University ofBasrah
Pharmacy College
Graduation project, 2014/2015

Age related risksinduced by Polycystic Ovary Syndromeassociated with diabetes mellitus, Obesity, Cardiovascular Disease, Anemia, andArthritis.

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Abstract

PCOS is one of the most common endocrine disorders, affecting 5-17% of women of reproductive age. It is characterized by oligo/anovulation, hyperandrogenism, and polycystic ovaries. PCOS is associated with acne, hirsutism, infertility, abdominal obesity, type II diabetes, hypertension and dyslipidemia, with the latter four being cardiovascular disease (CVD) risk factors.

This cross-sectional study was undertaken to evaluate the diabetes mellitus, obesity, cardiovascular disease, anemia, arthritis and genetic factors that relate to age in polycystic ovary syndrome (PCOS). METHODS: A total of 40 women with clinical and questioners feature suggestive of PCOS underwent metabolic and hormonal evaluation related with three ages(15-25, 25-35 and 35-45 yeas). A forward stepwise logistic regression model was created based on the results to determine variables related to PCOS status.

The results of our study showed that that significant (P≤0.01) increase in obesity, diabetes mellitus and arthritis at age 25-35 compared with other ages, while, a significant (P≤0.01) increase in anemia at age 15-25 years compared with other ages. There a significant increase in both the 15-25 and 25-35 age groups were observed in genetic, steroid and cardiovascular disease compared with 35-45 year. **CONCLUSION**: The results suggest that a significantrisk factor age in women with PCOS.

Keywords: polycystic ovarian syndrome, different ages, obesity, diabetic mellitus, cardiovascular disease.

Introduction

PCOS is one of the most common endocrine disorders, affecting 5-17% of women of reproductive age, and it is characterized by hyperandrogenism and ovulatory dysfunction(Hyejin, *et. al.*, 2013).

It is characterized by oligo/anovulation, hyperandrogenism, and polycystic ovaries. PCOS is associated with acne, hirsutism, infertility, abdominal obesity, type 2 diabetes, hypertension and dyslipidemia, with the latter four being cardiovascular disease (CVD) risk factors. Polycystic ovary syndrome (PCOS) in women is a complex disorder of unknown etiology, (Feng, *et. al.*, 2013).

Historical review

In 19th century scientific publications, references were made to what we now understand as PCOS, however, the syndrome was not described until 1935, in a paper by Irving Stein and Michael Leventhal (Stein and Leventhal, 1935). Both working at the department of obstetrics and Gynecology, Michael Reese Hospital, USA, described the clinical, the macroscopic characteristics and histological features of PCOS for the first time. Stein and Leventhal initially observed the association between amenorrhea, hirsutism, infertility and polycystic ovary in the first half of the 20th century (Louise, 2010). In 1935, Stein and Leventhal published a paper on their findings in seven women with amenorrhea, hirsutism, obesity, and a characteristic

polycystic appearance to their ovaries (one of the first description of a complex phenotype today known as the polycystic ovary syndrome) (David and Eharman, 2005).

Definitions and Prevalence

Polycystic ovary syndrome (PCOS) is a complex disorder of unknown etiology. The first attempt to define PCOS was made during an expert conference held at the National Institute of Health (NIH) in 1990, and this included both hyperandrogenism and ovulatory dysfunction(Louise, 2010). In 2003 the Rotterdarm conference, sponsored by the European Society for Human Reproductive Medicine and Embryology (ESHRE) and the American Society for Reproductive Medicine (ASRM), broadened the definition of PCOS by including PCO morphology, and the requirement for at least two of the three diagnostic feature for the diagnosis of PCOS.

Androgen Excess and PCOS Society (AES) proposed new diagnostic criteria(Louise, 2010). The Rotterdam diagnostic criteria of 2003 define PCOS as a syndrome consisting of two out of the three following disorders: chronic anovulation, clinical and/or biochemical evidence of hyperandrogenism and polycystic ovaries(Franks, 2006).

