Effect of environmental factors on The onset of polycystic ovaries

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بِسْمِ اللَّهِ الرَّحْمنِ الرَّحِيمِ

(وَإِذَا مَرِضْتُ فَهُوَ يَشْفِينِ)

صَدَقَ اللَّهُ الْعَظِيم

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Abstract
Background

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women of reproductive age. Polycystic ovary syndrome signs and symptoms often begin soon after menarche. In some cases, PCOS develops later during the reproductive years, for instance, in response to substantial weight gain(1).

Aim of the study to evaluate the effect of environmental factors on the onset of polycystic ovaries.

Patients and methods:- retrospective study done at gynecology outpatient clinic of AL-Batool Teaching Hospital in Baqubah -Diyala -Iraq, from February 2022 to April 2022. A total of 126 cases where studied, all have confirmed diagnosis of PCOS depending on The Rotterdam Criteria about 126 patients where included all are fully informed and gave their consent about the study.

Results: The study reveals that age significantly affects the onset of disease with peak incidence at the age of (20_30). Diet and physical activity are strongly related to the onset of the disease as the most affected females are with unhealthy diet (100%) and low physical activity. Diabetic patient and family history of PCOS are at higher risk. Smoking is also Risk factor.

Conclusion: Patients who are young and have increased body weight with sedentary lifestyle and positive family history of DM and continuous exposure to passive smoking is at higher risk to early onset of the disease

keywords: polycystic ovaries , Diabetes mellitus , Gonadotropin_ releasing hormone, Follicle stimulating hormone, luteinizing hormone

Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women of reproductive age. It is now recognized as a common, heterogeneous, heritable disorder affecting women throughout their lifetime. PCOS is characterized by hyperandrogenism, ovulatory dysfunction, and polycystic ovaries. However, there is considerable inter-individual variation in presentation. Although not required for diagnosis, the presence of insulin resistance and hyperinsulinemia is common and places those affected at increased risk of diabetes and cardiovascular disease. Thus, PCOS adversely affects endocrine, metabolic, and cardiovascular health.(2)

PCOS develops later during the reproductive years, for instance, in response to substantial weight gain.(1) The exact pathophysiology of polycystic ovarian syndrome is not well established but increase the amplitude of (GRnH) pulsation and abnormal secretion of (FSH) And (LH) during puberty are thought to results in androgen excess.(1)

Most clinicians use the Rotterdam criteria to diagnose POCS The criteria require the patient to have two of the following:-

1) Menstrual irregularities caused by oligo ovulation or anovulation.
2) Clinical or biochemical evidence of hyperandrogenism .
3)Presence of polycystic appearing ovaries.(3)

The underlying cause of POCS is Unknown. However a genetic basis that is both multifactorial and polygenic is suspected.as there is well documented aggregation of The syndrome with in families.(1) The prevalence of POCS in the United States is 6.5% to 8%. Risk factors include obesity, insulin resistance,DM, premature menarche, positive family history especially in the first degree relatives.(3)

The cardinal clinical features of PCOS are hirsutism and menstrual irregularity from anovulation. Obesity occurs in approximately 50% of hyperandrogenic anovulatory women, some of whom also have non-insulin-dependent diabetes mellitus.(4)

Pathogenesis:-
-Despite the heterogeneity of clinical presentations of women with polycystic ovaries, there is a common thread of biochemical features that links the spectrum of symptoms and signs. The endocrine hallmarks are hyperandrogenemia and, to a lesser extent, hypersecretion of luteinizing hormone.It seems likely, however, that abnormal gonadotropin secretion is a result, rather than the cause, of ovarian dysfunction.(5)(6)
Although it is clear that hypersecretion of adrenal androgens may contribute to the hyperandrogenemia of women with the polycystic ovary syndrome,(6)(7)

The biochemical basis of the putative disorder of ovarian androgen biosynthesis remains unclear. There is evidence, from both clinical and in vitro studies of human ovarian theca cells, of dysregulation of the rate limiting enzyme in androgen biosynthesis, cytochrome P-450c17a, which catalyzes both 17a-hydroxylase and 17,20-lyase activities.(8)(9)

-The polycystic ovary syndrome is a familial disorder, but the genetic basis of the syndrome remains controversial.(10)(11)
Determining the mode of inheritance of this syndrome is difficult because there has been no clearly described male phenotype and because it is a disorder that

affects principally women of reproductive age. However, a recent study of 150 subjects in 10 families of women with the syndrome revealed evidence of an autosomal dominant mode of inheritance, with premature balding in men being the putative male phenotype. (12)

