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HORMONAL BALANCE AND BODY MASS INDEX IN WOMEN INFERTILITY IN BAGHDAD

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ABSTRACT

Infertility is the inability to conceive a child for more than one year. The present study indicates that the obesity associated with infertility. The aim of the study to determine follicle stimulating hormone, luteinizing hormone, testosterone hormone and prolactin levels. and cholesterol and triglyceride concentration in 2nd inferetid women, the data were collected from 100 secondary infertilial women were age between 16-45 years old and grouped them in to obese (n = 45) and non-obese (n = 55). There was no significant difference between the two groups ($p < 0.05$). Body mass index in Infertile obese women is slightly higher than non-obese Infertile women which are statistically significant ($P < 0.001$). However, LH, TSH, cholesterol and triglyceride concentration in obese infertile women is significantly higher than non-obese infertile women ($p > 0.05$). The BMI was correlated positively with triglyceride in the obese group while BMI was positive correlation highly significant with cholesterol in the non-obese group. Regression analysis revealed obese to be strongly associated with observed infertility. The elevated prolactin values in secondary infertile women clearly show that there is a mechanism operating at the anterior pituitary level which shows an abnormal distribution of FSH and LH which may further explain the abnormal delay ovum maturation. This study also indicates obese associated with infertile of more than non-obese women.

KEYWORDS: Hormonal balance, body mass index, women infertility.

INTRODUCTION

Infertility defined as the inability of a couple to achieve pregnancy over an average period of one year (in a woman under 35 years of age) or 6 months (in a woman above 35 years of age) of unprotected sexual intercourse. Infertility can be due to the woman, the man, or both:

primary or secondary. For instance, if you or partner has a known fertility problem, you probably should not wait an entire year before seeking treatment. However, once you begin to explore your medical options, you'll find that fertility treatments offer more hope for a successful pregnancy than ever before. The vast majority of patients who seek care from a fertility specialist reach goal of becoming pregnant.[1]

Infertility may be caused by an underlying medical condition that may damage the fallopian tubes, interferes with ovulation, or causes hormonal complication. These medical conditions include pelvic inflammatory disease, endometriosis, polycystic ovarian syndrome, premature ovarian failure, uterine fibroids and environmental factors. Other causes of infertility in females include ovulation problems, tubal blockage, agerelated factors, uterine problems, previous tubal ligation and hormone imbalance while the main cause of male infertility is poor.[2]

Ovarian dysfunction could be caused by weight loss and excessive weight gain with body mass index (BMI) greater than 27 kg/ m2. Excess weight has also been found to have an effect on treatment efficacy and outcomes of assisted reproductive.[3] Fertility declines with age, and its peak between the ages of 18 and 24 years, while, it begins to decline after age 27 and drops at a somewhat greater rate after age 35, so age is the most important factor in female infertility.[4]

Infertility resulting from ovarian dysfunction may be due to the absence of eggs in the ovaries or due to a complete blockage of the ovaries. Polycystic ovaries syndrome (PCOs) is usually a hereditary problem and accounts for up to 90% of cases of ovulation.[5]

In PCOS the ovaries produce high amounts of androgens, particularly testosterone and thus amenorrhea or oligomenorrhea is quite common. The increased androgen production in PCO results in high levels of luteinizing hormone (LH) and low levels of follicle-stimulating hormone (FSH), so that follicles are prevented from producing a mature egg.[6] The hypothalamus, through the release of gonadotropin releasing hormones, controls the pituitary gland which directly or indirectly controls most other hormonal glands in the human body thus, alterations in the chemical signals from the hypothalamus can affect the pituitary gland, ovaries, thyroid, mammary gland and hence, hormonal abnormalities. Hormonal imbalance is an important cause of ovulation. Women with hormonal imbalance will not produce enough follicles to ensure the development of an ovul.[7]

Infertility may be caused by an underlying medical condition that maydamage the fallopian tubes, interferes with ovulation, or causes hormonal complications. Also, Triglycerides change dramatically in response to meals, increasing as much as 5 to 10 times higher than fasting levels just a few hours after eating. Even fasting levels vary considerably from day to day. Therefore, modest changes in fasting triglycerides measured on different days are not considered to be abnormal. These medical conditions include. About 40 percent of the issues involved with infertility is due to the man, another 40 percent due to the woman, and 20 percent result from complications with both partners.[8]

