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Impact effects of (AMH) anti- mullerian hormone positively with and androgen , insulin and in women with PCOS.

BY

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قال تعالى:

{فَتَعَالَى اللَّهُ الْمَلِكُ الْحَقُّ ۗ وَلَا تَعْجَلْ بِالْقُرْآنِ مِن قَبْلِ أَن يُقْضَىٰ إِلَيْكَ وَحْيُهُ ۖ وَقُل رَّبِّ زِدْنِي عِلْما}

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Abstract

Objective

Polycystic ovary syndrome (PCOS) falls among the most prevalent endocrine disorders affecting about 8–13% of women of reproductive age . The aim of this study was to determine AMH , insulin and androgen in women with PCOS to study the effect of these hormones on reproductive ability . and relationship between age and PCOS in addition to relationship between PCOS with pregnancy and IVF

Method

This study was conducted on 35 infertile women between age 18 and 41 years. The Questionnaire involve the age of women , AMH level , insulin level , androgen level , IVF and pregnancy occurrence without asked for their names or contact information, ensuring the privacy of survey respondents

Result

This study show there are significant increase in serum level of AMH and insulin in women with PCOS compare with healthy women but serum level of androgen does not show significant change in women with PCOS compare with healthy women . most women with PCOS in ages ranging from 25 to 30 .

Chapter One

1.Introduction

Polycystic ovary syndrome (PCOS) falls among the most prevalent endocrine disorders affecting about 8–13% of women of reproductive age . PCOS is regarded as a complicated endocrinological illness associated with dysregulations of the psychological, metabolic, and reproductive systems and is a major public health concern. Due to the defining trait of PCOS, anovulation, it is the most precipitating condition affecting female fertility. Following the initial description of this condition by Stein and Levanthal in 1935 , numerous studies on the pathophysiology of the disease were conducted. However, the etiology of the disorder is yet to be understood completely. (1)

Ultrasonographically, the ovaries have an increased volume with a different number of immature follicles (poly-cysts) . The main characteristic of this syndrome is imbalanced levels of sex hormones and chronic anovulation due to increased androgen levels (hyperandrogenism), in the absence of specific adrenal and/or pituitary diseases . PCOS increases the short-term and long-term risk of endometrial cancer , psychological problems (anxiety, depression) , pre-eclampsia , recurrent abortion , perinatal mortality and possibly breast cancer and long-standing risk of obesity , type 2 diabetes, metabolic syndrome, hypertension , fetal macrosomia (baby that weighs more than 4 kg) or anomalies , dyslipidemia , cardiovascular diseases , thyroid , and hyperplasia . The clinical features of this complication include infertility, hirsutism, dysfunctional uterine bleeding, pregnancy complications, irregular menstrual cycle, alopecia, and acne as shown in Figure (1).