The word syndrome mean a disease or disorder that can produce different collection of signs, the word syndrome, also, mean a collection of symptoms and physical sings that can be due to a variety of different diseases, however, the word syndrome in the polycystic ovary syndrome has both of these meanings. PCO morphology may be defined as bilateral, enlarged, tense ovaries that were often distinctly globular in shape from the inner margin to the outer margin in longitudinal cross-section(Fulghesu, *et. al*., 2001). PCOS is a heterogeneous disorder, characterized by chronic anovulation and hyperandrogenism. The heterogeneity of PCOS reflects the participation of multiple pathophysiological mechanisms; however how much each mechanism contributes to developing PCOS is still unknown(Ehrmann, 2005; Yarak, *et al*., 2005).

The prevalence of PCOS in the general population has been estimated to be 5% to 10% of fertile women around the world, but some researcher estimate the overall rate to be between 4-

26%(Levents, 2012). Studies in first-degree relative of patients who have PCOS found that 24% of mothers and 32% of sisters are affected, suggesting a major genetic association (Kashsar, *et. al*., 2001).

The Ovarian anatomy and Function

Ovarian anatomy

The word "ovary" is derived from the Latin word "ovum," meaning egg. Two ovaries are located in the pelvic cavity of female, each suspended between the peritoneum and the uterus by ligaments. The body of ovary, Figure2 **(**Theresa, 2006) is largely composed of stromal tissue, stratified into an inner medulla and outer cortex, which is encapsulated by the ovarian surface epithelium and an outermost covering of connective tissue(tunica albuginea)

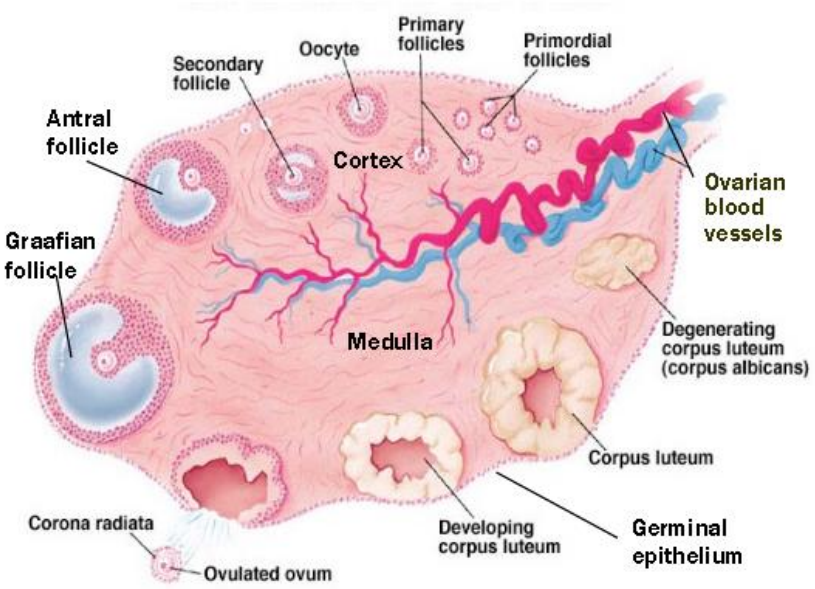


Figure 2: Anatomy of the ovary as described in the thesis text. Source of original drawing is unknown.

The cortical region of each ovary contains immature germ cells(oocytes), each surrounded by a single layer of squamous granulosa cells(GCs), collectively, this forms a structure called a primordial follicle (Findlay, *at. al*., 2009). The basement membrane separates the epithelial granulosa cells from the mesenchymalthecal and stromal cells.

The ovaries produce gametes, secondary oocytes that develop into mature ova(eggs) after fertilization and it also provides steroid and protein hormones required for maintenance of the ovarian cycle and the secondary sex characteristics (Tilly and Rueda, 2008).