Most cases of female infertility are caused by problems with ovulation. Without ovulation, there are no eggs to be fertilized. Some signs that a woman is not ovulating normally include irregular or absent menstrual periods. Infertility causes due to insufficiency or imbalance hormones, deficiencies in luteinizing hormone (LH), follicle stimulating hormone (FSH) and elevated prolactin level even slight irregularities in the hormone system can affect ovulation. Ovulation problems are often caused by polycystic ovarian syndrome (PCOS) in which the eggs only partially developed within the ovary and there are male hormones excess. Some women are infertile because their ovaries do not mature and release an egg.[9]

Primary ovarian insufficiency is another cause of ovulation problem. It is occurring when a woman's ovaries stop working normally before she is the 40s. Less common causes of fertility problems in women include the blockage of the Fallopian tube due to malformations, infections such as chlamydia and/or scar tissue.[10], or physical problems with the uterus. There are other factors that can affect awoman's chances of conceiving include being overweight or underweight, or her age as female fertility declines after the age of 35. Sometimes it can be a combination of factors, and sometimes a clear cause is never established. Ovarian dysfunction could be caused by weight loss and excessive weight gain with body mass index (BMI) greater than 27 kg/m^2.[11] Excess weight has also been found to have an effect on treatment efficacy and outcomes of assisted reproductive technique. Estrogen is produced by pelvic inflammatory disease, endometriosis, polycystic ovarian syndrome, premature ovarian failure, uterine fibroids and environmental factors.[12] The aim of the study was to compares between obese and non-obese secondary infertile women by estimate the levels of serum follicle stimulating hormone, luteinizing hormone prolactin and TSH levels cholesterol and triglyceride concern also included in this study with BMI and to investigate the correlation between all parameters in this study.[13]

BACKGROUND

Several epidemiological studies have emphasized the importance of body composition, especially of abdominal or android fat distribution patterns, as risk factors for cardiovascular and metabolic diseases such as diabetes mellitus.[14] It seems obvious that steroid hormones have effects on human adipose tissue metabolism and distribution.

In the female, body composition parameters and weight status are also clearly associated with reproductive function. The importance of body fat and energetics for female reproductive success was first pointed out during the 1970s Frisch.[15], although the so-called Frisch hypothesis has since been disproved.[16]

Although the energy costs of human reproduction are lower than those of any other group of mammals, human ovarian function is extremely vulnerable to an energy imbalance. Pregnancy requires about 50,000 calories over and above normal metabolic requirements, and lactation requires from 500 to 1000 calories per day.[17] Therefore, ovarian function shows a graded continuum from fully competent cycles through luteal phase suppression, follicular phase suppression, ovulatory failure, oligomenorrhea, or amenorrhea in response to endogenous and exogenous factors affecting energy balance.[18]

Just as a negative energy balance and low amount of body fat have a negative effect on human ovarian function, a highly elevated amount of body fat and android kind of fat patterning also seem to affect female reproductive function negatively.[19] Disturbed ovarian function seems to be associated with an extremely low or an extremely high amount of body fat and abdominal or android fat patterning, which is typical in healthy, postmenopausal women only.[20] Furthermore, an android kind of fat patterning is associated with significantly decreased conception rates.[21] In this way, body composition parameters as well as fat distribution patterns may be interpreted as extragenital markers of human ovarian function. The aim of the present study was to document body composition and fat patterning of young, infertile, normal weight women to test the hypothesis that body composition and fat distribution patterns are markers of potential female fertility.[22]

Luteinizing hormone (LH) Known as Lutropin is a hormone produced by the anterior pituitary gland. In females, an acute rise of LH called the LH surge triggers ovulation and development of the corpus luteum.[23] In conditions with high LH and normal or low FSH

levels, as in PCOS, AMH concentrations are positively correlated with LH concentrations, while they are not negatively correlated with FSH.[24]