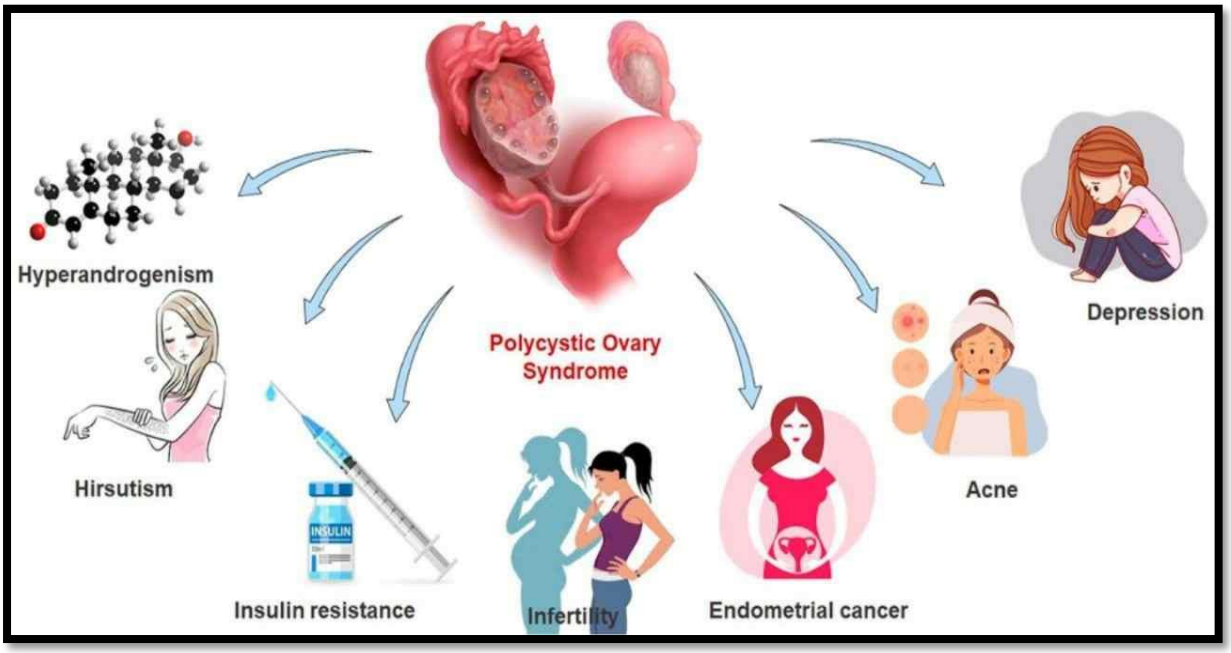


Figure 1. Clinical manifestations of polycystic ovary syndrome (PCOS).

