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Original article

Association of BMI and Hormonal Imbalance with Primary and Secondary Infertility: A Cross-Sectional Study

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ABSTRACT

Aims*. This cross-sectional study aims to evaluate the relationship of body mass index (BMI) and hormonal imbalance with primary and secondary infertility among 160 infertile Libyan women.* ***Methods****. We had collected the basic demographic data and laboratory hormone profile of infertile patients attended Fertility Center Albayda complaining of primary or secondary infertility.* ***Results****. The outcomes yielded a significant difference among the ages when related to the infertility type. Moreover, in the primary infertility group, a significant negative correlation of luteinizing hormone(LH) and follicle-stimulating hormone (FSH) with BMI was observed. In secondary infertility, serum FSH levels demonstrated a significant negative correlation with BMI. Upon division of the sample into obese and non-obese groups, significantly higher LH levels in the non-obese group were observed.* ***Conclusion****. We concluded that obesity can results in hormonal derangements, which may adversely influence fertility.*

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INTRODUCTION

Infertility is a widely prevalent problem of global significance. The World Health Organization (WHO) defines infertility as the inability to conceive after one year of regular unprotected intercourse [1]. Recent studies reported an infertility rate of 8% to 12% worldwide and estimated that approximately 8% to 10% of couples face difficulties getting pregnant [2]. Infertility is of two types: primary and secondary. Mascarenhas et al. carried out an analysis of fifty-three demographic health surveys to measure infertility in populations. The authors estimated that the primary infertility rate varied from 0.6% to 3.4%, whereas the secondary infertility rate ranged between 8.7% to 32.6% [3].

While multiple factors adversely affect reproductive capability, abnormal body mass index (BMI) remains a significant contributor. A critical amount of adipose tissue is vital for the maintenance of normal reproductive function. Extremes of weight negatively influence ovulatory function and thus, affect fertility [4].

Obesity, defined as having a BMI of greater than 30 kg/m^2, has been identified as a rising concern among women of reproductive age, resulting in a three-fold increase in infertility risk in developed nations [5]. Obesity is associated with an ovulatory infertility and ovulatory subfertility [6]. Although ovarian stimulation can reverse anovulation, obese women also have reduced gonadotropin sensitivity, decreased oocyte quality, decreased pre-implantation embryo development rates, and increased risk fora miscarriage relative to non-obese women [7, 8]. According to a past study, 43% of obese women experienced infertility issues, menstrual irregularities, and recurrent miscarriages [9].

While obesity is one of the prime factors affecting fertility, the opposite end of the spectrum must also be considered. Reduced fertility has also been observed in women with a BMI of less than 18.5 kg/m^2. In a study conducted by Dhandapani et al., 8.8% of the women with primary infertility and 7.5% of women with secondary infertility, were underweight [10]. These findings indicate that optimum body weight correlates with the normal functioning of the women's reproductive system.

Hormones play a crucial role in the development of reproductive function and regulation of the menstrual cycle. The complex and intricate hormonal equilibrium of the hypothalamic-pituitary gonadal axis is greatly influenced by BMI [11]. Reproductive disorders are often caused by a disturbance in the normal secretion of luteinizing hormone (LH) and follicular-stimulating hormone (FSH) in response to gonadotropin-releasing hormone (GnRH). Checking prolactin levels and thyroid-stimulating hormone (TSH) levels is considered an integral component of the infertility assessment of women [12]. Various studies have shown that hyper- and hypothyroidism are associated with an ovulatory cycles and reduced fecundity [13, 14]. Hyperprolactinemia also impairs the pulsatile release of GnRH, adversely affecting the fertility potential [13]. According to recent literature, adipose tissue may also secrete prolactin; this hints towards the possible link between obesity and hyperprolactinemia [15]. No published data exists that describes the relationship between differences in the BMI to infertility while keeping the hormonal profile of the Libyan women under consideration. Hence, this study aimed to evaluate the correlation of BMI alterations with hormonal imbalances in both primary and secondary infertility to elucidate the association between obesity and infertility, especially in terms of ovarian response.

METHODS

Study design and setting

This study is a cross-sectional study with a sample size of 160 women between 20 to 46 years of age, visiting with complaints of infertility or subfertility to Aljabal Alakhtar Center, Libya, in the first half of 2015.