Furthermore, an independent positive correlation between AMH and LH levels has also been found. Also shown that normal- weight women with PCOS presented higher LH values than overweight and obese women with the syndrome.[25] Thus, the lower LH concentrations observed in obese women may be attributed to the increased aromatization of androgens to estrogens which takes place in the peripheral fat tissue, resulting in the suppression of LH. Therefore, higher AMH levels seen in normal-weight women with PCOS compared to obese women.[26] Thyroid Function and Human Reproductive Health Via its interaction in several pathways, normal thyroid function is important to maintain normal reproduction. In both genders, change in sex hormone binding globulin (SHBG) and sex steroids are a consistent feature associated with hyper- and hypothyroidism and were already reported many years ago.[27] In females, thyrotoxicosis and hypothyroidism can cause menstrual disturbances. Thyrotoxicosis is associated mainly with hypomenorrhea and polymenorrhea whereas hypothyroidismis associated mainly with oligomenorrhea.[28] Thyroid dysfunction can lead to menstrual disturbance, anovulatory cycles, and decreased fecundity. Proper management of thyroid dysfunction can result in restoration of normal fertility. Therefore, it is very important to screen thyroid abnormalities among women with infertility.[29]

Anti-Mullarian Hormone (AMH) Anti-Mullerian hormone (AMH) is a dimeric glycoprotein belonging to the transforming growth factor-beta (TGF-β) super family, which acts on tissue growth and differentiation.[30] It is produced by the granulosa cells from pre-antral and small antral follicles. Together with two other factors, it inhibits the initiation of premature follicle growth and decreases the sensitivity of follicles to FSH.[31] AMH levels decline with age from adult hood toward menopause reflecting the size of the ovarian follicle pool.[32] Several studies have shown that serum AMH measurement is more accurate than serum FSH, inhibin B or estradiol in predicting ovarian response.[33] Furthermore, AMH levels appear to remain constant throughout the menstrual cycle and thus can be reliably measured at any time unlike FSH, LH, estrodiol and other hormone markers that must be measured in the early follicular phase.[34] Follicle stimulating hormone (FSH) Human Follicle Stimulating Hormone (FSH) is a glycoprotein (M.W. approximately 30000D). FSH is secreted by basophilic cells of the anterior pituitary. FSH is responsible for the proliferation of the follicular cell, for the development of the griffin follicle and for ovum maturation.[35] FSH is needed to protect a

portion of the follicles in the growing follicle pool from Atresia, stimulate the follicles to grow, and to select the highest quality follicle from its cohort to begin ovulation. Low levels of FSH are found during follicle development and high levels during ovulation. As the granulosa cells enlarge, the level of AMH is diminished, and the follicles enter the growing pool and become regulated FSH.[36]

In Egypt, the prevalence of infertility using WHO definition has been estimated to be between 10% to 15% among married couples and causes of infertility can be found in about 90% of infertile cases, however, about 10% of couples without explained causes. A WHO task force revealed that tubal factor accounted for 36%, ovulatory factor for 33%, endometriosis 6%, and no demonstrable causes in 40% of cases. A similar distribution was found in Asia, Latin America, and the Middle East, whereas in Africa, most infertile women had tubal infertility, its prevalence is particularly high in sub-Sahara ranging from 20% to 60% of couples.[37]

Recently, hormonal disturbances have been considered of great importance in the knowledge of causes and diagnosis of female infertility. An increase in FSH in women may indicate a reduction in the production of good quality eggs and embryos for fertilization. a woman's chances for pregnancy may be lower than expected for her age. However, it does not mean she has no chance of conceiving. She may have more difficulty conceiving and may require infertility treatment.[38]

LH is a hormone that is produced in the pituitary gland in both men and women. In women, LH is an important part of the menstrual cycle. It 9 works in conjunction with follicle-stimulating hormone (FSH). The rise in estrogen tells the pituitary gland to stop producing FSH and to start making more LH. The shift to LH causes the egg to be released from the ovary, a process called ovulation. general, higher than normal levels of LH in a woman may mean the ovaries are absent or not functioning. In a young woman, high levels may mean that puberty is early Low levels of LH in the blood may indicate anorexia, an issue in the pituitary gland, stress, or damage to the hypothalamus in both men and women.[39] Prolactin plays an important role in the reproductive health of both women and men. Its main role, however, is to stimulate the production of milk in women after childbirth. In other words, prolactin triggers lactation. levels of prolactin have been found to be a measure of sexual satisfaction in both men and women.[40]

MATERIALS AND METHODS

Subjects

The present investigation was carried out in Iraq, the data were collected from 100 women with secondary infertility their age rang (16-45) years and grouped into obese (n=46) and non-obese (n=49).