Ovarian Function

It is now clear that ovarian function is regulated by both hormonal and intraovarain signals acting in synchrony to control follicular development, steroid secretion, and ovulation(Lara, *et. al*., 2000). There are two basic functions of the ovary ***a)*** production of eggs to be nurture and extrude mature oocytes capable being fertilized by sperm in the reproductive tract and ***b)*** The ovaries make and produce three types of steroid hormones estrogen (E2) and progesterone (P4), testosterone (T) for both endocrine and intracrine purposes. Endocrine regulation of both these functions occurs through the hypothalamic-pituitary-ovarian(HPO) axis (Hillier, 2001).

Clinical features of PCOS

PCOS is characterized by oligo/amenorrhea, hyperandrogenism and polycystic ovaries. Oligo/amenorrhea is an indicator of oligo/anovulation and is associated with infertility. Oligomenorrhea is usually defined as a menstrual interval of >35 days and amenorrhea is defined as the absence of menstrual bleeding >90 days. Hyperandrogenism is caused by increased ovarian and/or increased adrenal androgen production. The typical symptoms of hyperandrogenism are hirsutism, acne and/or androgen alopecia; however, the latter being quite a poor marker of androgen excess (Rotterdam, 2004).

An illustration of the characteristic clinical features of PCOS and the possible secondary consequences are given in Figure3. The primary clinical indicator of hyperandrogenism is the presence of hirsutism (Rotterdam, 2004), which is a masculine pattern of body hair. The Ferriman-Gallwey system is a scoring system for the extent of hirsutism and seems to be the most widely used system today. The scoring system is based on five grades (with zero being absence of terminal hair) on 11 different body sites: chin, upper lip, chest, upper and lower back, upper and lower abdomen, arm, forearm, thigh and lower leg. However, even if there are many scoring systems, the assessment of the extent of hirsutism is likely to be relatively subjective and a considerable inter-investigator variability has been demonstrated (Azziz, *et. al*, 2006). In addition, women have usually treated themselves, before seeking medical attention for their disorder.

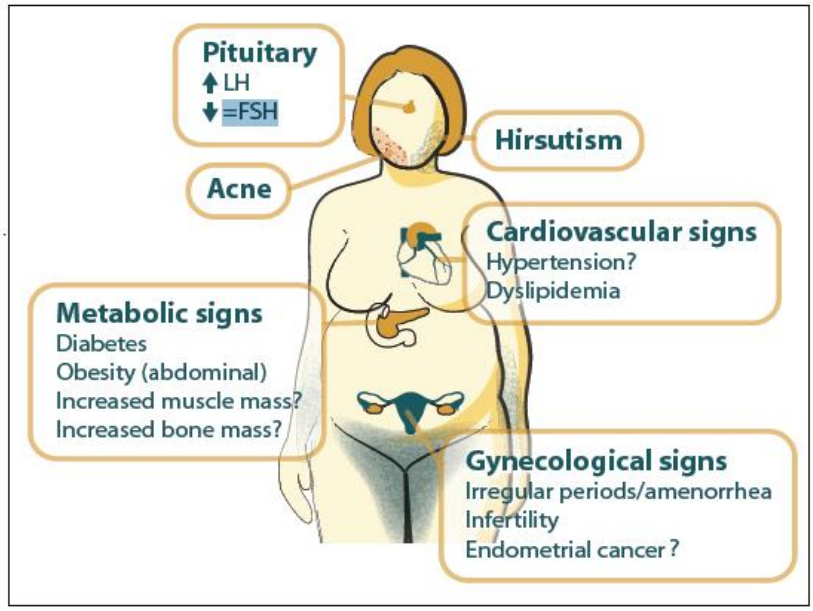


Figure 3. Illustration of the characteristic clinical features of PCOS women of fertile age and the possible long term consequences (Schmidt, 2010).

