Association of Obesity with Hormonal Imbalance in Infertility: A Cross-Sectional Study in North Indian Women

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Abstract Hormones play an important role in the development and regulation of reproductive function and the menstrual cycle of women. Extremes of body weight tend to affect the homeostasis of the hypothalamo–pituitary–gonadal axis. This cross-sectional study was carried out in 113 women (57 with primary infertility and 56 with secondary infertility) in the age group 20–35 years, presenting for hormonal evaluation of infertility in a tertiary care hospital. After preliminary clinical evaluation, anthropometric indices (height, weight, BMI, waist circumference and waist hip ratio) were measured in all subjects. Fasting blood sample drawn on second/third day of menstrual cycle was analysed for serum luteinizing hormone, follicle stimulating hormone (FSH), prolactin and thyroid stimulating hormone (TSH). Serum FSH levels showed a significant positive correlation with indicators of central obesity (waist circumference and waist hip ratio in both the study groups). In primary infertility, significant positive correlation was also observed between serum FSH levels and other markers of obesity like body weight, hip circumference and BMI. In secondary infertility, serum prolactin and serum TSH levels demonstrated a significant positive correlation with body weight and BMI. Obesity is associated with hormonal derangements which are responsible for infertility. In overweight women with infertility, weight loss should be considered as a first line treatment.

Keywords Primary infertility · Secondary infertility · Hormones · Body mass index · Waist hip ratio · Correlation

Introduction

Infertility is a complex disorder with significant medical, psychosocial and economic aspects recognized as a public health issue by the World Health Organization (WHO) [1, 2]. It is associated with severe social stigma and stress to the family, especially in the Indian milieu.

A critical mass of adipose tissue is essential for the normal development of female reproductive function. Extremes of weight can influence fertility by affecting ovulatory function [3]. Studies from western countries suggest that intricate and complex hormonal balance of the hypothalamo–pituitary–gonadal axis is affected by an individual's BMI [4]. Obesity has been shown to produce menstrual disturbances and subfertility. Overweight and obese women have been shown to have poorer outcomes following fertility treatment [5]. The severity of obesity and the distribution of fat tissue are important factors that influence the female reproductive system. Obesity has been reported as an increasing problem among women of child-bearing age leading to three times greater risk of infertility in developed countries [6]. An appropriate index for determining obesity is body mass index (BMI) and waist-hip ratio (WHR). Increased BMI is associated with ovulatory subfertility and anovulatory infertility [5].

Hormones play an important role in the development of reproductive function and in the normal regulation of the menstrual cycle. Disruption of the normal secretion of luteinizing hormone (LH) and follicular stimulating hormone (FSH) in response to pulsatile secretion of gonadotrophin releasing hormone is evidenced in a number of reproductive disorders in women [7, 8].

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Traditionally, measurements of prolactin and thyroid stimulating hormone are considered important components of the evaluation of women presenting with infertility [9]. Thyroid dysfunction interferes with numerous aspects of reproduction and pregnancy. Several studies have indicated the association of hyperthyroidism or hypothyroidism with anovulatory cycles, decreased fecundity and increased morbidity during pregnancy [10–12]. Hyperprolactinemia adversely affects the fertility potential by impairing pulsatile secretion of GnRH and hence interfering with ovulation [10, 13]. Recent studies have shown that prolactin may also be secreted from adipose tissue thus providing a link between obesity and hyperprolactinemia [14].

The pathogenetic mechanistic links between BMI, WHR and hormonal imbalance aren't clearly elucidated especially in North Indian population where sub-fertility and infertility are rampant both in obese and undernourished women. There is no published data on correlation of anthropometric indices with hormonal profile in Indian women and none of the studies in India have compared hormonal profiles of primary and secondary infertility in relation to their anthropometric measures. Hence this study was planned to evaluate the association of anthropometric variations with hormonal changes in both primary and secondary infertility.

Method

This cross-sectional study was carried out in 113 women in the age group 20–35 years, presenting for hormonal evaluation of infertility in the hormone lab of a tertiary care hospital in North India. All the women underwent a preliminary clinical examination in the gynecology OPD and those without any history of any medical illness in either partner were included. The group of infertile women selected consisted of those with regular menstrual cycle lasting between 28 and 30 days. Any gross physical abnormality was ruled out during clinical evaluation and those with abnormal semen parameters in the husband were also excluded. One hundred thirteen consecutive subjects were enrolled in the study after a written and informed consent. The study was approved by the Institutional Ethical Committee.