- Obesity has a substantial effect on the manifestation of polycystic ovary syndrome.(13) Excess weight exacerbates metabolic and reproductive abnormalities in women with the syndrome, and family studies suggest that weight gain might promote the phenotype of polycystic ovary syndrome in a susceptible population.(14)

-Women with polycystic ovary syndrome seem to have a level of peripheral insulin resistance that is much like that of women with type 2 diabetes, which is characterized by a 35–40% decrease in insulin-mediated glucose uptake.(15)Normoglycaemic women with the syndrome display both fasting and glucose-challenged hyperinsulinaemia,(16)Insulin resistance might contribute to hyperandrogenism and gonadotropin abnormalities through several mechanisms.(17)

Aim of the study to evaluate the effect of environmental factors on the onset of polycystic ovaries.

Patients and methods: A retrospective study done at gynecology outpatient clinic of AL-Batool Teaching Hospital in Baqubah -Diyala -Iraq, from February 2022to April 2022. A total of cases where studied , all have confirmed diagnosis of PCOS depending on the following criteria:1)Oligo or amenorrhea (8 or fewer cycles per a year) , use 2) signs of hyperandrogenism 3)ultrasound features of PCOS. about thirty patient where included all are fully informed and gave their consent about the study .So They classified according to their different age groups, weight, marital status, family history and Life style (Exercise, Diet, smoking) in order to evaluate the effect of environmental factors on the onset of polycystic ovaries

Results:

Table (1): Comparison between prevalence of the disease at different body weight categories

body weight	Frequency	Percent
50-70	26	20.6%
70-90	43	34.1%
90-110	57	45.2%

The table reveals the prevalence of polycystic ovaries at different body weight groups. There is a decreased in the percentage of affected females in the lower body weight group and an increase in the percentage at the higher body weight group.

Table (2): Comparison of between the onset of the disease at different age groups

Age	Frequency	Percent
13-20	42	33.33%
20-30	57	45.23%
30-40	27	21.42%

The table shows the most affect age groups (early adulthood) and the risks of the onset of disease increases in young females with the highest prevalence at the age of less than 30 years.

Table(3) : comparison between two groups one with family history of polycystic ovaries and other who are not

Family history of polycystic ovaries	Frequency	Percent
No	75	59.52%
Yes	51	40.47%
Total	126	100%

The table above shows a fairly equal opportunity to have early onset of the disease in females with family history and those who haven't positive family history because low sample size were included in the study so may not match with the global results of the studies that assume polycystic ovaries is highly associated with family history of PCOS.

Table(4) :_ Effect of The Type of food on the risk of having polycystic ovaries

Type of food	Frequency	Percent
Unhealthy	126	100%
Healthy	0	0

The disease is strongly related to the unhealthy food or improper food patterns that the patients usually consume. And 100% of those patients having unhealthy diet.

Table(5) :_ The effect of the physical activity on the prevalence of polycystic ovaries

physical activity	Frequency	Percent
Irregular Exercise	36	28.57%
Minimal activities	79	62.69%
Regular exercise	11	8.73%

Total	126	100%

This table is clarifying that the disease is affected by the physical activity and increases with sedentary lifestyle and the percentage decrease with those who had regular exercise regime and activities.

Table(6) : Comparison between the patient who have family history of DM and the patient who are diabetics or both

DM	Frequency	Percent
History of DM	11	8.73%
Family history of DM	59	46.82%
Both personal and family history of DM	3	2.38%
No personal or family history of DM	53	42.06%

This table review the association with history of DM (family ,personal or both) and shows that there is high percentage of the studied cases have previous family history (46.8%). But there is also a fairly same percentage of cases that do not have a previous history (42.0%). as the percentage shows that there is noticeable percent of diabetics affected by the disease but dual positive personal and family history of DM Is not well explained by this study because of the small number of studied subjects.

Table(7):_Comparison between the patient who are smoker or passive smoker

Smoking	Frequency	Percent
Active	0	0

Passive	98	77.77%
Non smoker	28	22.22%

The table above shows that most of the studied cases had have exposed to cigarette smoking by passive way (77.7%).

Discussion: _

The results of this study that there were significant contributions of the life style and environmental factors on the onset of the symptoms of polycystic ovaries.

The risks increase as the body weight increases (45.2%) in women with body weight over than 90kg. Young females are at risk to develop the disease (45.23%).