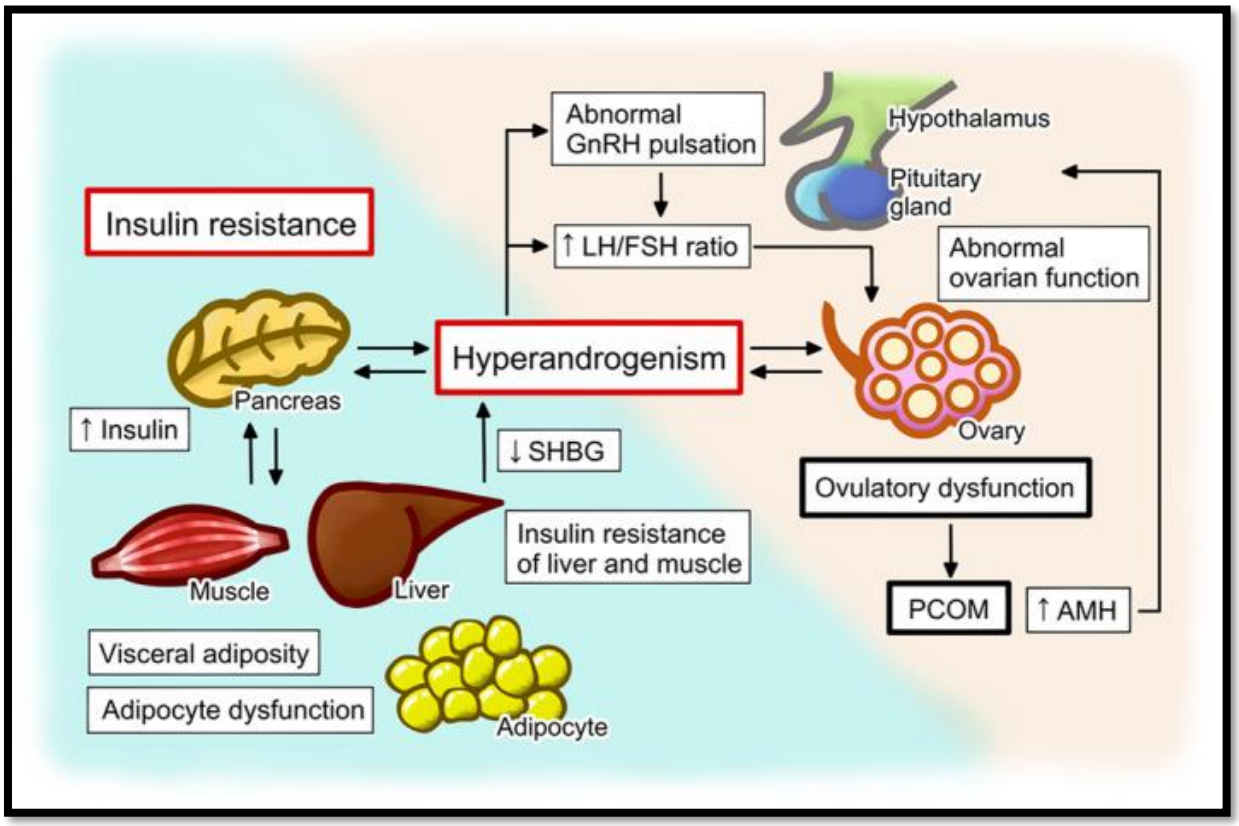
1.1 Pathophysiology of PCOS

The main cause of difficulties in understanding the pathophysiology of PCOS is its heterogeneous and complex nature. Hyperandrogenism, ovulatory dysfunction, aberrant gonadotropin-releasing hormone (GnRH) pulsation and the resulting abnormal gonadotropin secretion, and insulin resistance have been implicated in the pathophysiology of PCOS; these factors interact and exacerbate one another (Figure 2). Ovarian dysfunction involves the hypersecretion of androgens, which is associated with aberrant follicular growth and ovulatory dysfunction, causing PCOM. High concentrations of anti-Müllerian hormone (AMH), secreted by pre−/small antral follicles that accumulate in PCOS ovaries, further exacerbate the ovarian dysfunction by altering the follicular microenvironment and/or GnRH pulsation.

Hyperandrogenism causes a dysregulation of the pulsatile secretion of GnRH, which can at least in part be explained by aberrant negative or positive feedback by progesterone and estrogen, causing the abnormal secretion of gonadotropins and, specifically, excess secretion of LH.

High concentrations of LH and the resulting imbalance in the LH/FSH ratio exacerbate the dysregulation of follicular growth, as well as causing the

hypersecretion of androgens from thecal cells. Insulin resistance is another key component of the pathophysiology of PCOS, although it is not included in the diagnostic criteria . This insulin resistance manifests in insulin-sensitive organs, such as liver and muscle, and is associated with visceral adiposity and adipocyte dysfunction. Excess androgen secretion increases the level of insulin resistance, and hyperinsulinaemia, which develops secondary to the insulin resistance, further increases androgen secretion and induces the production of sex hormone-binding globulin (SHBG) in the liver, thereby increasing the circulating concentration of bioactive free testosterone and further aggravating the disorders associated with hyperandrogenism [2]



Pathophysiology of PCOS

1.2 Anti-Müllerian hormone

Adescribed by Alfred Jost in the 1940s . It belongs to the TGFβ super family and plays an important role in sexual differentiation and regulation of folliculogenesis. It derives its name because of its ability to inhibit the development of mullerian duct structures in the male fetuses . AMH is composed of two identical glycoprotein subunits, each of which has a larger N-terminal prodomain and a smaller C-terminal mature signaling domain, both connected by disulfide bridges. Pre-proAMH is a precursor molecule that undergoes proteolytic cleavage, producing biologically inactive proAMH which then yields the biologically active form of AMH. AMH attaches to specific receptors on cells of target tissues. The C-terminal of AMH binds to the extracellular domain of AMH type 1 and type 2 serine/threonine kinase receptors, producing an intracellular Smad signal, which in turn regulates target gene transcription. Anti-Mullerian hormone plays a major role in sex differentiation . The gonads are indifferent until the sixth week of fetal life. Genetic sex is determined by the sex chromosomes. The sex determining region of the Y chromosome (SRY) in male (XY) fetus allows the indifferent gonad to develop into testes. The Leydig cells secrete testosterone that stimulates development of Wolffian duct structures and Sertoli cells secrete Anti-mullerian hormone that suppresses the development of Mullerian duct structures. In female (XX) fetuses, the absence of SRY allows the gonads to develop into ovaries, and the absence of AMH in early fetal life allows Mullerian ducts to develop into fallopian tubes, uterus, cervix, and the upper third of the vagina [3]. AMH or Mullerian inhibiting substance (MIS) is a glycoprotein hormone, with a molecular weight of 140 kDa, and pro-duced by granulosa cells in ovarian follicles from 36 weeks of gestation until menopause. It is first made in the pri-mordial follicle stage but the highest production is in the preantral and small