The PCOS is also associated with obesity, insulin resistance, diabetes, hyperinsulinemia, hypertension and Dyslipidemia. There is considerable heterogeneity of the signs and symptoms among women with PCOS and for each woman they may vary over time. Weight gain is usually associated with an aggravation of symptoms, while weight loss usually ameliorates the symptoms and the endocrine and metabolic disturbances. Interestingly, an effective weight loss of only around 5% can reverse the PCOS associated anovulation.

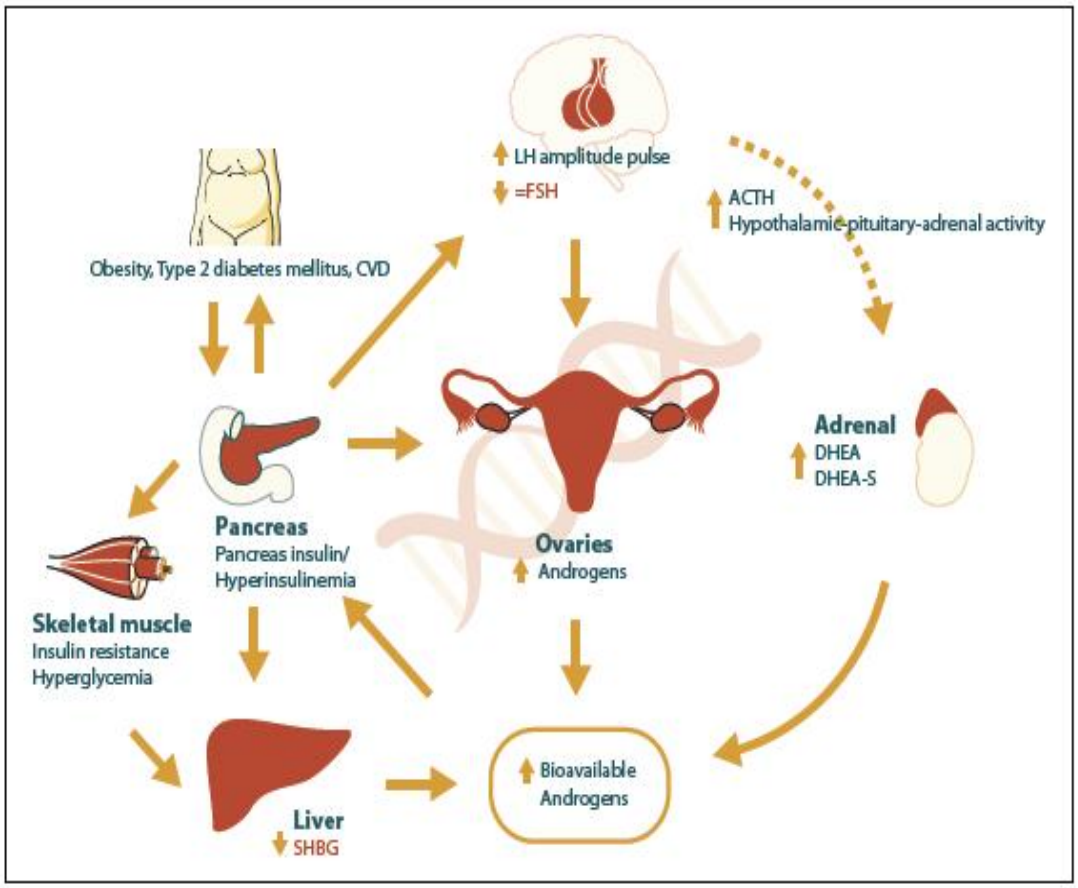
Depending on the criteria used, the prevalence of the classical clinical features of PCOS varies with approximately 66-75% with menstrual dysfunction 60-69% with hirsutism/acne (2, 17, 18), 48-80% with increased androgens levels (Azziz, *et. al*, 2004), and in patients defined by the AES criteria ~75% had PCO morphology (Azziz, *et. al*, 2006).

