Evaluation of some physiological parameters for obese women suffering from pregnant disturbance in Basrah Governorate, Iraq-Case Study

Evaluación de algunos parámetros fisiológicos para mujeres obesas que sufren trastornos del embarazo en la gobernación de Basora, Iraq: estudio de caso

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Abstract

Background: Obesity is a public health problem spreading markedly since 1980 till now, which has been increased for more than threefold. The World Health Organization (WHO) estimated that more than 700 million adults are obese, while 2.3 billion are overweight worldwide and nearly 4.3 million adults die every year from obesity and overweight health disturbance. This phenomenon coincided with an increase in infertility women.

Aim of study: evaluation the most common disorders in infertile obese women and compare them with the group of fertile obese women by testing some physiological parameters.

Subjects and methods: The study was conducted on patients attending to the gynecological consultations in Ibn Ghazwan maternity and children hospital and infertility center in Basrah governorate from August 2020 to February 2021. The study was included a random sample of 64 infertile women, obesity or overweight suffering from Endometriosis and polycystic ovarian syndrome in addition to 22 women volunteer who are fertile obese or overweight as control group.

Results: Statistical results for endometriosis subjects showed significant reduction in the concentration of Testosterone, LH and AMH hormones while the concentration of estrogen, leptin hormones, TNF-alpha and MDA were significantly higher compared with control group, while there was no significant difference for progesterone hormone concentration. Furthermore, the results of PCOS patients showed a significant rise in concentration of testosterone, LH, AMH, leptin hormones, TNF-alpha and MDA while the concentration of estrogen, progesterone and FSH hormones were significantly reduced.

Resumen

Antecedentes: La obesidad es un problema de salud pública con una marcada expansión desde 1980 hasta la actualidad, que se ha incrementado en más del triple. La Organización Mundial de la Salud (OMS) estimó que más de 700 millones de adultos son obesos, mientras que 2300 millones tienen sobrepeso en todo el mundo y casi 4,3 millones de adultos mueren cada año por problemas de salud relacionados con la obesidad y el sobrepeso. Este fenómeno coincidió con un aumento de la infertilidad femenina.

Objetivo de estudio: evaluar los trastornos más comunes en mujeres obesas infértiles y compararlas con el grupo de mujeres obesas fértiles mediante la prueba de algunos parámetros fisiológicos.

Sujetos y métodos: El estudio se realizó en pacientes que asistieron a las consultas ginecológicas en el hospital maternoinfantil y centro de infertilidad Ibn Ghazwan en la gobernación de Basora desde agosto de 2020 hasta febrero de 2021. El estudio se incluyó en una muestra aleatoria de 64 mujeres infértiles, con obesidad o sobrepeso. de endometriosis y síndrome de ovario poliquístico, además de 22 mujeres voluntarias que son fértiles, obesas o con sobrepeso como grupo de control.

Resultados: Los resultados estadísticos para los sujetos con endometriosis mostraron una reducción significativa en la concentración de testosterona, hormonas LH y AMH, mientras que la concentración de estrógeno, hormonas leptina, TNF-alfa y MDA aumentaron significativamente en comparación con el grupo de control, mientras que no hubo diferencias significativas para la hormona progesterona. concentración Además, los resultados de los pacientes con SOP mostraron un aumento significativo en la concentración de testosterona, LH, AMH, hormonas leptina, TNF-alfa y MDA, mientras que la concentración de estrógeno, progesterona y hormonas FSH se redujeron significativamente.

Obesity is a public health problem spreading markedly since 1980 till now, which has been increased for more than threefold. The World Health Organization (WHO) estimated that more than 700 million adults are obese, while 2.3 billion are overweight worldwide and nearly 8.2 million adults die every year from obesity and overweight health disturbance. This phenomenon coincided with an increase in infertility women[108].

Obesity is defined as an excessive accumulation of fat in different body parts which becomes harmful to human health[109] and as a result of energy imbalance between eating food (calories consumed) and consuming it as body energy (calories expended) [87,102]. It can have a considerable impact on human health, including sexual performance which can be a consequence of obesity. Most studies have also shown that weight reduction leads to an improvement in sexual performance.[57] Fundamentally, can determination total obesity by using Body mass index used to refer to total obesity [BMI = weight (kg)/(length)^2] [106].