antral stages (\4-mm diameter) of folliculogenesis. During these stages, follicles are micro-scopic and cannot be seen by ultrasonography, thus limit-ing their ability to be counted by ultrasound. Production of AMH gradually decreases as the follicle grows further and then finally stops once the follicle reaches 8-mm diameter. AMH levels do not change significantly throughout the menstrual cycle. Normal serum AMH level range is 2–6.8 ng/ml (14.28–48.55 pmol/l) in any phase of the cycle. In recent years, accumulated data indicate that serum AMH may fulfill the requirements to be the best test to predict ovarian reserve. [4] Serum AMH levels are significantly higher in normogonadotropic anovulatory women especially those with polycystic ovarian morphology compared to age-matched normoovulatory premenopausal women . Mean AMH levels in in vitro ovarian granulosa cells from anovulatory PCOS women are 75-fold higher compared to in vitro ovarian granulosa cells from age matched normal ovulatory controls . In cells from PCOS women, luteinizing hormone (LH) increased AMH and follicle-stimulating hormone (FSH) decreased AMH [3]

1.3 Effect of AMH on fertility of female and IVF

Serum AMH levels in women are lower than those in men through-out life . One potential advantage of using an AMH test as a marker of ovarian reserve, is that it does not seem to change over the course of the menstrual cycle; FSH, on the other hand, must be measured on day 2 or day 3 of the menstrual cycle or on day 10 if it is drawn as a part of a clomid challenge test (CCT). Another point which is in favour of using it as a marker of OR is that AMH decreases with age . Some studies on in vitro fertilization (IVF) patients have shown lower AMH levels in women who responded poorly to fertility drugs . A correlation was found between the number of eggs which were retrieved and the AMH levels. The women with low AMH levels tended to get fewer eggs during IVF than the

women with high AMH levels. Pregnancy rates were also lower in the women with low AMH levels . [4]

1.4 The relationship between hyperandogenasim and PCOS

Hyperandrogenism represents a chief attribute of PCOS as elevated androgen levels are the most constant feature, with the majority (−60%) of patients exhibiting hyperandrogenism (Rotterdam definition) . Women with hyperandrogenic PCOS present with elevated levels of various androgens, including testosterone (T) and the pro-androgens androstenedione (A_4) and dehydroepiandrosterone sulfate (DHEAS), as well as the enzyme required to convert pro-androgens to bioactive androgens, 3β-hydroxysteroid dehydrogenase (3β-HSD) in serum . Excess androgens can be induced by insulin resistance and hyperinsulinaemia, as they cause a reduction in sex hormone binding globulin levels, which lead to a subsequent increase in free androgens and unfavourable metabolic profiles . The ovarian PCOS morphological traits of enlarged, multi-cystic ovaries and theca interstitial hyperplasia are reported in women who are subjected to high levels of androgens as a result of endogenous adrenal androgen hypersecretion in congenital adrenal hyperplasia , or exogenous testosterone treatment in female-to-male transsexuals . Additionally, cultured human theca interna cells removed from PCOS ovaries exhibit higher androgen secretion that continues during long-term culture . These observations corroborate a role for androgens in the acquisition of the PCOS ovarian features. [6]

1.5 Insulin level in PCOS

PCOS is associated with insulin resistance and compensatory hyperinsulinemia [7-8], is a key feature in the pathogenesis of PCOS [11] ; Women often

experience PCOS (hirsutism, acne, and alopecia), irregulate menstrual cycles, and biochemical alterations associated with elevated testosterone levels, These changes are linked to insulin and hyperinsulinaemia resistance [12] WhiIe it is true that not all women with insulin resistance have PCOS, those who have PCOS are more likely to come to the attention of the medical community , these women are at increased risk of having the metabolic syndrome (syndrome X),This is characterized by dyslipidemia, central obesity, hypercoagulability, impaired fibrinolysis, and an increased risk of development of hypertension, type 2 diabetes mellitus, and coronary artery disease [8]

