HORMONAL AND BIOCHEMICAL STUDY OF THE EFFECT OF OBESITY ON WOMEN INFERTILITY

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Abstract

Examining the impact of obesity on infertility among women. Via eleven biochemical parameters, such as progesterone, estrogen, Luteinizing Hormone, Follicle-Stimulating-Hormone, Prolactin, Cholesterol, Triglyceride, Thyroid-Stimulating-Hormone, Very-Low-Density-Lipoprotein, High-Density-Lipoprotein, and Low-Density-Lipoprotein, were tested in 107 women with infertility and 54 control group. The result showed there was a significant elevation in the concentration of estrogen, progesterone, FSH, LH, prolactin, TSH, cholesterol, TG, VLDL and LDL in infertile women, compared to the healthy women at a significant level of P = 0.025 (72.1 ± 30.9 pg/mL), P = 0.01 (1.94 ± 0.83 ng/mL), P = 0.019 (5.15 ± 0.12 mlU/mL), P = 0.016 (6.19 ± 3.0 mlU/mL), P = 0.02 (32.7 ± 21.5 pg/mL), P = 0.0013 (2.09 ± 1.04 µlU/mL), P = 0.001(186.3 ± 34.1mg/dL), P = 0.001 (162.5 ± 83.7 mg/dL), P = 0 008 (32.5 ± 16.6 mg/dL) and P = 0.007 (113.3 ± 34.4 mg/dL), respectively. Obesity had a strong positive relationship with LH, cholesterol, TG, VLDL, and LDL, whereas an unwanted correlation with HDL was noted. Also, an association has been found between hormonal and biochemical parameters, and WHR and BMI. WHR demonstrated a significant negative correlation to HDL. Finally, the study showed that obesity is a new indicator of increasing the infertility risk for women of all ages through BMI and WHR.

Keywords*:* Infertility, Obesity, BMI, Waist To Hip Ratio (WHR), Female Hormones

Introduction

Infertility is a global health issue. The purpose and significance associated with this will vary depending on the geographical location and socio-economic conditions (1, 2). Infertility is characterized by the fact that no pregnancy occurs without contraception in women < 35 years of age after one year of daily sexual intercourse and in women > 35 years after six months (3). It has two types: main infertility and secondary infertility (main infertility) if it is not followed by any pregnancy, or maybe secondary (secondary infertility) if it follows a preceding pregnancy, just once, if it ends with the birth of a living or dead fetus or ends with the inability to conceive within one year (4). Obesity, as a critical health issue, is a traditional reproductive-age problem among women. Obesity and overweight comprise an unusual and uncontrolled build-up of fat that has an inverse effect on individuals' wellbeing. The main mechanism is a chronic caloric imbalance between body energy expenditure and food consumption (5). If the BMI is equal to or greater than 25 kg/m^2, it is considered overweight while if the BMI is equal to or greater than 30 kg/m^2, it is considered obesity (6). For example, high BMI is associated with increased health risks such as breast cancer and endometriosis (7). Due to the lack of studies in this field, the aim was to study the hormonal and biochemical variables of the effect of obesity on the cases and types of infertility by studying the analysis of the results and finding the statistical correlation between hormonal and biochemical factors. As a result of changes in lifestyle and the presence of environmental pressures, the rate of infertility has increased dramatically and has become the third most dangerous disease after cancer and cardiovascular disease.

Materials and Methods

Sample collection

Cross-sectional study was performed in the hospitals in Duhok/Iraq from 6 June 2017 to 20 March 2018.

Group of infertile patients

One hundred and seven infertile women (Primary and Secondary) were enrolled in this study, diagnosed by specialists at the Azadi Teaching Hospital/Azadi Center for Infertility, and In Vitro Fertilization (IVF) and Shelaan

Hospital. Their ages ranged from 18-43 years. BMI was about 20-58.59 kg/m^2, the WHR exceeded 0.8 and clinical data were obtained for each case in a questionnaire prepared for this purpose. Excluded conditions include diabetes, high blood pressure, and thyroid disease.