The sedentary lifestyle is associated with (62.69%) of cases. Unhealthy diet is major contributor to the onset of the disease with (100%) risk to develop the disease if the patient is insisting on unhealthy diet. unmarried patients are at fairly higher risk.

Family history of DM and both personal history and family history have higher risks to develop the disease Passive smoking is important factor in the onset of the disease (77.77%) family history of polycystic ovaries show fairly equal chances between no family history (59.52%) and having a family history (40.47%).

 the relation between obesity and the development PCOS is complex and involve many variables.(18) This study show a high percentage of PCOS in those who have a high body weight (90-110kg) but there also recognizable percentage in cases weighted (70-90kg).a study by barber et al stated that Polycystic ovary syndrome is an obesity-related condition. As such, weight-gain and obesity contribute towards the development of PCOS. However, there are also mechanisms whereby the development of PCOS can contribute towards further weight-gain and hamper efforts to establish effective weight-loss.(19)

Other study stated that :- PCOS is not an exclusive condition for females who are overweight or obese. Normal weight females also exhibited PCOS, especially females deemed to be PCOS candidates due to biochemical and metabolic dysfunctions. Due to the confounding factors connected with body fat and PCOS, weight gain is feasible for these females. Nevertheless, it was discovered that more than half of the females with PCOS studied in this research were overweight or obese.(20)

 The age is important factor as the study explain and the prevalence is peak during adulthood this was discussed by the following studies : _

One by lauritsen et al :- PCOS prevalence significantly decreased with age from 33.3% in women < 30 years to 14.7% in women aged 30-34 years, and 10.2% in women ≥ 35 years (P < 0.001).(21)

A progressive decline in circulating androgens was observed with advancing age. Patients 21–30 years old had lower plasma glucose and insulin levels, lower area under the oral glucose tolerance test curve and lower homeostasis

model assessment of insulin resistance index, and higher glucose/insulin and quantitative insulin sensitivity check index than patients 31–39 years old. The prevalence of PCOS phenotypes changed with age. More specifically, the distribution of the phenotypes did not differ substantially between patients ≤20 years old and patients 21–30 years old. However, a decline in the prevalence of phenotype 1 (characterized by anovulation, hyperandrogenemia, and polycystic ovaries) and an increase in the prevalence of phenotype 4 (characterized by anovulation and polycystic ovaries without hyperandrogenemia) were observed in patients 31–39 years old.

This study concluded that In women with PCOS, hyperandrogenemia appears to diminish during reproductive life whereas insulin resistance worsens(22).

My result may be attributed to the fact that the diagnosis of PCOS start early in our community since the marriage age are early and the complain are mainly infertility

this study show that both diet and lifestyle have vital role in the progression of the disease and this proven by many studies :-

There are emerging global data that women with PCOS have different baseline dietary energy intakes compared with women without PCOS. These alterations in diet may exacerbate clinical symptoms and compound risk of chronic disease in patients(23).
it seems that diet plays a very important role on the clinical picture and laboratory findings of PCOS. According to the included studies, the change in the diet of women brought positive results in terms of clinical appearance of the syndrome(24).

There is also evidence of Diet and lifestyle modifications for effective management of polycystic ovarian syndrome (PCOS), A Systematic Review and Meta-Analysis by kim et al, Which identified evidence supporting the effectiveness of lifestyle modifications in PCOS patients with obesity. Lifestyle modification as a first-line treatment of obese women with PCOS may effect outcomes, and accompanying moderate weight loss is also expected to improve the metabolic index. Lifestyle modification using combination therapy is a promising therapeutic approach that can be employed in the management of PCOS patients with obesity(25).

The study reveals that none of the cases have actively smoked but this is mainly due to the fact that our conservative society and female smokers are not prevalent in the community, on the other hand passive smoking contribute a

major percentage. Other studies in the other countries which strongly suggest smoking have strong association with polycystic: -

A study by pau et al suggests that Women with polycystic ovary syndrome (PCOS) are at risk for metabolic syndrome, which may be exacerbated by smoking. They hypothesized that smoking worsens androgen levels and the metabolic profile in women with PCOS(26).

In women with PCOS, smoking was associated with statistically significantly increased levels of fasting insulin and calculated free testosterone (cFT) and with a raised free androgen index (FAI) score, which resulted in aggravated scores on the homeostatic model for assessment of insulin resistance (HOMA-IR). However, no differences were observed between the smoking and nonsmoking groups with regard to the clinical parameters for hirsutism, acne, ovulatory function (classified as eumenorrhea, oligomenorrhea, and amenorrhea), or polycystic ovaries using the ultrasound criteria recommended according to the Rotterdam definition(27).