Sampling

The blood was collected during the mid cycle (14–16) day on fasting by venipuncture. The blood was allowed to clot, then serum was collected for analysis. The serum was stored at (–20) C.

Clinical investigation

The physical examination of body weight was calculated by taking the weight in kilogram (kg), and height was measured in centimeters [9]. Age, height, weight, BMI The Body Mass index was calculated from the formula; BMI = weight (kilograms)/ height (m2), FSH, LH, testosterone, TSH were estimated by immuno enzymatic assay by mini VIDAS reader, cholesterol and triglyceride were estimated by using the kit method (Biomerieux, ITV12I5696 –france).

Statistical Analysis

The significance of the difference between the groups was tested using the student t-test analysis, and the results of hormones (FSH, LH, Testosterone, TSH) cholesterol and triglyceride, were expressed as mean ± SD and correlation between parameters had been examined by using Microsoft excel and Statistical Package for the Social Sciences (SPSS) Software 14.0 version. The fat cells and primary sex organs and thus, state of high body fat or obesity causes increase in estrogen production which the body interprets as birth control, limiting the chances of getting pregnant also, too little body fat causes insufficient estrogen production and thus menstrual irregularities with an ovulatory cycle. Proper nutrition in early life had been linked to being a major factor for later fertility. Fertility can be negatively affected by obesity. In women, early onset of obesity favors the development of menstrual irregularities, Obesity in.[41]

RESULTS

RESULTS Baseline characteristics The results of all infertile women (n=100) in this study showed significant increase in the level of the body mass index (BMI), leutial hormone (LH),

thyroid stimulating hormone (TSH), anti-mularian hormone (AMH) and thyroglobuline hormone (TG) table (1) except triiodothyronin (T3) & follicular stimulating hormone (FSH), show significant decrease than that of the control group (n=50) ($p \leq 0.05$),while thyroxin hormone(T4) level show no significant difference in its concentration , table (1). ($P \leq 0.05$).

The correlation of different laboratory parameters with AMH among patients There was a negative relationship between age and serum anti-Mullerian hormone concentration, while a positive correlation is present between BMI and serum AMH level.

Table 1: Correlation coefficient

Parameters	Correlation coefficient	P value
Age	-0,12	0,12
BMI	-0,32	0,23
FSH	-0,123	0,000
LH	-0,11	0,001
TSH	-0,20	0,121
T3	-0,12	0,213
T4	-0,21	0,431
TG	-0,23	0,100

Table 2: Anthropometric Parameters of Obese and Non-Obese Infertile Groups.

Parameters	obese group n=45 Mean ± SD	Non-obese group n=55 Mean ± SD	P value
Age (year)	34.213 ± 5.0431	24.203 ± 3.823	0,001
Height (cm)	165.693 ± 6.116	157.541 ± 6.356	0,131
Weight (kg)	79.714 ± 8.331	51.440± 4.528	0,000
BMI (kg /m2)	31.29 ± 2.123	23.112 ± 2.314	0,000

Many other studies have proved significant deviation in FSH, LH and testosterone levels in obese infertile women.[10] Body fat plays a critical role in human reproduction. Both excess and deficiency of body fat lead to reproductive failure. Body weight disorders are one of the first potential causes of reproductive failure in both men and women.[42] This is a problem that can be corrected by the affected individual and the infertile couple.

DISCUSSION

Via its interaction in several pathways, normal thyroid function is important to maintain normal reproduction. In both genders, changes in sex hormone binding globulin (SHBG)and sex steroids are a consistent feature associated with hyper- and hypothyroidism and were already reported many years ago.[43] In females, thyrotoxicosis and hypothyroidism can cause menstrual disturbances.