Overweight and obesity in women with pcos can worsen IR [13], . With the increased rates of weight gain and prevalence of excess weight in women with PCOS IR is further exacerbated ([9, 10] ,Many of the symptoms women with PCOS experience, such as changes in menstrual cycles and infertility, are a result of androgen excess . For these women, high insulin levels and free insulin growth factor stimulate the ovary to increase the production of androgens [18] Several interventions (pharmacological, nonpharmacological) have been assessed with the condition. Metformin an insulin sensitizer (500 mg three times a day or 850 mg twice a day[17] has been extensively used in PCOS patients with IR.It works by decreasing gluconeogenesis and lipogenesis enhancing glucose uptake in the liver, skeletal muscle, adipose tissue [14] . and ovaries, Metformin treatment is also associated with increased HDL cholesterol, decreased LDL cholesterol, and decreased triglycerides[16] and may improve fertility, facilitate weight loss, improve the lipid profile, reduce the incidence of diabetes, and prevent atherosclerosis, myocardial infarction, and stroke. Clinical trials verifying these benefits in patients with PCOS are urgently needed.

The International Evidence-based Guideline for the for Assessment and Management of PCOS also emphasized the importance of diet in PCOS and recommended dietary and exercise interventions as the first-line management for women with PCOS[15] .

Chapter 2

2.1. Method

2.1.1. Research design & data collection

This is a questionnaire-based study that was carried out from May 2023 to June 2023. Participants were selected from female students of college of pharmacy ,Basrah University.

Participants consented to participate after they were given full details of the study and its intended aims. All participants were made aware that this study is for research purposes only and their participation was voluntary. They were not asked for their names or contact information, ensuring the privacy of survey respondents ,The required hormones that were collected are AMH, INSULIN, ANDROGEN , Various cases of different ages, ranging from 19-45 years were seen , The whole thing took a month and a half , 34 samples were collected in order to know the extent of the impact of PCOS on the ability to conceive, and the extent to which these hormones are affected by PCOS.

2.1.2. Study population (inclusion/exclusion)

Inclusion: We included females ≥18 years of age. Exclusion: female students , People who were less than 18 years old ,this study was included patient who were easily access for data collection , Those who did consent to participate or did not feel comfortable giving information were excluded from the study

2.1.3. Questionnaire

The questionnaire contained Fourteen question questions divided into four sections , the questions that was included: the age of patient , Is the patient suffering from PCOS or not , did she become pregnant or not , did she undergo IVf or not

2.1.4.ethics

All participants in the collected samples have been informed about the purpose of this study and the importance of the information that they provide to us , It was assured to the participants that the owners of this data will be completely anonymous

2.1.5 Data Statistical analysis

are expressed as mean ± standard Error (SE) , statistical analysis was performed by IBM SPSS statistics , version 26 (IBM Co., Armonk , NY, USA) . The statistical analysis was performed by one- results way Analysis Of Variance (Qi The seqweer) The, followed by Duncan's test at (p-value ≤ 0.05) significant level

Chapter 3

3.The Result

Comparative study between hormones AMT, insulin and androgen on women with and without PCOS

TABLE 1-3 comparative study between AMH with PCOS and AMH without PCOS .

Parameters	Mean / Std. Error
AMH 1	31.08±1.95
AMH 2	25.88±0.82

Table 1-3 show significant increase of serum level of AMH in women with PCOS compare with women without PCOS

Table 2-3 comparative study between androgen with PCOS and androgen without PCOS

parameters	Mean / Std. Error
Androgen 1	0.74 ±0.10
Androgen 2	0.54 ± 0.04

Table 2-3 show not significant increase of serum level of androgen in women with PCOS compare with women without PCOS

Table 3-3 comparative study between insulin with PCOS and insulin without PCOS

parameters	Mean / Std. Error
Insulin 1	6.92 ± 0.58

Insulin 2	1. 0.22

Table 2-3 show significant increase of serum level of insulin in women with PCOS compare with women without PCOS