Etiology and pathophysiology of PCOS

The pathogenesis of PCOS is multifactorial and far from completely understood. Multiple causative mechanisms are discussed, involving interactions between certain genes and environmental factors (Norman, *et. al.*, 2007), dysfunction/regulation by the gonadotropins and

intraovarain factors, hyperinsulinemia as well as hyperandrogenism. An illustration of the proposed pathophysiological characteristics of the PCOS is given in Figure 4.

Taken together, impaired folliculogenesis and steroidogenesis in PCOS seem to be multifactorial and are probably influenced by extra ovarian factors such as androgen, insulin, neuroendocrine alterations, and intraovarain local and intrinsic factors**.** Increased androgen production has been demonstrated by genomic and molecular studies to be an intrinsic steroidogenic defect in PCOS theca cells (Legro, R.S. et al,1998 and Nelson, V.L. et al. 1999).



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Gonadotropin aberrations: The increased frequency of LH pulses from the pituitary gland is secondary to increased frequency of GnRH pulses in the hypothalamus. This leads to increased

pituitary production of LH. Ovarian aberrations: The elevated levels of LH lead to increased androgen production from the theca cells. The relatively lower FSH levels contribute to arrested follicular development in the ovary, which, in turn leads to disturbed negative feedback. This results in continued aberrations in the secretion of LH and FSH. Aberrations in the adrenal gland: Impaired adrenal androgen production leads to increased levels of DHEA and DHEAS, which, in turn, also increases the circulating pool of free and bioavailable androgens. Pancreatic aberrations: The increased levels of bioavailable androgens lead to increased insulin resistance in peripheral tissues (mostly in the skeletal muscle). This leads to hyperinsulinemia, which, by facilitating the stimulatory role of LH, leads to increased ovarian androgen production. Moreover, increased release of free fatty acids from adipocytes is seen, due to insulin resistance and hyperandrogenism. Liver aberrations: Insulin-induced decreased production of SHBG leads to an increased amount of free androgens. Peripheral tissue: The insulin resistance and the hyperinsulinemia could cause obesity and T2DM, which increases the CVD risk and could lead to CVD. Genetic factors: All the aberrations mentioned could, in concert with genetic factors, lead to the PCOS and eventually in an adverse CVD risk profile. ACTH=adrenocorticotropic hormone, CVD=cardiovascular disease, DHEA = dehydroepiandrosterone, DHEAS = dehydroepiandrosterone sulfate, FSH=follicle-stimulating hormone, GnRH=gonadotropinreleasing hormone, LH=luteinizing hormone, SHBG=sexual hormone-binding globulin.

PCOS may increase susceptibility to RA in elderly women. This proposal would be compatible with the hypercytokinemia of patients with PCOS, which may be a result of the increased visceral adiposity and hyperinsulinism of these patients (Alfonse T. and George P 2003).

Menorrhagia is more common in PCOS because of lack of ovulation and unopposed oestrogen action. The absence of regular menstruation induced by progesterone withdrawal may lead to endometrial hyperplasia and uncontrolled bleeding (Hardiman, Pillay and Atiomo, 2003). Heavy periods that could lead to sever loss of blood and anemia.

PCOS Therapy

Multiple concomitant therapies have been applied in PCOS to address the variety of symptoms and to achieve better results.Medications should only be described as an adjunct to diet and exercise. 1) Oral contraceptive pills (OCPs), depending on the estrogen dose, can inhibit androgen, LH and FSH production and stimulate regular menstrual cycles. 2) Insulin-sensitizing drugs (ISD) metformin, rosiglitazone, pioglitazone, D-chiro-inositol. 3)androgen-blocking drugs, spironolactone, flutamide, cyproterone, finsteride. 4)Fertility drugs, Clomiphene,(Clomid) is generally the first fertility medication, Human Chorionic Gonadotropin (HCG) or Pergonal are

the groups of medications used for PCOS treatment(Christoffer, 2005, Nestler, 2008 and Tang *et. al*., 2010).

Materials and Method

In January 2015, the graduation Project took the first steps in collecting information on Iraqi women with PCOS, targeting women of different age groups in Basrah city.