Control group (reference group)

This study was attended by fifty-four young fertile women (control group), ages ranging from 17-43 years with a BMI of 18-24.9 kg/m^2 and a WHR of below 0.8.

For the two groups the collection of blood samples was carried out after 12 hours of overnight fasting, during the early follicular period (cycle day 2 or 3) for estrogen (E2), Follicle Stimulating Hormone (FSH), Luteinizing Hormone (LH), Prolactin, Cholesterol, Triglyceride (TG), Thyroid Stimulating Hormone (TSH), and progesterone, luteal prolactin (cycle day 21), in the test tube (5ml), and centrifuged for serum separation within an hour of blood collection, and the serum was stored in a deep freezer at a temperature of -20^{o}C for subsequent analysis. Samples were analyzed in batches of 100 to be omitted between analytical variations. Before the analysis, samples were allowed to reach room temperature. Then using commercial kits (Bio Merieux kits) were measured by mini VIDS type (69280-Marcy-Letiole) from Biomerieux –Italy Co., the principle of this technic is Enzyme-Linked Fluorescent Assay. The lipid profile also included Total Cholesterol, Triglyceride (TG), High-Density Lipoprotein (HDL) analysis and was measured using commercial kits (Biolabo Kits) were measured by UltraViolet & Visible Spectro method. Low-Density Lipoprotein (LDL) and Very-Low-Density lipoprotein (VLDL) were determined indirectly, utilizing the Friedewald formula. BMI and WHR were calculated, using the following formula: BMI (kg/m^2) = Weight (kg)/Height (m^2) and WHR= W (Waist)/ H (Hip).

Statistical analysis

Analysis of the data was conducted using SPSS tools. T-test, Duncan test was used to compare the parameters between the total number of control and patients, based on the occupancy at p≤0.05, p≤0.01, and p≤0.001, respectively, and Pearson correlation coefficient test. The Duncan-tests is used to indicate the differences when comparing more than two groups of the same chemical parameter (a, b, ab means the difference, and if all are the same, it indicates no significant statistical difference), which is identical to the p-value (8).

Results and Discussion

The anthropometric parameters

Table 1 results showed that the infertile group's BMI and WHR were significantly higher than the control group this agrees with another study (9), may because the BMI and WHR affect women's reproductive system, as upper abdominal obesity affects ovulation or accumulated fat in the abdomen are associated with diminished ovulation.

Table 1: Age and anthropometric parameters in infertile women, compared with the control group

Age & anthropometric parameters	Infertile group Mean ± SD	Control group Mean±SD	P-value
Age (years old)	30 ± 6.06	27.04 ± 5.55	0.003**
Height (m)	158.5 ± 0.08	162.5 ± 0.01	0.05*
Weight (Kg)	77.7 ± 13.6	62.9 ± 5.14	0.001***
Waist (cm)	110 ±0.06	86 ± 0.07	0.001***
Hip (cm)	120 ± 0.03	110 ± 0.025	0.001***
BMI (kg/m2)	30.93 ± 4.99	23.81 ± 1.71	0.001***
WHR	0.912 ± 0.097	0.767 ± 0.042	0.01**

*Significant differences at P ≤ 0.05,
**Significant differences at P ≤ 0.01,
***Significant differences at P ≤ 0.001

Comparison between the level of hormonal and biochemical parameters of infertile women and the control group