Out of these one hundred thirteen women, 57 women presented with primary infertility and 56 with secondary infertility. The subjects selected were of different socioeconomic milieu and were mainly medium-statured. All the women reported for hormone analysis on the second or third day of menstrual cycle. Fasting blood samples were collected between 9 a.m. and 12 noon. The following definitions were used for group selection-primary/secondary infertility.

Primary infertility	Couple that has never conceived despite exposure to the risk of pregnancy for a period of 1 year
Secondary infertility	Couples who fail to conceive following a previous pregnancy despite cohabitation and exposure to the risk of pregnancy (in the absence of contraception, breastfeeding or postpartum amenorrhea) for 1 year

Critically ill patients, patients on any kind of hormone treatment or those with LH and FSH levels suggestive of menopausal state were excluded from the study.

Determination of Anthropometric Indices

Body mass index was used to determine whether individuals are underweight, overweight or obese.

$$\text{BMI} = (\text{weight in kg}) / (\text{height in meter})^2$$

BMI classification proposed by WHO Western Pacific Regional Office in collaboration with International Obesity Task Force (IOTF) steering committee (2000) for Asian population was adopted. BMI <18.5 (regarded as underweight), 18.5–22.9 (Normal), BMI of 23.0–24.9 (at risk-obesity) and ≥ 25.0 were regarded as obese [15–17].

Waist hip ratio is the ratio of the circumference of the waist to that of the hips. It was calculated by measuring the smallest circumference of the natural waist and dividing by the hip circumference at its widest part of the buttocks or hip.

A WHR of 0.7 for women correlate strongly with general health and fertility.

Waist circumference was measured by a single observer to reduce inter-observer variation. The cut-off criteria for abnormal waist circumference measurements [18] depicting central obesity is ≥ 80 cm for women.

Sample Collection and Analysis

Five millilitre fasting venous blood sample was drawn from the subject on day 2 or day 3 of menstrual cycle using standard venipuncture techniques. One ml blood was dispensed in vacutainer containing sodium fluoride for estimation of plasma glucose. Rest of the sample was collected in plain vacutainers without any additive. Serum separated after clotting was divided into two aliquots. One aliquot was used for routine biochemical tests—analysis of liver function tests—serum bilirubin, alanine transaminase (ALT), alkaline phosphatase (ALP), aspartate transaminase (AST) and kidney function tests—blood urea and creatinine on Beckman Synchron CX9 Clinical Chemistry

Analyzer using standard kits and reagents from Randox (UK). The routine biochemical tests were carried out to ensure that patients had a normal renal and liver function and were not diabetic.

The other aliquot was used for assessment of hormones—serum LH, FSH, Prolactin and TSH on Chemiluminescent Analyzer Beckmann ACCESS 2.0.

Statistical Analysis

Statistical analysis was performed using SPSS 17.0 version for Windows. The data is presented as mean $\pm$ SEM. Kolmogorov–Smirnov test was used to assess the normality of the data. The difference between various anthropometric measures and hormones between the primary and secondary infertility groups was determined by ANOVA. Pearson's correlation and regression analysis were used for determining the correlation between anthropometric and hormonal factors. $p < 0.05$ was considered as statistically significant.

Results

The age and anthropometric measurements of women included in both the groups was compared. There was a statistically significant difference in the age group of the women within the two groups which can be expected as per the selection criteria used. The mean BMI of the primary infertility group was in the overweight range (as per standard criteria), however the difference in BMI between the two groups was not significant (as shown in Table 1). The average duration of infertility in primary group was 1.67 ± 0.39 years and in secondary infertility group it was 3.98 ± 0.42 years ($p = 0.009$).

The waist circumference and hip circumference was higher in women with secondary infertility but the difference was not found to be significant. In fact none of the anthropometric indices demonstrated a significant difference between the two groups.

Women with primary infertility had slightly higher mean levels of LH as compared to women with secondary infertility. However, this difference was not statistically significant. FSH levels were slightly higher in secondary infertility than in primary infertility, however the difference was insignificant statistically. However, the ratio of LH/FSH was significantly higher in women with primary infertility as compared to secondary infertility ($p < 0.05$) as shown in Table 2. No significant difference was observed in serum TSH and prolactin levels between the groups.