Data collection procedure

The results were obtained in the laboratory of the El-Beyda Fertility Centre. All the women were examined thoroughly in the gynecology outpatient department (OPD) before they were involved in this study. Any gross physical abnormality was excluded during a clinical examination. Exclusion criteria consisted of post-menopausal women, patients with thyroid abnormalities or tubal disorders in history; those coming in with male infertility cause such as abnormal semen parameters were also excluded. The selected group of infertile women comprised of those with regular menstrual cycles (28 to 30 days). The Institutional Ethical Committee approved the study. Written informed consent was obtained from the patients before enrolling them in the study.

The entire population sample was divided into primary and secondary infertility. Couples, who have never conceived, despite having unprotected sexual intercourse for at least one year, were defined as primary infertility. In contrast, couples who failed to conceive following a previous pregnancy, despite exposure to pregnancy risk for one year, were defined as secondary infertility.

Anthropometric measurements

Weight and height were measured using electronic scales and a wall-mounted stadiometer, respectively, while patients wore light clothes and no shoes. BMI was calculated to determine whether an individual is underweight, overweight or obese.

BMI = (Weight in kg) / (Height in meter^2)

BMI was evaluated according to the Canadian Guidelines for Body Weight Classification in Adults (2003). A BMI of 18.5-24.9 kg/m^2 was regarded as standard; BMI between 25.0-29.9 kg/m^2 was regarded as overweight, whereas grade-I and grade-II obesity was diagnosed when the BMI was between 30.0-34.9 kg/m^2 and 35.0-39.9 kg/m^2, respectively. Participants were classified as having grade-III obesity, also referred to as morbid obesity, when the BMI exceeded 40.0 kg/m^2 [16].

Sample collection and analysis

A fasting venous blood sample of 5 milliliters (ml) was drawn from each patient during the early follicular phase (3rd to 5th day) and was collected in a lithium heparin tube. For the serum separation, each sample was centrifuged for 3 to 5 minutes at 3000 revolutions per minute (rpm). The separated serum was then tested for hormone levels. A fluorescence enzyme immunoassay procedure was used to quantify FSH, TSH, LH, and prolactin levels. AIA-360 (Japan) was used as an automated immunoassay analyzer.

The standard reference ranges for hormones levels are as follows:

TSH = 0.4-4.20 mIU/ml

LH = 2.4-6.6 mIU/ml

FSH = 3.3-21.6 mIU/ml

Prolactin = 5.18-26.53 ng/ml

Statistical analysis
Data were analyzed using Statistical Package for Social Sciences (SPSS) version 21.0 for Windows. The results of the study were reported as mean ± standard deviation (SD) for continuous variables. The difference in mean between the groups in continuous variables (mean age and mean hormone levels) was determined using the t-test. The difference between BMI categories and age groups between primary and secondary infertility was analyzed using Pearson's chi-square test. Correlations between BMI and hormone levels were evaluated using Pearson's correlation test. For all statistical comparisons, the level of significance was set at $p < 0.05$.

RESULTS
Our study comprised 160 infertile women with a mean age of 32.8 ± 5.7 years. The entire sample was categorized into two groups: primary and secondary infertility. Out of these 160 women, 72.5% of the participants had primary infertility, while the remaining 27.5% had secondary infertility. Our results showed that most of the infertile women were overweight (31.3%), followed by women having grade-I (18.1%), grade-II (17.5%), and grade-III (11.3%) obesity. Healthy BMI was seen only in 8.8% of the population under consideration. BMI of the remaining 11.4% of the cases remained undocumented, however, their physical appearance was highly suggestive of them having a BMI below 30.0 kg/m^2. Table 1 classifies the sample based on the type of infertility and varying BMI.

Table1: Distribution of Sample in Accordance to Infertility Type and BMI Indexing (N=160).

Criteria	Frequency(n)	Percentage %
On the basis of type of infertility		
Primary	116	72.5
Secondary	44	27.5
On the basis of BMI (kg/m²)		
Normal (18.5_24.9)	14	8.8
Overweight (25.0_29.9)	50	31.3
Grade_ I obesity	29	18.1
Grade_II obesity	28	17.5
Grade_III obesity	18	11.3
Missing	21	11.4

As demonstrated in Figure1 the sample was further classified into non-obese (BMI <30 kg/mand obese (BMI 30kg/m²) groups.