Patients

40 Iraqi women with PCOS aged 15-45 years were questioned for the study. Their medical histories, age, body weight and height were noted. PCOS patients had already been diagnosed and the diagnosis was confirmed according to the European society of human reproduction and embryology and American society for reproductive medicine criteria; PCOS is diagnosed if there are any two of the following:

- Presence of polycystic ovary on ultrasound examination.
- Clinical or biochemical hyperandrogenemia.
- Menstrual dysfunction with an ovulation.

Survey methodology

This first stage of information gathering for the Project was to design a forum that contain the main questions. Eight main parameters were included in the forum:

Age	Height	Weight	Marital status	CVD	DM	Arthritis	Hereditary	Drugs

The findings of this preliminary questionnaire will provide a necessary focus for the explanation of the possible presence of a link between risk factors of PCOS and a specific age group.

In order to gather as many PCOS cases as possible, we asked friends and family members who have or previously had PCOS. We also distributed paper and electronic copies of the project forum at different hospitals (IbnGhazwan Hospital and Al Basrah General Hospital), gynecologists and ultrasound clinics and went back to collect them every week.

Response

This study lasted about 4 months and a total of 100 questionnaires were distributed, 40 were returned, giving a response rate of 40%.

Age group	Number of cases
15-25	21
26-35	17
36-45	2

Results and Discussion

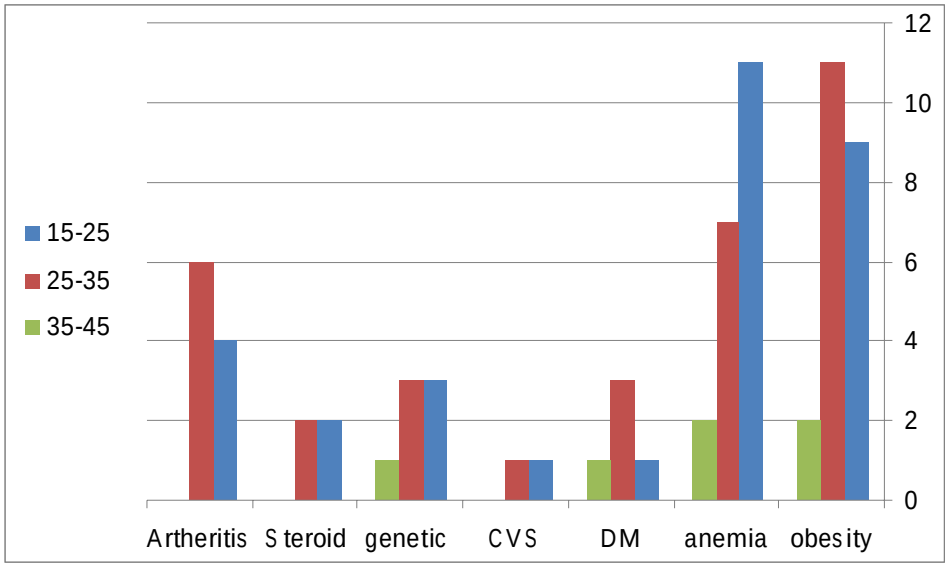
Figure (5) Histogram showing that significant increase in obesity at age 25-35 compared with other ages, while a significant($P \leq 0.01$) increase in age 15-25 was appear compared with age 35-45, this finding is in agreement with(Adul-Nabi, 2013) who reported , About 69.8 % of women with PCOS were overweight (BMI 25.0–29.9 kg/m^2) or obese (BMI $\geq$ 30).

Our results are in line with those previous of studied Karimzadeh*et al*., (2012) found that women with PCOS showing significant increased in obesity and body weight due to an increase in adipose tissue of abdominal cavity. Based on the fact that the inflammatory cytokines are the products of adipocytes, an increase in serum C-reactive protein (cytokine) along with increase testosterone levels and body weight could be all indicative of possible increase in adipocytes in PCOS women. On other hand, raising androgen levels result in an increase in the hypertrophy of adipocystes and by affecting expression of enzymes and proteins involved in the metabolism of carbohydrates and lipids, result in the oxidative stress and differentiation of pre-adiopcytes to mature adipocystes.