Thyrotoxicosis is associated mainly with hypomenorrhea and polymenorrhea, whereas hypothyroidism is associated mainly with oligomenorrhea.[44] In the present study show that disturbance in thyroid function lead to menstrual cycle abnormalities and increase in the concentration of AMH in all infertile women, that show an increase in TSH concentration and decrease in T3 concentration (P≤ 0.05 ,0.001 respectively). So thyroid dysfunction has been linked to reducing fertility. Data listed showed that there was a significant increase in TSH and TG levels (P≤0.05, & P≤0.000 respectively), and a significant decrease in T3 levels (P≤0.001), while there were no significant differences in T4 levels. Both the thyroid and ovarian are part of the endocrine system and belong to a common hormonal axis consisting of hypothalamus-pituitarythyroid-ovarian[45], and according to recent studies, many pieces of evidence showed that women who suffered from PCOs present in most cases thyroid disorders which are often associated with hypothyroidism or at risk of future hypothyroidism.[46] The hypothyroidism may lead to lower sex hormone binding globulin (SHBG), which in turn leads to high concentration of testosterone, one of the factors that contribute to the onset of some symptoms of PCOs such as infertility.[47] While, the correlation between AMH and thyroid disturbances, there is a negative correlation in patients. Hypothyroidism is associated with a broad spectrum of reproductive disorders ranging from abnormal sexual development through menstrual irregularities to infertility. The impact of hypothyroidism on the menstrual cycle has been identified since the 1950s and leads to changes in cycle length and blood flow.[48] Joshi et al found 68% of menstrual abnormalities in 22 women with hypothyroidism compared to only 12% in 49 controls.[49] In the study by Krassas et al, the prevalence of menstrual irregularities (mainly oligomenorrhoea) reached 23% among 171 hypothyroid patients, while being only 8% in 214 controls. An author also showed an association between the severity of menstrual abnormalities and higher serum TSH levels[50], which are in agreement with our study (P≤0.05). Severe hypothyroidism is common.

Obese women experience first a change in their reproductive cycles. Their cycles become irregular, unpredictable and often heavy and prolonged. Heavy, prolonged cycles correlate with increased estrogen production in the forms of estrone and estriol. In addition, obese women will often notice the appearance of dark (terminal) hair on the lower abdomen, face and between the breasts. This terminal hair results from the increased ovarian production of androstenedione that occurs with obesity. The initial sign of altered anovulation. Women with hormonal imbalance will not produce enough follicles to ensure the development of an

ovule.[51] Yet, body weight is often considered last in an infertility evaluation, the body weight of both partners of the infertile couple should be considered first when there is an obvious slender or obese body form in either partner. Also, awareness of the importance of body weight on reproduction enables couples to maintain appropriate body weight or to correct a body weight disorder before subjecting themselves to expensive, time consuming infertility evaluation and treatment reproductive cycles are similar to that of obese women. Obesity affects approximately half of the general population.[52] and is thus a common problem among the fertile population. Obese women have a higher prevalence of infertility compared with their lean counterparts. The majority of women with an ovulatory disorder contributing to their infertility have polycystic ovary syndrome (PCOS) and a significant proportion of women with PCOS are obese. Ovulation disorders and obesity-associated infertility represent a group of infertile couples that are relatively simple to treat. The incidence of hyperprolactinemia in women was found to be 62.16%[52], and 0%.[53] The levels of FSH, LH and Prolactin onodotropic hormones in infertile women were evaluated by many researchers. According to.[54] the higher level of FSH, LH in infertile women with a proper menstrual cycle is rarely found. A however lower concentration of those hormones observed only in 8% of cases.[55] also states that 65.5% of infertile women with proper two-phase menstrual cycles suffered from luteal phase defects but in 28.7% of cases lower values of FSH and LH were noticed.[56]

Kohler (Givens et al, 1986) States that women with higher values of prolactin and luteal phase defects have lower levels of FSH, and LH during their menstrual cycle. Both luteinizing hormone (LH) and Follicle-stimulating hormone (FSH) are required for follicle development and estrogen production. Due to elevated prolactin, the follicle-stimulating hormone and luteinizing hormone are decreased and causes infertility.[57] The obesity influences the reproductive cycle by impaired estrogen metabolism causing menstrual disturbance and ovulation. The present study clearly indicates that all the obese patients increased in serum prolactin level and decreased FSH levels. The hypothalamus, through the release of gonadotrophin releasing hormones, controls the pituitary gland which directly or indirectly controls most other hormonal glands in the human body. Thus, alterations in the chemical signals from the hypothalamus can affect the pituitary gland, ovaries, thyroid, mammary gland and hence, hormonal abnormalities. Hormonal anomalies that affect ovulation include hyperthyroidism, hypothyroidism, polycystic ovary syndrome (also known as Stein-Leventhal syndrome) and hyperprolactinemia.[58]

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