In general, obesity is divided into two types according to the distribution of excess stored fat in tissues the first one Gynoide obesity which Excess fat is deposited from the body's need in the hip and thigh area specifically in women[77]. While, the second type is Central Obesity also called (android type) It is characterized by the distribution of fat in the abdominal region and around viscera so it is called as visceral obesity or abdominal obesity[34] and is clinically measured by (waist/hip circumference)[24]. This type of obesity is hallmark of polycystic ovary syndrome[61].

Obesity plays a big role in the incidence of polycystic ovary syndrome through multiple mechanisms, including hyperandrogenism, increased bioavailability of free androgen, changes in granulosa cells function, maturation and evolution of the follicles disorder, menstrual disorder, ovulation and pregnancy difficulty[76].

Obesity are linked with many diseases, including the difficulty of pregnancy and reproduction, such as anovulation, menstrual cycle disorders, miscarriages and infertility[15,98]. Polycystic ovarian syndrome, is one of endocrine reproductive disease including increased in tunica , thickness of cortical and subcortical stroma which known then as polycystic ovaries women which are signs of hyperandrogenism (high testosterone level), anovulation multi-small follicle on ovaries, insulin resistance and obesity[2,8,68,85].

Moreover, obesity considered as a risk factor for endometriosis.[91]Endometriosis is one of gynecological women disease occurred in reproductive age mostly in 25-39 years old also in younger women in adolescents or in menopause[18,113]. It is recognized by growing endometrial tissue outside the uterus mostly in ovaries, rectovaginal area, fallopian tube and pelvic cavity[106]. Women with this disease suffering from dysmenorrhea, bleeding menstrual, pelvic pain and dyspareunia[20]. Therefore, the rate of infertility will increase.[99] However, 25% of endometriosis women do not suffer from any symptoms[19], that may belong to the difference in ethnicity[17]. In the study of [36,46] found that 25.2% of endometriosis women have overweight and 14.3% are obese. While other studies have emphasized that BMI had no association with endometriosis[86,99].

In general, infertility is divided into three types; the first one is primary infertility which is the inability of couple to obtain natural pregnancy at all after one year or more despite normal sexual relationship and without using protective or contraceptive methods[11,111]. The Secondary infertility can be defined as incapability to conceive again after the first successful pregnancy or the inability of couple to obtain pregnancy either by aberration or by birth[96,112] .

Finally, there is unexplained infertility it refers to the case where no apparent medical reason for each partner to prevent pregnancy and all fertility analysis are normal[39].

Commonly, many causes were detected to induce women infertility, such as polycystic ovary syndrome, premature ovarian failure, fallopian tubes retardation, endometriosis, uterine Adhesions and hormonal disorders[41,89].

Hormonal disturbance is one of most popular reasons for infertility in both male and female. Khmil et al [54] indicated that there was connection between sex hormone imbalance and infertility in women caused by PCOS. There findings showed a significant increase in AMH, LH, Estradiol and Testosterone and decreased FSH levels of PCOS women comparison with healthy women.

Likewise, inflammation have role in induced infertility by many routs such as reduction the quality of oocytes and effecting the implantation of embryo[56]. Tumor necrosis factor-alpha (TNF-α) considers as a good marker for diagnose this relation. AL-Azawy [3] asserted the relationship between inflammation and infertility. the study finds a significant increase in serum TNF-α in group of infertile women comparison with fertile.

Leptin has a critical role in metabolism, appetite and reproduction also had immunoregulatory and proinflammatory function, so it may lead to drive fertility disorder[16]. The study of Hussein et al [48] indicated a significant increase in the level of serum leptin in Endometriosis women than in healthy fertile women while Al-Fartosy et al [5] showed non-significant difference in the level of leptin in unexplained infertility when compared with healthy fertile women.

oxidative stress one of various reasons that have been recognized for reproductive pathologies and affecting women fertility also, influence the keeping of a viable pregnancy[45,101]. So, any changes in the balance between oxidant/ antioxidant toward oxidant leading to a pathological role causing Endometriosis, PCOS and infertility[47]. also, Al-Helaly [6] found increased in MDA level in infertile women compare with fertile women.