Since a significant difference was observed in the mean age group of women with primary and secondary

Table 1 Clinical and anthropometric parameters of women with primary and secondary infertility

	Primary infertility (mean $\pm$ SEM)	Secondary infertility (mean $\pm$ SEM)	<i>p</i> value of the difference
Age (years)	23.79 ± 0.69	28.72 ± 0.65	$p < 0.001$
Duration of infertility (years)	1.67 ± 0.39	3.98 ± 0.42	$p = 0.009$
Height (m)	1.51 ± 0.03	1.58 ± 0.01	$p = 0.759$
Weight (kg)	53.54 ± 1.89	55.62 ± 1.34	$p = 0.62$
Waist circumference (cm)	71.80 ± 1.47	73.67 ± 1.35	$p = 0.49$
Hip circumference (cm)	87.54 ± 1.73	91.46 ± 1.25	$p = 0.19$
BMI (kg/m ²)	23.17 ± 0.81	24.56 ± 0.62	$p = 0.37$
Waist–hip ratio	0.84 ± 0.007	0.89 ± 0.01	$p = 0.12$

infertility, we evaluated the correlation between age and anthropometric and hormonal profile of the women in both the groups (Table 3). However, no significant correlation was observed between age and anthropometric measures and hormones evaluated in the present study. The duration of infertility showed a significant positive correlation with BMI ($p = 0.03$).

Correlation of anthropometric measures with hormone profile was evaluated in both primary and secondary infertility as shown in Tables 4 and 5.

By univariate regression analysis, serum FSH levels were found to have a significant positive correlation with indicators of central obesity (waist circumference and waist hip ratio in both the study groups). In primary infertility, significant positive correlation was also observed between serum FSH levels and other markers of obesity like body weight, hip circumference and BMI. In secondary infertility, serum prolactin and serum TSH levels also demonstrated significant positive correlation with body weight and BMI.

Discussion

This cross-sectional study evaluated the anthropometric indices (height, weight, waist circumference, hip circumference, BMI and waist hip ratio) and hormone profile (LH, FSH, prolactin and TSH levels) in women presenting with primary or secondary infertility.

In the present study, the mean age of the patients presenting with secondary infertility (28.72 ± 0.65 years) was significantly higher than the women in the primary infertility group (23.79 ± 0.69 years) ($p < 0.001$). Since age

Table 2 Comparison of hormone profile of women with primary and secondary infertility

	Primary infertility (mean $\pm$ SEM)	Secondary infertility (mean $\pm$ SEM)	<i>p</i> value
Serum LH	11.14 $\pm$ 1.41	9.09 $\pm$ 2.23	<i>p</i> = 0.42
Serum FSH	9.72 $\pm$ 1.65	12.08 $\pm$ 1.62	<i>p</i> = 0.33
Serum prolactin	17.349 $\pm$ 2.33	14.39 $\pm$ 1.81	<i>p</i> = 0.67
Serum LH/FSH ratio	1.52 $\pm$ 0.17	0.89 $\pm$ 0.24	<i>p</i> = 0.03*
Serum TSH	4.89 $\pm$ 1.23	3.91 $\pm$ 0.73	<i>p</i> = 0.29

p* < 0.05Table 3** Correlation of age with anthropometric and hormonal factors in primary and secondary infertility patients

	Primary infertility	Secondary infertility
Body weight	<i>R</i> = −0.126, <i>p</i> = 0.557	<i>R</i> = −0.036, <i>p</i> = 0.0869
Waist circumference	<i>R</i> = −0.103, <i>p</i> = 0.631	<i>R</i> = −0.019, <i>p</i> = 0.929
Hip circumference	<i>R</i> = −0.022, <i>p</i> = 0.92	<i>R</i> = 0.043, <i>p</i> = 0.842
Body mass index	<i>R</i> = −0.018, <i>p</i> = 0.614	<i>R</i> = 0.055, <i>p</i> = 0.798
Waist hip ratio	<i>R</i> = −0.158, <i>p</i> = 0.461	<i>R</i> = −0.104, <i>p</i> = 0.630
Serum LH	<i>R</i> = −0.111, <i>p</i> = 0.607	<i>R</i> = 0.108, <i>p</i> = 0.617
Serum FSH	<i>R</i> = −0.174, <i>p</i> = 0.417	<i>R</i> = −0.077, <i>p</i> = 0.721
Serum prolactin	<i>R</i> = −0.117, <i>p</i> = 0.585	<i>R</i> = 0.300, <i>p</i> = 0.154
Serum TSH	<i>R</i> = −0.171, <i>p</i> = 0.425	<i>R</i> = 0.102, <i>p</i> = 0.635

Table 4 Correlation of anthropometric measures with hormonal profile in primary infertility