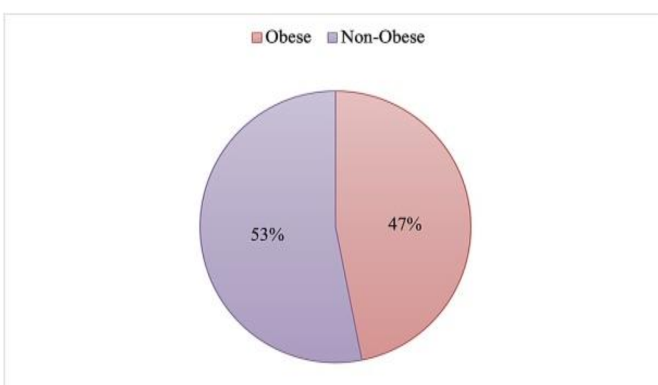

Figure 1. Classification of Sample on the Basis of obese and Non-Obese(N=160)

To evaluate the effect of age on type of infertility, the sample was also categorized into two age groups: ≥ 35 years and > 35 years. Almost two-thirds of the sample was 35 years of age or younger (figure 2).

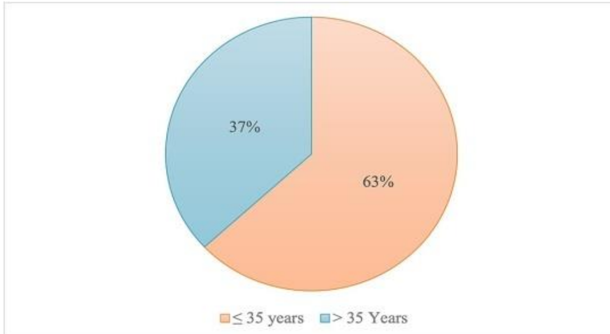

Figure 2. Classification of Sample Group Based on Age Over or Less Than 35 Years of age

Table 2 demonstrate a significant influence of increase age on the type of infertility. Primary infertility was more common in women ≤ 35 years of age, whereas, secondary infertility was more common in women > 35 years of age.
Upon comparison ages, BMIs and hormone profiles of women with primary and secondary infertility, a statistically significant difference in the ages was noted. In contrast, no significant association was found between BMIs of women with primary and secondary infertility. Women with primary infertility revealed slightly higher mean levels of prolactin than women with secondary infertility: however, this difference was statistically insignificant. No significant difference was observed in mean serum level of FSH and LH between women with primary and secondary infertility. Although women with primary infertility had slightly higher mean TSH levels, the difference observed was not statistically significant (Table 2).

Table 2. Categorization of infertility type in respect to age of sample

variables	Normal range for hormones (according to 3rd day of menstrual cycle)	Secondary infertility (n=44) Mean ± SD	Primary infertility (n=116) Mean ± SD	P_ value
Age (years)	-	32.8 ± 5.7	31.8 ±5.6	0.00
BMI (kg/m²)	-	32.3 ±6	31.6 ±6.4	0.58
Serum prolactin ng/ml	5.18 – 26.53	18.3 ±13	22.7 ±17.5	0.13
Serum LH (mIU/ml)	2.4 – 6.6	5.7 ±3.9	5.8 ±4	0.84
Serum FSH (mIU/ml)	3.3 - 21.6	7.5 ±2.9	7.4 ±3.3	0.81
Serum TSH (mIU/ml)	0.4 - 4.2	2.2± 12	2.4 ±1.9	0.48

The ages and hormone profiles of women in the obese and non-obese groups were compared, as demonstrated in table 3. Although prolactin levels were higher in the obese group and mean serum FSH levels were slightly higher in the non-obese group, the differences observed were deemed statistically insignificant. However, mean serum LH levels were significantly higher in the non-obese group. Moreover, no statistically significant difference in age was observed between the two groups.

*Table 3. Categorization of age, BMI, and Hormone profile in women with primary and secondary infertility (*P< 0.05)*

Variables	Normal range for hormones (according to 3rd day of menstrual cycle)	Non-obese (N =75) Mean ± SD	Obese (N = 85) Mean ± SD	P_ value
Age (years)	-	32.4 ± 6	33 ± 5.3	0.4
Serum prolactin (ng/ml)	5.18 – 26.53	20.2 ± 12.6	23 ± 19.7	0.3
Serum LH (mIU/ml)	2.4 – 6.6	6.5 ± 3.6	5.0 ± 3.7	0.015*
Serum FSH (mIU/ml)	3.3 – 21.6	7.5 ± 2.9	7.4 ± 3.3	0.06
Serum TSH (mIU/ml)	0.4 – 4.2	2.2 ± 1.2	2.4 ± 1.9	0.21

Correlation of hormone profile within both primary and secondary infertility was evaluated, as shown in Table 4. Serum FSH levels were found to be significantly, negatively correlated with BMI in both the primary and secondary infertility groups. In women with primary infertility, a significant negative correlation was also observed between serum LH levels and BMI; however, no significant correlation was observed between serum LH levels and BMI in the secondary infertility group. Moreover, no significant correlation was noted between serum prolactin and TSH levels in both the primary and secondary infertility groups.