Materials and methods

The current study involves (86) volunteer women aged between 19-40 years old, twenty tow were healthy (fertile) and (64) were (infertile). All the volunteer diagnosed by specialized doctors in Ibn Ghazwan maternity and children hospital and infertility center in Basrah Governorate. The blood samples were collected in collaboration with the laboratory of gynecological department staff Then samples were divided into two groups based on endometriosis and PCOS cases, approximately (5mL) of ulnar vein blood were collected and kept in gel tube left it till 15 minutes after that centrifuging the blood at 3500 rpm to prepared serum which divided and placed in Eppendorf's, and the samples were preserved to a degree (-20oC) until tests were carried out.

Assessment of hormone concentration

Serum concentration of Testosterone, Estrogen, Progesterone, FSH and LH were evaluated by Enzyme-Link Immunoassay (ELISA) Type (Biotek-USA) and the specific kit for each hormones used in the study prepared by)Accu bind USA) and (Bt-laboratory china) According to the method of[33,43,52,55,107]. While AMH and Leptin have also been measured according to the competitive interaction between the sample and hormone (hormone-enzyme conjugate) according to kits serial number (E1052Hu, E1559Hu) respectively.

Determination of SHBG, TNF-alpha and MDA levels

the competitive interaction between the sample and hormone (hormone-enzyme conjugate) by ELISA (Enzyme-Link Immunoassay) was used to estimate the level of TNF-alpha and MDA using Bt-laboratory china kits according to kits serial number (E0082Hu, E1371Hu) respectively.

Statistical Analysis

The Statistical Package for the Social Sciences (SPSS ver.23) used to analyze the data statistically. One Way ANOVA was performed contrast analysis test. The Tuky test was also used to show differences among groups (pair ways comparison) at significant levels P ≤ 0.05, P ≤ 0.01, P ≤ 0.001, P ≤ 0.0001.

Results

Body Mass Index (BMI)

No significant difference was detected in the Values of BMI among endometriosis, PCOS and control group (p=0.612) as explained in (Table 1).

Table 1. BMI value in women with certain types of fertility disorders (n = 64) and control group (n = 22)

	Mean) ± (Standard error
Groups	BMI (kg/m^2)
Control	[a]1.057 ± 31.895
Endometriosis	[a]0.669 ± 32.431
PCOS	[a]0.768 ± 33.329

(a)similar letters = no significant difference

Concentration of some sexual hormones in the serum

Table 2 showed a significant decrease in the Concentration of testosterone hormone in endometriosis women (0.016±0.175ng/dl), while it was significantly higher in PCOS women (0.206±1.840ng/dl) when compare with control group (0.043±0.385ng/dl).

In contrast, estrogen hormone Concentration in the endometriosis group showed a significant increase (0.993±14.157pg/ml) in (P≤0.0001) in comparison with control group, while it was decreased significantly at the PCOS group (0.152±4.589pg/ml) compared to the control group (0.496±8.129pg/ml) (Table 2).

In turn of progesterone hormone concentration at Endometriosis group (0.065±0.543ng/ml) at (P = 0.063) while it was decreased significantly in the PCOS group (0.024±0.119ng/ml) compared to the control group (0.075±0.575ng/ml).

Table 2. Concentrations of sex hormones in women with some types of fertility disorders (n = 64) and control group (n = 22)

Groups	(Mean ± Standard error) Physiological criteria		
	Progesterone(ng/ml)	Estrogen(pg/ml)	Testosterone(ng/dl)
control	[a]0.075±0.575	[a]0.496±8.129	[a]0.043±0.385
Endometriosis	[a]0.065±0.543	[b]0.993±14.157	[b]0.016±0.175
PCOS	[b]0.024±0.119	[b,c]0.152±4.589	[b,c]0.206±1.840

- (a b c) Different letters = having a significant difference

Table 3 revealed a considerable increase in the FSH hormone concentration in the endometriosis group (0.479±11.619 mIU/ml) at (P≤0.0001) and a significant decrease in the PCOS group (0.293±7.624 mIU/ml) in comparison to control group (0.247±9.133 mIU/ml).

Inferential analysis also showed a significant decrease in LH hormone concentration in the group of endometriosis patients (0.318±1.109 mIU/ml) at (P≤ 0.0001) when comparison with the control group, while it was significantly higher in the group of PCOS (0.289±15.815 mIU/ml) than the control group (0.407±6.109 mIU/ml) and endometriosis group (P≤0.0001). as it obvious in Table 3.