	Serum LH	Serum FSH	Serum prolactin	Serum TSH	Serum LH/FSH ratio
Height (m)	<i>R</i> = −0.027 <i>p</i> = 0.877	<i>R</i> = −0.024 <i>p</i> = 0.890	<i>R</i> = −0.058 <i>p</i> = 0.740	<i>R</i> = −0.112 <i>p</i> = 0.523	<i>R</i> = −0.044 <i>p</i> = 0.803
Weight (kg)	<i>R</i> = −0.051 <i>p</i> = 0.772	<i>R</i> = 0.467 <i>p</i> = 0.005	<i>R</i> = −0.086 <i>p</i> = 0.624	<i>R</i> = 0.118 <i>p</i> = 0.499	<i>R</i> = −0.345 <i>p</i> = 0.048
Waist circumference	<i>R</i> = −0.003 <i>p</i> = 0.986	<i>R</i> = 0.603 <i>p</i> < 0.001	<i>R</i> = 0.063 <i>p</i> = 0.718	<i>R</i> = 0.192 <i>p</i> = 0.268	<i>R</i> = −0.279 <i>p</i> = 0.104
Hip circumference	<i>R</i> = −0.059 <i>p</i> = 0.736	<i>R</i> = 0.487 <i>p</i> = 0.003	<i>R</i> = 0.023 <i>p</i> = 0.893	<i>R</i> = 0.185 <i>p</i> = 0.287	<i>R</i> = −0.234 <i>p</i> = 0.175
BMI (kg/m ²)	<i>R</i> = −0.050 <i>p</i> = 0.776	<i>R</i> = 0.474 <i>p</i> = 0.004	<i>R</i> = −0.056 <i>p</i> = 0.749	<i>R</i> = 0.162 <i>p</i> = 0.353	<i>R</i> = −0.296 <i>p</i> = 0.079
WHR	<i>R</i> = 0.115 <i>p</i> = 0.510	<i>R</i> = 0.346 <i>p</i> = 0.048	<i>R</i> = 0.106 <i>p</i> = 0.545	<i>R</i> = 0.121 <i>p</i> = 0.489	<i>R</i> = −0.122 <i>p</i> = 0.485

Bold values indicate significant correlation between anthropometric measures and hormones

plays a major role in the fertility potential of both men and women [19], it may have a contributory role in decreasing fecundity in the women who had been successful in having their first pregnancy. However, as shown in Table 3, none of the studied parameters (anthropometric and hormonal) were significantly associated with age of the women in the present study.

The mean waist circumference and hip circumference was found to be slightly higher in women with secondary infertility as compared to the women with primary infertility, however the difference was not found to be statistically significant. The higher waist and hip circumference observed in the secondary infertility group could be attributed to fat deposition in these areas due to first pregnancy or it could be an age-related phenomenon [20].

The women with primary infertility showed slightly higher levels of serum LH as compared to their counterparts in the secondary infertility group. LH is known to stimulate ovarian theca cells to produce androstenedione. Additionally it is also responsible for ovulation and luteinisation. Serum FSH levels in primary infertility were lower than those observed in secondary infertility, though the difference was found to be statistically insignificant.

These differences in LH and FSH concentration when compared individually were not significant between the two groups, however when LH/FSH ratio was calculated, it was significantly higher in primary infertility as compared to secondary infertility (1.52 $\pm$ 0.17 vs. 0.89 $\pm$ 0.24, *p* = 0.03). Elevated levels of LH as well as LH/FSH ratio are predictive of polycystic ovary disease [21]. In primary infertility group, serum LH/FSH ratio more than 2.0 was observed in 12 patients. These patients were referred for ultrasonography despite the fact that these patients had normal menstrual cycles.

Table 5 Correlation of anthropometric measures with hormonal profile in secondary infertility

	Serum LH	Serum FSH	Serum prolactin	Serum TSH	Serum LH/FSH ratio
Height (m)	$R = 0.066$ $p = 0.758$	$R = -0.204$ $p = 0.339$	$R = 0.367$ $p = 0.078$	$R = 0.119$ $p = 0.580$	$R = 0.059$ $p = 0.786$
Weight (kg)	$R = -0.069$ $P = 0.750$	$R = -0.140$ $p = 0.514$	$R = 0.433$ $p = 0.035$	$R = 0.498$ $p = 0.013$	$R = -0.059$ $p = 0.784$
Waist circumference	$R = -0.071$ $p = 0.743$	$R = 0.403$ $p = 0.043$	$R = 0.300$ $p = 0.154$	$R = 0.264$ $p = 0.213$	$R = -0.173$ $p = 0.419$
Hip circumference	$R = -0.163$ $p = 0.447$	$R = 0.107$ $p = 0.618$	$R = 0.406$ $p = 0.042$	$R = 0.347$ $p = 0.091$	$R = -0.229$ $p = 0.282$
BMI (kg/m^2)	$R = -0.108$ $p = 0.614$	$R = -0.079$ $p = 0.713$	$R = 0.421$ $p = 0.039$	$R = 0.527$ $p = 0.008$	$R = -0.094$ $p = 0.664$
WHR	$R = 0.094$ $p = 0.663$	$R = 0.508$ $p = 0.011$	$R = 0.011$ $p = 0.960$	$R = 0.014$ $p = 0.947$	$R = 0.122$ $p = 0.485$