The association of polycystic ovaries and diabetes has been suggested in many occasions And my study reveals that there is a relation between personal history and family history of DM with the development of the disease which is agreeable by the following studies :

A study by cheng et al suggested that:-

The prevalence of a parental history of DM significantly higher in PCOS patients than non-PCOS women.(28)

Other study suggested that:-

Insulin resistance, polycystic ovary syndrome, and type 2 diabetes mellitus, which its results stated that, several studies have suggested that insulin resistance plays an important role in the pathogenesis of the syndrome. As a consequence of insulin-resistance, women affected by PCOS often present abnormalities of glucose metabolism and lipid profile, and have an increased risk of type 2 diabetes and cardiovascular disease over-time. Besides insulin-resistance, it has been demonstrated that some of these women also have alterations in beta-cell-function. Both disorders (insulin-resistance and beta-cell-dysfunction) are recognized as major risk factors for the development of type 2 diabetes. Long-term studies, evaluating the glucose-insulin system in women affected by PCOS, have shown a higher incidence of glucose intolerance, including both impaired glucose tolerance and type 2 diabetes, compared to age and weight matched control populations(29).Insulin resistance affects between 10% and 25% of the general population. Two common disorders frequently associated with insulin resistance are PCOS, affecting 4% to 6% of reproductive-aged women, and type 2 diabetes mellitus, which is observed in about 2% to 6% of similarly aged women. Overall, about 50% to 70% of women with PCOS and 80% to 100% of patients with type 2 diabetes mellitus

have variable degrees of insulin resistance. Insulin resistance and its secondary hyperinsulinemia appear to underlie many of the endocrine features of PCOS in a large proportion of such patients. The risk of type 2 diabetes mellitus among PCOS patients is 5- to 10-fold higher than normal. In turn, the risk of PCOS among reproductive-aged type 2 diabetes mellitus patients appears to be similarly increased(30).

The family history of polycystic ovaries is Risk factor in many cases and Familial aggregation of polycystic ovary syndrome has been recognized for many years.(31)(32)this was also discussed by the following study:

The development of the polycystic ovary syndrome: family history as a risk factor, which stated that:-
Three general genetic models for the development of the polycystic ovary syndrome (PCOS) can be proposed, namely: (1) the "single-gene Mendelian" model, which considers the majority of defects present in PCOS to be unique; (2) the "multifactorial" model, which suggests that the defects present in PCOS are not unique, and simply represent the conglomeration of abnormalities already present separately, and to a significant degree, in the general population (e.g. as in cardiovascular disease and non-insulin-dependent diabetes); and (3) the "variable expression-single gene" model, a modified version of the above two. Overall, data support this third model, suggesting that PCOS is a familial disorder, with a single autosomal dominant gene effect, and a variable phenotype. Family history can then be considered as an important factor determining the risk of developing PCOS. preliminary data indicate that a woman's risk of developing PCOS is approximately 40% if her sister is affected. Alternatively, only 19% of mothers were affected, suggesting that the inheritance of PCOS may be preferentially paternal, although expanded clinical studies will be required to confirm these findings. Considering PCOS to be a dominant genetic disorder with a high degree of expressivity, we propose that the risk of developing the disorder is governed by family history and the degree of exposure to the selected environmental and/or other genetic influences(33).

Conclusion:_ the study reviews the risk factors and their effect on the disease prevalence.there is association between those risk factors and the disease Patients who are young and have increased body weight with sedentary lifestyle and positive family history of DM and continuous exposure to passive smoking

is at higher risk to early onset of the disease.this may provide us information on how to reduce the prevelace and the incidence by reducing the risk mainly the modifiable one .

Recommendations:_ Polycystic ovary syndrome is a wide and complex female endocrine disorder, which is presently recognized as a major economic health burden that is likely to expand together with obesity. And it have many health consequences . an individualized treatment plan can be developed for the adolescent girl with features of PCOS. Attention to the history, physical examination, and laboratory data is important to identify adolescent girls at risk to develop PCOS. Whereas deferring diagnostic labeling may be appropriate, treatment of clinical features and comorbidities is vital to the health and self-esteem of these patients. One future goal includes prevention through timely identification of at-risk prepubertal and early pubertal girls through lifestyle interventions and eliminating or reducing the modifiable risk factors.an individualized treatment plan can be developed for the adolescent girl with features of PCOS.

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