A significant decrease in the AMH hormone concentration was demonstration in the endometriosis group (0.098±0.492) at (P≤ 0.0001) compared to the control group (0.223±3.035ng/ml) while it increased significantly in the PCOS group (0.462±7.275ng/ml) compared to the control at (P≤0.0001) also it was increased in pcos group (0.462±7.275ng/ml) compare with endometriosis (Table 3).

Table 3. Concentration of sex hormones in women with some types of fertility disorders (n = 64) and control group (n = 22)

	(Mean ± Standard error) Physiological criteria		
Groups	AMH (ng/ml)	LH (mIU/ml)	FSH (mIU/ml)
Control	[a]0.223±3.035	[a]0.407±6.925	[a]0.247±9.133
Endometriosis	[b]0.098±0.492	[b]0.318±1.109	[b]0.479±11.619
PCOS	[b,c]0.462±7.275	[b,c]0.289±15.815	[b,c]0.293±7.624

- (a b c) Different letters = having a significant difference

Leptin concentration

Leptin concentration in patient with endometriosis and pcos were significant rise (0.960±18.985 ng/ml and 1.272±17.348 ng/ml) respectively at (p≤ 0.0001) compared to control group (0.397±9.12 ng/ml) (Table 4).

Table 4. Concentration of lipid hormone in women with some types of fertility disorders (n = 64) and control group (n = 22)

	Mean) ± (Standard error
Groups	Leptin (ng/ml)
Control	[a]0.397±9.125
endometriosis	[b]0.960±18.985
PCOS	[b]1.272±17.348

- (a b) Different letters = having a significant difference

Concentration of TNF-α

Similarly, the concentration of TNF-α showed a significant increase in patients with endometriosis and PCOS (4.628±85.826 ng/l and 4.850±96.690 ng/l), respectively at (p≤ 0.0001) compared to its concentration in the control group)4.962±62.300 ng/l) (Table 5).

Table 5. TNF- α concentration in women with some types of fertility disorders (n = 64) and control group (n = 22)

	Mean) ± (Standard error
Groups	TNF-α (ng/l)
Control	[a]4.962±62.300
Endometriosis	[b]4.628±85.826
PCOS	[b]4.850±96.690

- (a b) Different letters = having a significant difference

Concentration of MDA

One Way ANOVA test results showed a significant raise in MDA concentration in both patients group (1.841±35.709 nmol/ml and 2.192±33.721 nmol/ml) at (p≤ 0.0001) in comparison with control group concentration (1.076±18.694 nmol/ml) (Table 6).

Table 6. MDA concentration in women with some types of fertility disorders (n=64) and healthy group (n = 22)

	Mean) ± (Standard error
Groups	MDA (nmol/ml)
Control	[a]1.076±18.694
endometriosis	[b]1.841±35.709
PCOS	[b]2.192±33.721

- (a b) Different letters = having a significant difference

Discussion

Body Mass Index Value

Inferential analysis between healthy and patients groups (endometriosis and PCOS) showed there was no significant difference in the BMI value. This can be attributed to the study design that included the overweight and obese women and the BMI was between 25 and 40 kg/m^2.

Concentration of sex hormones in serum

The current results showed a significant decrease in concentration of testosterone hormone in women with endometriosis comparing to the control group. Simultaneously, to a significant reduction in LH concentration which was recorded currently that may support the decline in testosterone, as LH activate theca cell of primary follicles to rise the production of androgen[23] which in turn used by granulosa cell to produce estrogen under the control of FSH[12, 37,50]. This result was in consistent with the previous results of [30,31] which found a decline in testosterone in women with endometriosis in comparison with healthy women.

Likewise, immunological alternations that coincidence with endometriosis produce cytokine in blood that simultaneously leads to hormonal disorder especially in steroid hormones by modulating the expression of sex steroid hormones and rising aromatase activity therefore increased convert testosterone to estradiol[42].