*Table 4: Correlation of Hormonal Factors with BMI in Women with Primary and Secondary Infertility (*p<0.05)*

variables	Secondary infertility (n =44)				Primary infertility (n = 116)			
	Prolactin	LH	FSH	TSH	prolactin	LH	FSH	TSH
BMI (kg/m²)	R = -0.28	R = -0.24	R = -0.37	R = -0.15	R = 0.14	R = -0.25	R = -0.2	R= 0.11
P value	P = 0.4	P= 0.2	P= 0.03*	P = 0.4	P = 0.2	P= 0.01*	P= 0.02*	P= 0.3

DISCUSSION

The present cross-sectional study evaluated the BMI and hormone profile (FSH, LH, TSH, and prolactin) in 160 Libyan women known to have an infertility problem. Evidence states that 8% to 15% of all women experience primary or secondary infertility at some stage in their reproductive life [17].

Our results revealed that more than two-thirds of the population under consideration had primary infertility, suggesting that primary infertility is predominant in the Libyan community. Similarly, several studies have also reported a higher prevalence of primary infertility than secondary infertility among women [10,18-21]. Dhandapanii et al., in a cross-sectional study among infertile women of Mangalore, observed the prevalence of primary infertility in 76.2% of the cases; the authors hypothesized that the discrepancy in the prevalence of primary and secondary infertility in different populations could be attributed to variability in the definition of infertility considered by the authors [10]. Moreover, Benksim et al. reported a 67.37% prevalence of primary infertility in a Moroccan population, while Mesbahi et al. reported 79% in an Iranian population [18-19]. Goynumer et al. and Yilmaz et al. revealed that 69% and 65% of the infertile Iranian women, respectively, had primary infertility [20-21].

In contrast, a study conducted on the sub-Saharan African population revealed a relatively low prevalence of primary infertility [22]. We believe that a higher prevalence of primary infertility may be because childless couples are more likely to seek help than those who already have children. Long-standing untreated sexually transmitted infections (STI's), and older age at the time of marriage may also contribute to a higher prevalence of primary infertility.

A balanced amount of adipose tissue is essential for the proper development of reproductive function. Problems like insulin resistance and hyperandrogenism are shared amongst obese individuals and may also affect fertility. The abnormal secretion of hormones like leptin in obese women indicates that infertile obese women carry a higher risk of reproductive dysfunction [23,24]. In the present study, only 8.8 % of the women recruited had a healthy BMI. 31.3% were overweight, and 46.8% had Grade-I, Grade-II, and Grade-III obesity. Thus, overall, nearly 78% of the infertile women had a BMI above thenormal range. These results are comparable to the study conducted Al-Azemi et al. in which 73.6% of the infertile women had a BMI exceeding the normal range [25]. A study performed by Norman et al. revealed a consistent decline in fertility with rising weight in women [26]. The mean BMI was relatively higher in the secondary infertility group than the primary infertility group in our study, however, this difference in BMIs between the two groups was not statistically significant. The higher mean BMI observed in women with secondary infertility could be due to fat accumulation either due to previous pregnancy, nutritional modifications, or it could be a phenomenon linked to age [27]. Increasing age in women is an essential factor, negatively influencing time to pregnancy.

The mean age of infertile women in our study was 32.8 ± 5.7 years. Alawan et al. demonstrated the decline in female fertility starting at 31 years of age [28]. Moreover, our results indicated that primary infertility was more common in women ≤ 35 years of age, whereas, secondary infertility was found to be more common in women > 35 years of age. In line with our study, Yilmaz et al. and Seth et al. also observed that women with primary infertility were comparatively younger than women with secondary infertility [21, 29]. We believe that secondary infertility in women greater than 35 years of age may be attributed to the long wait before deciding to have more children. Moreover, complications during the first birth and inadequate health care access may also justify the delay in the next pregnancy. Menken et al. and Jaffe et al. reported a fertilityreduction with advancing age [30-31]. They describe the ages of 35-40 years as critical forpregnancy. These ages were related to increased incidence of pelvic infections, endometriosis and anovulation.