The level of hormonal and biochemical parameters for infertile women as compared with the control group, as shown in Table 2. The concentration of estrogen (E2) has increased significantly. Due to the increased body weight and fatty tissue, it may be associated with sex hormone imbalance and a low level of sex hormone-binding globulin (SHBG). This may respond to the high concentrations of estrogen in obese women compared to normal-weight women, which is in agreement with finding from (10). It can affect the pituitary-hypothalamic gonadal axis (HPG) and the high estrogen triggers negative feedback to decrease the secretion of gonadotropin-releasing hormone (GnRH) that causes menstrual dysfunction and anovulation, and there has been a significant decrease in the concentration of progesterone that could be attributed to anovulation. Also, as shown in Table 2, the concentration of LH increased significantly, while the concentration of FSH decreased significantly. The major cause for infertility appears to be the lack of long ovulation due to hyperandrogenism, due to obesity, and this in agreement with other studies (6, 11). The concentration of prolactin hormone in infertile women was significantly increased compared with healthy women.

Hyperprolactinemia adversely affects the fertility capacity by impeding the pulsatility of GnRH and thus the ovarian function. Also, there has been a significant increase in the concentration of TSH. Obesity is also followed by a chronic low inflammatory disorder and improved TSH levels observed in obese women, which could result from higher concentrations of circulating thyroid antibodies, as agreed in other studies (4, 12). Thyroid dysfunction includes a wide range of reproductive disorders, ranging from atypical sexual development to menstrual inconsistencies, infertility, and high miscarriages (4).

Also in Table 2, the cholesterol, TG, VLDL, and LDL concentrations increased significantly. Infertile women have seen a significant reduction in HDL concentration,

which is incompatible with the findings of Fontana & Della Torre, 2016, this indicates the likelihood of a correlation between impaired lipoprotein metabolism and female infertility. Dyslipidemia is also seen with high levels of free fatty acids (FFA) and plasma TG, significantly decreased LDL and lowered HDL in obese subjects. Perhaps the levels of cholesterol and FFA assess reproductive function at the ovarian, placenta, and uterine levels. The cause of the oocyte dysfunction and infertility was atypical lipoprotein (2).

Table 2: A comparison between the level of hormonal and biochemical parameters of infertile women and the control group

Hormonal and biochemical parameters	Infertile group (Mean±SD)	Control group (Mean±SD)	P-value
Estrogen (E2) (pg/mL)	72.1 ± 30.9	56.53 ± 26.4	0.025*
Progesterone (ng/mL)	1.94 ± 0.83	3.96 ± 2.4	0.01**
FSH (mlU/mL)	5.15 ± 0.12	6.84 ± 1.69	0.019*
LH (mlU/mL)	6.19 ± 3.0	3.84 ± 1.5	0.016*
Prolactin (ng/mL)	32.7 ± 21.5	15.68 ± 7.1	0.02*
TSH (µlU/mL)	2.09 ± 1.04	1.55 ± 0.66	0.0013**
Total Cholesterol (mg/dL)	186.3 ± 34.1	151.93 ± 33.5	0.001***
Triglyceride (TG) (mg/dL)	162.5 ± 83.7	110.1 ± 55.4	0.001***
VLDL (mg/dL)	32.5 ± 16.6	21.87 ± 10.9	0.008**
HDL (mg/dL)	41.44 ± 8.7	68.1 ± 26.89	0.0016**
LDL (mg/dL)	113.3 ± 34.4	85.51 ± 26.8	0.007**

*Significant differences at P ≤ 0.05,
**Significant differences at P ≤ 0.01
*** Significant differences at P ≤ 0.001

The comparison of the level of hormonal and biochemical parameters in infertile women with different BMI