In contrast, the results have also revealed a significant increase in the concentration of testosterone hormone in women with polycystic ovary syndrome in comparing to the control group. This finding is consistent with the results of [69,103] which noted that one of the reasons for the high concentration of testosterone hormone in polycystic ovary syndrome patients was adipose tissue. In details, hyperandrogenism in women with polycystic ovary syndrome could be attributed to the elevation in fat deposition in the abdominal region and subcutaneous adipocytes in turn that promote metabolic disorders[35]. Thus, that lead to the availability of free fatty acids that directly affect the liver[110] causing lower in SHBG synthesis and affecting testosterone hormone concentration[63].

The ability of adipose tissues to collect and metabolize hormones through enzymatic reactions also has a significant effect on the hormonal reproductive axis[95]. The relative lack of FSH hormone secretion may cause weakness in follicles maturation and reduce aromatase activity, resulting hyperandrogenism in women with polycystic ovarian syndrome[27].

Furthermore, hyperinsulinism can cause hyperandrogenism by increasing the level of free testosterone hormone in the circulatory system as a result of reducing in the production of the sex hormone that associated with globulin SHBG production by the liver [4,25,29,61,84].

Moreover, Azziz et al [10] demonstrated that high levels of AMH hormone in polycystic ovary syndrome patients inhibited the functioning of FSH, that leads to hyperandrogenism. High levels of AMH activate the release of LH

in GnRH-neuron through the AMH receptor[26]. The rising in AMH hormone inhibits the expression of hormones in granulosa cells, impeding the conversion of androgen to estrogen and thus its elevated level[63].

Current results showed a significant decline of LH and a significant rise of FSH in the group with endometriosis comparing to the control group. This was in consistent with[65]. In the natural cycle of fertile women, the pituitary gland secretes the hormone that stimulates the follicles FSH and luteinizing hormone (LH) to stimulate the growth of ovarian follicles. They also provide positive and negative feedback to the pituitary gland culminating in the flow of LH to indicate optimal ovulation[92]. Endometriosis associates with changes in the hypothalamic-pituitary ovarian axis (HPO axis), hormonal levels of LH / FSH in serum, peritoneal fluid and follicular fluid that drive a dysfunction in feedback pathways and thus prevents normal periodic changes in the ovaries for the development of follicles, this causes defective ovulation and weak fetal engravings which are characteristic or symptomatic of endometriosis[14].

Conversely, the finding revealed a significant decrease in FSH and a significant rise in the level of LH in the polycystic ovary syndrome group compared to the control group, that could be attributed to an increase in pulse frequency that are released by the GnRH hormones in women with PCOS which causes an increase in LH secretion on FSH hormone[27].

Moreover, the low levels of progesterone hormone recorded among PCOS patients in the current study may explain the high levels of LH, because progesterone inhibits the release of LH from the pituitary gland through feedback action by inhibiting the rate of excretion of gonadotropin[49], also the disturbance in leptin secretion stimulate GnRH then increased secretion of LH[9].

The results of the present study also showed that there was a significant decrease in the level of AMH in endometriosis group compared to the control group, our results agreed with Pedachenko et al [79] and Suardi et al [93]. The lining of the endometriosis can affect the follicles either through the pressure of the ovarian wall surrounded by the cyst, which can obstruct circulation and cause loss of the follicle, and thus lowering AMH as a result of the reduction in the number of follicles or by inflammatory reaction in endometriosis, that may cause a damage to the follicles and decreases the level of AMH[53] .On the other hand, the reduction in AMH may be produced by the chronic inflammatory which induce follicular damage and disorders in their functions[58]. Furthermore the increased in reactive oxygen species in ovaries of endometriosis women may cause a reduction in AMH level[58] In addition, the reduction in the testosterone level in the patients suffering from endometriosis can promote the apoptosis of granulosa cell causing poor ovarian reserve and decreasing in AMH[74].

While in the group of PCOS the level of AMH increased significantly compared to the control group, these results are consistent with the results of [28],[82]. Polycystic ovary syndrome is characterized by an increase in the number of follicles, which has been shown to occur in the pre-ovulation stages, therefore the level of AMH production increases 75 times higher per granulosa than the normal ovary cells[80].

AMH is positively associated with androgen levels which have shown that women with hyperandrogenism and PCOS have high levels of AMH, that may be explained by increasing the total number of primary follicles in the polycystic ovary, resulting in an increase in level of androgen, hence, the androgens stimulate the expression of (FSHR) FSH receptors and promotes the effect of FSH causing the growth of follicles, that in turn leading to increase production of the hormone AMH[64] .