Also, figure (5) revealed that a significant ($P \leq 0.01$) increase in anemia factor at age 15-25 compared in other groups. This result agreement with Faranak*et. al*., (2011) observed that

oxidative stress induces ferritin synthesis to reduce further oxidative damage, given that ferritin neutralizes highly toxic unbound iron.Our results strongly suggest that increased body iron stores in PCOS women may be attributed to a consequence of amenorrhea and long of menstrual cycle. Menstrual irregularity is frequently early and dominant symptoms of the anovulatory component of PCOS. The incidence of cycle irregularity in women with PCOS seems to be quite variable may contribute within anemia.

Figure (5): Study different age PCOS groups related with obesity, anemia, DM, CVS, Genetic, steroid treatments and arthritis in women with PCOS.



On the other hand, figure, was also observed that significant (P≤0.01) increase in diabetic mellitus and cardiovascular disease at age 25-35 compared with other groups study. This result agreement (192)Obesity, particularly central visceral obesity as indicated by an increased waist to hip ratio is a risk factor for the development of diabetes and heart disease and, when present in a woman with PCOS, worsens the clinical features (anovulation, hyperandrogenism and insulin resistance) of the syndrome.It has been reported that hyperinsulinemia, frequently associated with PCOS increases both the risk of cardiovascular diseases and the development of diabetes mellitus (Abbott *et. al.*, 2002). The present results also corresponded with other studies Kahn and flier (2000) and Goldstein (2002) have shown that impaired insulin-stimulated glucose uptake at the muscle, adipose tissues and liver; hepatic glucose overproduction and release; increase

lipolysis in adipose tissue and consequent increased circulating free fatty acids (FFA); reduced lipogenesis from circulating triglyceride and impairment of glycogen synthesis. Similarly, David *et. al*., (1995) reported that PCOS is important cause of infertility also associated with features of metabolic syndrome (Adiposity, insulin resistance, low grade inflammatory state, dyslipidemia, cardiovascular disease and type 2 DM). Also, Ehrmann*et. al*., (2005) found that Forty percent of obese women with PCOS develop impaired glucose tolerance, with up 10% developing T2DM.

Figure(5) revealed that significant ((P≤0.01) increase in genetic , steroid and arthritis factors in groups 15-25 and 25-35 compared with 35-45 age group.

This finding is in line withChen *et. al*., (2011**)** reportedthat multiple family studies demonstrate clustering of the disorder, with increased prevalence of hyperandrogenism, metabolic disturbance and PCOS morphology in female relatives of affected women Genetically, PCOS has been experimentally" linked" to possible causative or hyper-susceptible genes. Interaction between multiple genetic and environmental factors is probably necessary for the development of PCOS which several lines of research suggest that there is a genetic component to the pathophysiology of the syndrome.

Conclusion

Polycystic ovarian syndrome (PCOS) is the most common endocrine disorder of reproductive-age women. The diagnosis of PCOS is mainly based on the following three components: (1) hyperandrogenism, (2) oligo-amenorrhea, and (3) the observation of polycystic ovaries on a sonogram. The comorbidities may include insulin resistance, type II diabetes mellitus, hypertension and cardiovascular disease. Importantly, the diagnostic criteria and complications related to PCOS are age-dependent. Hyperandrogenism and chronic anovulation are the primary disturbances in younger women with PCOS; whereas, obesity, insulin resistance, and metabolic disturbances are predominant in older women with PCOS. There is no cure for PCOS. Medical treatments aim to manage and reduce the symptoms or consequences of having PCOS. Medication alone has not been shown to be any better than healthy lifestyle changes (weight loss and exercise). If body weight could be controlled properly, younger hyperandrogenic PCOS women might reduce their risk of insulin resistance and metabolic disturbances later in life.

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