Table 4-3 relationship between age and PCOS

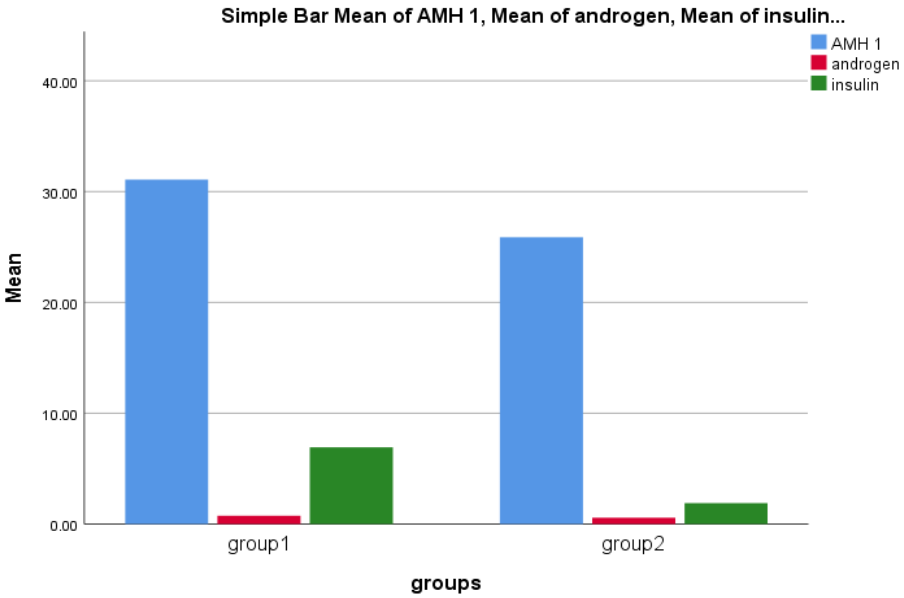
AGE	PCOS
20-25	6
25-30	8
30-35	7
35-40	5

Table 4-3 show that more PCOS occur in age between 25-30

Table 5-3 relation between successful pregnancy after IVF and unsuccessful pregnancy after IVF

PC0S	pregnancy	IVF
5	YES	YES
12	NO	YES
9	NO	NO

Figure 1-3 correlation between hormones AMT insulin and androgen on women with and without PCOS


Simple Bar Mean of AMH 1, Mean of androgen, Mean of insulin...
AMH 1
androgen
insulin
40.00
30.00
20.00
10.00
0.00
Mean
group1
group2
groups

Chapter 4

4.1 Discussion

This study was designed to evaluate the AMH , androgen , insulin levels in the woman's with PCOS.

the level of AMH is two- to three-fold higher in women with PCOS than in healthy women of childbearing age, probably owing to the increased follicular mass or follicular hypersecretion .

Our study showed that women with PCOS had significantly higher AMH levels compared with woman's without PCOS , 25 case from 26 cases with PCOS showed increase in AMH , while only one case was show increase in AMH in non PCOS woman's .

The study also show significant increase in Androgen level in woman's with PCOS . hyperinsulinemia is the primary cause of excessive androgen production , PCOS characterized by an increased frequency of gonadotropin-releasing hormone (GnRH) that selectively increases luteinizing hormone (LH) secretion. LH stimulates multiple steroidogenic enzymes in the ovary, leading to increase testosterone production .

In general, women with PCOS develop IR and hyperinosemia owing to abnormal insulin signaling and metabolic dysfunction in insulin-responsive tissues, with a high incidence of IR in PCOS and a significant negative impact on health , there was significant increase in insulin level in 21 cases from 26 case in woman's with PCOS .

AMH levels peak around 25 years old , After that there was decline in AMH . Androgen level start rising during 19- 25 age and after that There was decline in androgen level with increasing age .

Table 4-3 showed that there is a high incidence of PCOS around age 25-30 there were 8 cases , and showed little decrease in PCOS incidence around age 35-45 there were 5 cases .

Table 5-3 show that there is an effect of PCOS on fertility, there were 5 cases with PCOS had a successful pregnancy after undergoing IVf , and 12 cases with PCOS failed to get pregnant after IVf , and there were 6 cases with PCOS had a successful pregnancy without IVf ، and 9 cases with PCOS failed to get pregnant without IVf .

4.2 Conclusion

Polycystic ovary syndrome is a reproductive endocrine disease with menstrual disorder, androgen excess, and polycystic ovarian changes as the main clinical manifestations and is the main cause of ovulation dysfunction and infertility. which affects the physical and mental health of PCOS patients and also increases the risk of type 2 diabetes and cardiovascular disease ,

This research has explained the association of AMH , androgen, insulin with the pathophysiology and clinical observations of PCOS. To summarize, AMH represses follicular developments, recruitments, and cause anovulation.

There was a positive correlation bet these hormones and PCOS .

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