In endometriosis, the reduction of LH / FSH is associated with the reduction of AMH, indicating a lower ovarian reserve and lower ovarian testosterone hormone[30, 92].

Meanwhile, we found increased in TNF-α concentration in women with endometriosis. In the pathophysiology of Endometriosis, the inflammation plays a very important role, mainly by changing immune cells function and rising the level of pro-inflammatory factors in the peritoneal cavity, blood and Endometrium. These immune modifications suppress apoptotic pathways and fast the adhesion and proliferation of endometrium cells and injury in the neurogenesis and angiogenesis of endometrium[21,32]. In addition, sex hormones especially estradiol enhances the expression and release of pro-inflammatory factors and extreme inflammation in Endometriosis disease that participate to alter of hormone regulation by changing sex hormone receptors expression and rising aromatase activity. Furthermore, dysregulation of the inflammatory pathway causes alteration in cellular responses to sex hormone involvement to disease progression [42].

In PCOS women the concentration of TNF-α increased in contrast with healthy women this result agreed with [7,90]. This increased linked directly with hyperandrogenism and insulin resistance in PCOS women which failed to inhibit monocyte-derived cytokines like TNF-α as a response to glucose intake[44] Serum TNF-α also increased fundamentally because of obesity and hyperandrogenism in PCOS women[100,75,88]. As well as, the oxidative stress which occurred by accumulation of adipocyte induces a hypoxia, it may also have a role in TNF-α increase by considering it as strong triggers of inflammatory response[38,70].

Malondialdehyde (MDA) high level findings as marker of oxidative stress in endometriosis and PCOS women were similar to [67, 71], who found high MDA in endometriosis women serum than in healthy women. These two cases are considered as types of inflammation and macrophage cells act an essential role in regression of red blood cells that release chemical induce oxidative stress and proinflammatory mediators like heme and iron[22,60]. Ito et al [51] explained that accumulation of iron, heme and hemoglobin induces oxi-

dative stress which leading to DNA hypermethylation and histone alteration these conditions connect to disturbed endometrium growth in endometriosis women.

With regard to rising MDA in PCOS women our result corresponds with Fathi [40] which found increase in serum MDA in the PCOS women in comparing with healthy women. That rising may be explained through the fact that hyperandrogenism in PCOS leads to increase MDA level[94] or by insulin resistance and high blood glucose in women with PCOS[59]. The possible explanation of oxidative stress appearance in PCOS is the excess production of reactive oxygen species in the ovarian follicles that inhibits the antioxidants protection of follicular fluid and breaks down immature ovum[1].

At last, the present study showed that there is a significant increase in leptin in both endometriosis and PCOS women compare with control group this result was agreement with olszanecka-Glinianowicz [73] who found the high level of serum leptin in PCOS women in the same age and body mass index. Leptin plays an important role in controlling the metabolic pathways of reproductive ability through presenting information about the level of body energy for GnRH neurons[105] thus, increased leptin level in serum have role in pathophysiological features of PCOS by enhancing GnRH release, activating pituitary gonadotrophs or reproductive organs[81]. Because Leptin produce from fatty tissue so any increased in body fat leads to more production of it[72] and that fact are in constant to current finding because all study cases are obese or over weight. Furthermore, the finding of our study about the increased of leptin in endometriosis women was similar to Hussein et al [48] who found a significant increase in serum leptin in endometriosis women than in healthy women. Hyperleptinemia have linked with proinflammatory and chronic inflammatory in obese patients so there is a continuous loop between them[78]. The possible reason for that belong to the nature of endometriosis as chronic inflammatory and the role of proinflammatory cytokine like TNF-α on induce leptin secretion[66].

Conclusions

In conclusion, The common reason of pregnancy disturbance in obese women in Basrah Governorate, were Endometriosis and Polycystic Ovarian Syndrome that based on the current results showed high percentage of infertility among women suffering from Endometriosis or PCOS, Furthermore the irregular in sex hormones and leptin have essential role in increasing pregnancy disturbance in addition to TNF-alpha and MDA .Further study are required to investigate the effect of more physiological and immunology parameters on women infertility.

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