	0.623	<0.001	0.221	0.411	<0.001
Total number of follicles	r	-0.137	0.051	0.067	-.393**	-0.035	0.034	-.387**
	p-value	0.094	0.535	0.413	<0.001	0.675	0.678	<0.001
E2 on hCG day	r	-.200*	.206*	0.131	-.410**	-.173*	0.031	-.431**
	p-value	0.014	0.012	0.109	<0.001	0.034	0.708	<0.001
Day of oocyte retrieval	r	.177*	0.024	.189*	0.089	0.008	0.124	0.077
	p-value	0.030	0.772	0.021	0.278	0.921	0.130	0.349
Number of retrieved M2 oocytes	r	0.040	.452**	0.098	-0.149	-0.156	0.065	-.234**
	p-value	0.631	<0.001	0.234	0.069	0.057	0.429	0.004

r = Pearson correlation coefficient.
*. Correlation is significant at the 0.05 level (2-tailed).
**. Correlation is significant at the 0.01 level (2-tailed).

DISCUSSION

Obesity is one of the leading global risk factors affecting both men as well as women[9]. The prevalence of obesity has increased dramatically over the past two decades. In the United States, about 66.7% of women and 75% men of are overweight or obese; out of which, nearly 50% of the women are of reproductive age, and about 17% of their children are aged 2-19 years[15]. In India, according to the National Family Health Survey (NFHS), the percentage of ever-married overweight/obese women (aged 15-49 years) has increased from 11% in NFHS-2 to 15% in NFHS-3[16].

Obesity is usually assessed using body mass index (BMI), which is calculated by dividing the weight (kg) of a person with the square of her/his height (m2)[17]. The World Health Organization (WHO) considers a person as obese if her/his BMI ≥30 kg/m2[16].

Besides the association of obesity with cardiovascular diseases, diabetes, ortho-arthiritis, etc., a raised BMI is also related with a high risk of reproductive complications in women such as menstrual dysfunction, anovulation, and infertility[18]. The women with a higher BMI also show a lower conception rate and higher abortion rate (AR), and they usually experience other reproductive complications[19]. Alteration in the secretion of pulsatile gonadotropin-releasing hormone (GnRH), sex hormone-binding globulin levels, ovarian and adrenal androgens, and luteinizing hormone might be the probable reasons for this dysfunction. Other mechanisms suggest an increased serum and follicular fluid leptin concentration, which in turn inhibits ovarian steroidogenesis. A decrease in serum adiponectin levels might cause hyperandrogenaemia[20]. However, mechanisms underlying the adverse outcomes of raised BMI, whether ovarian or endometrial, still remain to be fully elucidated.

In-vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) involve the process of embryo transfer (ET) using embryos prepared from either self-oocytes (SE), donated oocytes (DE), or vitrified/frozen embryos (VE). Females using DE are generally incapable of producing their own oocytes due to their advanced age or other conditions leading to poor ovarian reserve[21]. The verification of embryos plays an important role in assisted reproduction technology (ART) by offering the patients a prospect to take more chances to conceive without undergoing another fresh cycle[22].

It has been reported that women with BMI more than 35 kg/m2 are at high risk during ART[17]. Therefore, many prior studies have investigated the impact of raised BMI on the pregnancy outcomes of IVF/ICSI but with disparate results[23]. Some studies conducted on the patients undergoing IVF/ICSI using

DE reported the negative impact of BMI, whereas others reported no difference in the reproductive outcomes in obese and normal DE recipients[24-26]. Similarly, there has been a debate on the effect of BMI on IVF patients using VE[22, 27].

The relationship between raised BMI and poor reproductive outcomes is an ambiguous issue. Endometrium and ovaries, alone or together, might result in poor reproductive outcome in overweight/obese women. Many studies suggest the effect of alteration in ovarian response leading to significant changes in the follicular fluid levels of insulin, lactate, C-reactive protein, and androgens (Robker *et al*., 2009). Though many extra-ovarian factors also contribute to the adverse outcomes of pregnancy in obese infertile women, the accurate mechanism is still unclear.

The risks associated with obese women who conceive naturally are similar to those who conceive with IVF[28, 29]. However, the effect of obesity on ART is controversial due to contradiction in the studies reported by various researchers. A bunch of studies report poor pregnancy outcomes in obese women undergoing ART[17,30,31]. As per studies, obesity increases pregnancy risks in women undergoing ART. They need a higher level of gonadotropins as compared to women having normal BMI. The procedure to recover oocytes is more tedious and challenging in an obese woman. The number of oocytes retrieved during the IVF of an obese woman is comparatively lesser than in a woman with normal BMI. However, the quality of oocytes is unaffected by variation in BMI. The increased risk of early pregnancy loss is also observed in obese women[20]. Many studies suggest that the pregnancy outcome followed by ART is not influenced by BMI. However, they might require a high dose of gonadotropin and a longer period of stimulation[23,31].

Oocytes number is essential to be measured for the successful outcome of ARTs. A woman with raised BMI might retrieve a lesser number of oocytes as observed in previous studies[32, 33]. A retrospective cohort study conducted by Zhang *et al.*[32] reported a retrieval of less oocytes from obese women as compared to normal women. However, in the present study, the SE group retrieved the highest average M II oocytes (8.68 ± 4.34) in the BMI ≥ 30.00 kg/m2, whereas the lowest average number of oocytes (7.72 ± 4.39) was obtained in the lowest BMI range (<18.50 kg/m2). However, the difference among the groups was insignificant. The results indicated that the BMI does not affect the number of oocytes retrieved. A study by Sneed *et al.*[34] suggested that the chance of positive IVF pregnancy declines steadily with age, whereas obesity plays a limited or no role in older women. In the present study, difference in mean age was found to be significant in the SE as well as VE groups. In the SE group, a trend was observed, where BMI was found to be increasing with advancing age.

CONCLUSION

The anthropometric measures, only the waist circumference, waist/hip ratio and waist/height ratio were related to ovarian response (*p-value* = 0.014, 0.004 and 0.020, respectively) and to the occurrence of clinical pregnancy (*p-value* = 0.017, 0.030 and 0.010, respectively).

The measures, however, were modest predictors for either outcome. A waist circumference ≤0.81 cm could predict good ovarian response with a sensitivity of 35% and specificity of 100% (AUC = 0.656), and a waist circumference >98 cm could predict clinical pregnancy with a sensitivity of 61% and specificity of 80% (AUC = 0.609).

A waist/hip ratio ≤ 0.82 could predict good ovarian response with a sensitivity of 62.4% and specificity of 68% (AUC = 0.652), and a ratio >0.84 could predict clinical pregnancy with a sensitivity of 56.3% and specificity of 70.9% (AUC = 0.612).

On the other hand, a waist/height ratio ≤0.54 could predict good ovarian response with a sensitivity of 48% and specificity of 92% (AUC = 0.651), while a waist/height ratio >0.62 cm could predict clinical pregnancy with a sensitivity of 61% and specificity of 80% (AUC = 0.609).

CONFLICT OF INTEREST

There are no conflict of interests.

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