Bold values indicate significant correlation between anthropometric measures and hormones

The elevation of early follicular phase FSH represents a standard clinical marker of reduced ovarian reserve and diminished responsiveness of the ovary to ovulation induction [22]. A significant finding of the present study was a positive correlation of FSH levels with markers of central obesity—waist circumference and WHR in both the study groups. A similar situation is also observed during menopause, where FSH levels rise due to decreased negative feedback from inactive ovaries. Even menopause is often associated with increased weight gain and more fat deposition around the waist resulting in android type of obesity. However, the cause-effect relationship needs to be evaluated in experimental models. The positive correlation of FSH with obesity observed in the present study is in contrast to the findings in Italian fertile women where obesity was inversely related with LH and FSH levels [23].

Serum TSH levels were evaluated in all the women as an indicator of thyroid status. Twenty out of 57 women in the primary infertility group were found to be suffering from subclinical hypothyroidism (TSH levels >5.6 $\mu\text{IU}/\text{ml}$), whereas two women had severe hypothyroidism (TSH >100 $\mu\text{IU}/\text{ml}$). In contrast, subclinical hypothyroidism was detected in only 10 women out of 56 included in secondary infertility group. This finding is in contrast to a recent study in Bangladesh where prevalence of subclinical hypothyroidism was reported to be higher in secondary infertility as compared to primary infertility [20]. In the present study, no significant difference was observed in the mean levels of serum TSH in primary and secondary infertility, indicating that serum TSH levels are independently related to infertility.

Hyperprolactinemia is a common problem in reproductive dysfunction affecting about one-third of infertile women [25]. Hyperprolactinemia (prolactin levels more than 23 ng/ml) was detected in 12 women out of 57 women enrolled in primary infertility group and in 10 women enrolled in secondary infertility group. There was no statistically

significant difference in the prolactin levels between the primary and the secondary infertility group. This was consistent with a study on women in Ludhiana [26]. Our findings are in contrast to a recent study in Bangladeshi women where prevalence of hyperprolactinemia was stated to be higher in primary infertility as compared to secondary infertility [24]. It has been suggested that hyperprolactinemia interferes with the action of the gonadotrophin at the ovarian level and results in impaired gonadal steroid secretion, which in turn alters positive feedback effects at the hypothalamic and pituitary levels. This leads to lack of gonadotrophin cyclicity and to infertility [27]. Prolactin can inhibit the follicular estradiol production resulting in infertility [28].

In the secondary infertility group, a significant positive correlation was observed between the body weight and serum TSH levels and also between BMI and TSH levels. These findings can be explained by the fact that obesity is often associated with chronic low inflammatory state and raised TSH levels observed in obese patients could be due to increased levels of circulating antibodies to thyroid. Another independent study evaluating the thyroid status in morbidly obese population also reported raised TSH levels in obese individuals [29]. This may be a cause of alarm as it has been seen that it may be a component leading to metabolic syndrome [30].

In the secondary infertility group, a significant positive correlation of prolactin was observed with body weight and BMI indicating that prolactin may be related to obesity. However, this is in contrast to a recent study in general population where no correlation was observed between serum prolactin and obesity [31]. Conversely, another study comparing basal and TRH stimulated prolactin levels in obese and non-obese individuals reported higher basal levels of prolactin in obese individuals [32].

The findings in the present study suggest that there is a positive association of obesity with various hormonal derangements which can contribute to infertility. Hence

management of the obese patient with infertility should start with a goal of achieving a significant weight loss. Intervention undertaken for control of central and visceral obesity would definitely provide a beneficial effect by correcting the hormonal imbalance. Hence infertile women, if overweight or obese should try for an effective weight loss which will improve their hormonal milieu more appropriate for fertility. Weight loss regularizes menstrual cycles and increases the chance of spontaneous ovulation and conception in anovulatory overweight and obese women.

Conclusion

Obesity is associated with hormonal derangements which may be responsible for infertility, hence it should be primarily targeted in the management of these individuals before starting any therapy to correct their hormonal imbalance. The patients should be educated to adopt a healthy body weight by lifestyle based interventions before they undertake any medical or surgical management for infertility. A holistic approach to weight regulation and reproductive health needs to be adopted to increase the chances of conception in overweight women, this will also ensure a positive impact on their general health.

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