For each unit of BMI, the risk of pregnancy has decreased by 5% if it reaches 29 kg/m^2. Obesity gives infertility through numerous pathways, including oocyte qualitative and quantitative growth, impaired ovarian follicular production, implantation, and the growth of fertilization-embryo (13, 14). Table 3 data indicates a significant increase in the level of LH and a decrease in the level of FSH in infertile women when classified as BMI this which agreed with other studies referring to hyperleptinemia an impact obesity-related hypogonadism, PCOS, and type 2 diabetes. Within these energy abundance states, reproductive-defect mechanisms include central leptin resistance, in addition to direct gonadal-level impacts (14, 15). Although no major difference was observed in estrogen, progesterone, prolactin, and TSH. The concentration of TG with an increase in BMI was significantly increased in infertile women with BMI, ranging from 35–39.9 kg/m^2. High levels of BMI in follicular fluid are correlated with high levels of TG, and high levels of fatty acids contribute to increased generation of reactive oxygen species (ROS) with subsequent mitochondrial dysfunction, endoplasmic reticulum stress, and ultimately apoptosis. Oocytes and granulosa cells are affected by reproductive processes, resulting in low oocyte production and impaired oocyte maturation, and this agreed with others (16, 17).

The correlation between hormonal and biochemical parameters and the effect of BMI and WHR on infertility

The data presented in Table 4 show a correlation between infertility and BMI in all ages which confirms that obesity is an indicator that increases the risk of infertility. LH, FSH, TSH, cholesterol, TG, LDL, and VLDL contribute positively to infertility and BMI. Infertility and BMI have a significant negative association with estrogen, prolactin hormone, and HDL; while progesterone showed no statistically significant correlation.

The data presented in Table 4 also showed a correlation between infertility and WHR, confirming that obesity is an indicator for increasing the risk of infertility. Infertility and WHR are positively correlated with LH, FSH, TSH, cholesterol, TG, LDL, and VLDL. There is a significant negative correlation between infertility and WHR with estrogen, progesterone, prolactin hormone, and HDL.

The number of miscarriages with BMI

Figure 1 shows that the greater the body mass index, the higher the number of miscarriages, since at BMI of 33.8 of miscarriages were repeated three times. Some endocrine disorders, such as hypothyroidism, PCOS, and insulin resistance, are more typical of overweight women, and the percentage of increases in miscarriage in these diseases is documented. While PCOS is closely linked to obesity, it appears that obesity can also cause individual miscarriages (18).

Whereas when obese women showed a body mass index of 31 without miscarriages, it may be due to genetic causes and primary infertility that cannot be treated.

Conclusion

The results of this study showed that obesity, using BMI and WHR, is a new risk factor for increasing infertility among women in all age groups. Consequently, obesity is correlated to hormonal deficiency and dyslipidemia, which is responsible for infertility, quantitative oocyte development, and impaired ovarian follicular and qualitative development.

Women should also be informed on the importance of weight loss pre-pregnancy and advised to lose weight before diagnosis, to minimize the bad obstetric result due to obesity; this would also have a positive impact on their general well-being.

Table 3: A comparison of the level of hormonal and biochemical parameters in infertile women with different BMI

BMI / Hormonal & biochemical parameters	20-24.9 No= 19 (Mean ± SD)	25-29.9 No= 28 (Mean ± SD)	30-34.9 No= 45 (Mean ± SD)	35-39.9 No= 12 (Mean ± SD)	40≤ No= 3 (Mean ± SD)	P-value
Estrogen (E2) (pg/mL)	70.72 ± 28.0(a)	66.7 ± 34.6(a)	75.1 ± 29.2(a)	74.9 ± 28.13(a)	94.03 ± 8.5(a)	N
Progesterone (ng/mL)	1.71 ± 0.68(a)	1.62 ± 0.62(a)	2.47 ± 1.51(a)	1.35 ± 0.76(a)	1.03 ± 0.66(a)	N
FSH (mIU/mL)	6.83 ± 2.5(ab)	4.75 ± 3.0(a)	4.17 ± 1.8(a)	9.44 ± 1.2(b)	4.67 ± 1.4(a)	0.02*
LH (mIU/mL)	5.89 ± 2.7(ab)	4.28 ± 3.49(a)	6.24 ± 3.0(ab)	12.01 ± 1.2(b)	8.94 ± 2.2(ab)	0.01**
Prolactin (ng/mL)	12.24 ± 5.3(a)	27.31 ± 5.7(a)	18.95 ± 8.84(a)	15.53 ± 5.5(a)	21.69 ± 9.08(a)	N
TSH (µlU/mL)	1.98 ± 0.48(a)	2.24 ± 1.08(a)	2.017 ± 1.08(a)	1.89 ± 0.82(a)	2.203 ± 1.69(a)	N
Total cholesterol (mg/dL)	176.2 ± 22.3(a)	179.9 ± 41.3(a)	188 ± 29.7(a)	199.9 ± 25.6(a)	207 ± 8.54(a)	N
Triglyceride (TG) (mg/dL)	110.33 ± 87.1(a)	151 ± 82.4(ab)	163.67 ± 72.2(ab)	216.58 ± 112.5(b)	197 ± 48.1(ab)	0.05*
VLDL (mg/dL)	22.37 ± 17.5(a)	30 ± 16.53(a)	32.97 ± 14.1(a)	34.32 ± 22.5(a)	37 ± 9.8(a)	N
HDL (mg/dL)	49.16 ± 14.5(a)	42.17 ± 8.3(a)	40.62 ± 8.4(a)	39.05 ± 6.2(a)	38.01 ± 7(a)	N
LDL (mg/dL)	104.2 ± 16.5(a)	107.01 ± 36.8(a)	117.46 ± 32.5(a)	119.22 ± 41.9(a)	129.6 ± 5.5(a)	N