A hormonal imbalance may result in reduced fertility. The levels of reproductive hormones likeFSH, LH, prolactin and TSH are measured through blood tests. Measurement of these hormonesat day 2 or day 21 of the menstrual cycle can indicate whether a successful pregnancy can occur.

Physiologically LH regulates androgens' production from theca interna, while FSH is responsible for the maturation of ovarian follicles. FSH also stimulates the aromatization of androgens to estrogen [32]. High serum concentrations of prolactin and reduced FSH and LH levels indicate an ovulatory disorder [33]. In our study, the women in the primary infertility group reported slightly higher serum LH levels compared to the women in the secondary infertility group. Serum FSH levels were lower in primary infertility relative to their counterparts. However, these differences were found to be statistically insignificant. These findings are parallel to the study conducted by Seth et al., which also reported relatively higher LH levels in the primary fertility group and relatively higher FSH levels in the secondary infertility group [29]. Moreover, in a study conducted by Yilmaz et al., women with primary infertility also had higher LH levels; however, contrary to our results, FSH levels were also found to be higher among the primary infertility group [21].

Several studies show that reproductive hormonal parameters did not vary between thin and obese women [24, 34-35], whereas other studies have found that these parameters varied substantially [36-37]. Upon comparing women's hormone profiles in the obese and non-obese group, significantly lower LH levels were observed in the obese group. Although FSH levels were also lower in the obese group, the difference was statistically insignificant. Moreover, our results also revealed that FSH levels were inversely related to BMI in the secondary infertility group. In contrast, the primary infertility group showed an inverse correlation between FSH and LH with BMI. These results were independent of the age factor and were determined following regression analysis. In line with our study, Pergola et al. also reported an inverse correlation of FSH and LH levels with BMI [38]. However, in contrast to our findings, a significant positive correlation of FSH levels with BMI was observed by Seth et al. [29].

Physiologically increased serum prolactin is seen during pregnancy and lactation. A common cause of secondary amenorrhea is the increased prolactin level among women of reproductive age [39]. Thus, prolactin fluctuations can contribute to reproductive dysfunction. Association between hyperprolactinemia and obesity has been established [40]. The results of our study, although statistically insignificant, indicated that mean prolactin levels were higher in the obese group as compared to the non-obese group. Contrastingly, Ernst et al. reported no relationship between obesity and prolactin levels [41]. Moreover, similar to Yilmaz et al. and Seth et al., mean serum prolactin levels were found to be relatively higher in the primary infertility group than the secondary infertility group in our study [21,29]. However, the difference in prolactin levels between women with primary and secondary infertility was insignificant. This was parallel to the results obtained from women in Ludhiana [42]. Hyperprolactinemia has been suggested to intervene with the action of gonadotrophin at the ovarian level and subsequently impairs gonadal secretion, which disrupts the positive feedback response at the hypothalamic and pituitary levels. This causes a lack of gonadotrophin cyclicity and infertility [43].

No significant correlation was observed between BMI and serum TSH levels in both the primary and secondary infertility groups in the present work. However, although insignificant, mean TSH levels were higher in the obese group than the non-obese group. Another study reported increased TSH levels in obese individuals [44]. Our results can be explained by circulating antithyroid antibodies in obese individuals leading to a rise in TSH. This study poses two main limitations. Firstly, this research is a single center-based study that prohibits us from drawing definitive conclusions that would reflect the entire Libyan population.

CONCLUSION

In conclusion, the present study shows that fluctuating BMI, hormonal imbalance and age extremes are prime contributors to fertility problems. Weight management and targeting hormonal imbalance may solve fertility problems. Maintenance of normal BMI is particularly useful and an easily attainable solution for obese infertile women. Patient education about a healthy weight through lifestyle modifications must be the utmost priority. To increase the probability of pregnancy, adopting a holistic strategy to reduce weight and maintain reproductive health, especially in overweight women is essential.

Disclaimer

The article has not been previously presented or published, and is not part of a thesis project.

Conflict of Interest

There are no financial, personal, or professional conflicts of interest to declare.

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