*Significant differences at P ≤ 0.05,
**Significant differences at P ≤ 0.01
N = No significant differences, a, b, ab denote Duncan-test

Table 4: The correlation between hormonal and biochemical parameters, and the effect of BMI and WHR on infertility

Hormonal and biochemical parameters	Effect of BMI on infertility		Effect of WHR on infertility	
	R-value	P-value	R-value	P-value
Estrogen (E2) (pg/mL)	-0.140	N	- 0.003	N
Progesterone (ng/mL)	0.0	N	-0.005	N
FSH (mIU/mL)	0.060	N	0.034	N
LH (mIU/mL)	0.218	0.024*	0.082	N
Prolactin (ng/mL)	-0.122	N	-0.072	N
TSH (µlU/mL)	0.056	N	0.074	N
Total Cholesterol (mg/dL)	0.238	0.01 **	0.15	N
Triglyceride (TG) (mg/dL)	0.217	0.025*	0.18	0.05*
VLDL (mg/dL)	0.208	0.031*	0.157	N
HDL (mg/dL)	-0.260	0.007***	-0.221	0.022*
LDL (mg/dL)	0.218	0.024*	0.109	N

*Significant differences at P ≤ 0.05, **Significant differences at P ≤ 0.01
*** Significant differences at P ≤ 0.001, N = No significant differences

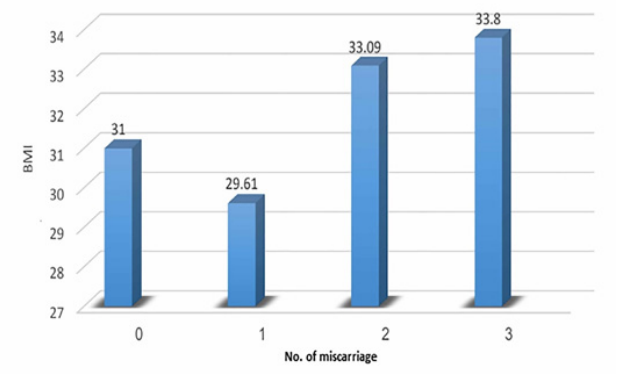

Figure 1: Number of miscarriages as a function of BMI

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Competing Interests

The authors declare that they have no competing interests.

Ethical approval

The research was carried out in compliance with all applicable national legislation, institutional policy, and

the values of the Helsinki Declaration, and was approved by the institutional review board of authors (210/R.A.D, 6/4/2017).

Consent

All participants' rights were protected and oral informed consent was obtained according to the Helsinki Declaration.

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