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The Role of Hormonal and Genetic Factors in the Pathogenesis of Polycystic Ovary Syndrome: A Review

Rawaa G. Farhood *PhD*, **Athraa F. Alshimerry** *PhD*

Dept. of Pathology and Forensic Medicine, College of Medicine, University of Babylon, Babylon, Iraq.

Abstract

Polycystic ovary syndrome (PCOS) is one of the most common healthy problems that frequently affects women during her reproductive life. It is a prevalent endocrinopathy that affects 6-10% of women in reproductive age. The pathophysiology of the condition is complex it caused by a hormonal imbalance and it is considered as a complex illness resulting from the combinations of intrauterine, hereditary, hormonal, and environmental variables. PCOS increases the chance of women to have type 2 diabetes, dyslipidemia, and systemic arterial hypertension. They also have a higher accidental of having a heart disease during menopause.

Keywords Polycystic ovary syndrome (PCOS), pathogenesis, clinical manifestations

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List of abbreviations: DENND IA = DENN domain containing 1A, DM = Diabetes mellitus, FSH = Follicle stimulating hormone, HPA = Hypothalamus-pituitary- adrenal axis, IGF-1 = Insulin like growth factor-1, INSR = Insulin receptor, IR = Insulin resistance, IUGR = Intrauterine growth retardation, LH = Luteinizing hormone, OSA = Obstructive sleep apnea, PCOS = Polycystic ovary syndrome, SHBG = Sex hormone-binding globulin, SUMO1P = Small ubiquitin-related modifier 1 protein, THADA = Thyroid adenoma associated, TOT3 = Target of temperature3, T2DM = Type 2 diabetes mellitus, ZNF217 = Zinc finger protein 217

Introduction

Polycystic ovary syndrome (PCOS) is a common disorder. It has a mixing of genetic and endocrine disorder in its etiology, which is modulated by many factors, such as prenatal androgen exposure, nutritional status in the uterus, ethnicity, insulin resistance of puberty. Environmental factors, such as obesity, seem to be worsen the underlying genetic predisposition. The incidence of PCOS is between 5 and 10%. It is common in women in the reproductive age group. It is characterized by menstrual disturbances, ovulatory dysfunction and polycystic ovaries and clinical and biochemical manifestations of hyperandrogenism [1].

Although the clinical features appear in adolescent, Yet, it is believed that intrauterine environments are where the illness first emerged. This implies that it can have an impact on many life stages [2].

The exposure to steroids (primarily glucocorticoids and/or androgens) is the main cause in gene expression changes that can notice throughout fetal development are represented by the developmental programming. Certain metabolic and reproductive phenotypes are linked to PCOS in extrauterine life, and these characteristics are connected to the stage of pregnancy where the fetus was overexposed to steroids [3]. The vital features that have been applied for diagnosis of PCOS are hyperandrogenism (hirsutism), oligoanovulation and polycystic ovaries; the three major diagnostic schemes use various

combinations of these criteria [4]. Seventy percent of PCOS patients have hirsutism, which is regarded as a key clinical sign of an increase in androgen [5], also the increase level of dihydrotestesterone in hair follicles is an important cause of acne in these patients [6].
Infertility is the main complication account 40% and have an abnormality in follicular growth and development, the follicles reach size 4-8 mm, so ovulation does not succeed; some patients suffering from recurrent abortion [7].
Group of patients with PCOS can be presented with type 2 diabetes mellitus (T2DM), this occur because of pancreatic β cell dysfunction and insulin resistance (IR), which have been are a serious cause in the pathogenesis of glucose intolerance in PCOS [4] (Figure 1).

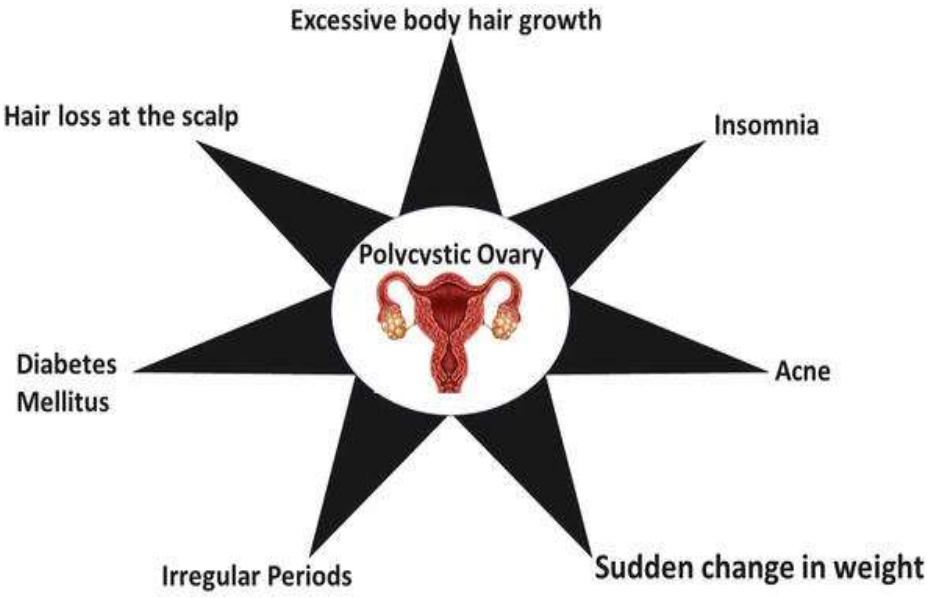

Figure 1. The main symptoms of PCOS [7]

Pathogenesis of PCOS

The syndrome was first descried by Stein and Leventhal in 1935, but its pathogenesis remains unclear. There are few pathways that are crucial in the pathophysiology of PCOS, including hormonal imbalance, genetic inheritance, intrauterine factors, neuroendocrine substances and insulin resistances [8] (Figure 2).

Role of developmental programming in the pathogenesis of PCOS

The term "developmental programming" states to certain modifications in the expression of the gene brought on by epigenetic modifications, these changes lead to permanent alteration and modifications in the function and structure of fetal circulation and organs at serious stage, this because of augmented level of steroid hormone. This phenomenon may be due to either the increase level of maternal androgen during pregnancy or result from the effect of fetal hypoxia and growth retardation (raised level of glucocorticoids) [9], associated with programming of endocrine pathway during postnatal. These changes may be due to the molecular origin in developmental programming related to the phenotype in metabolism and reproduction PCOS-afflicted ladies display throughout their lives [3,9].

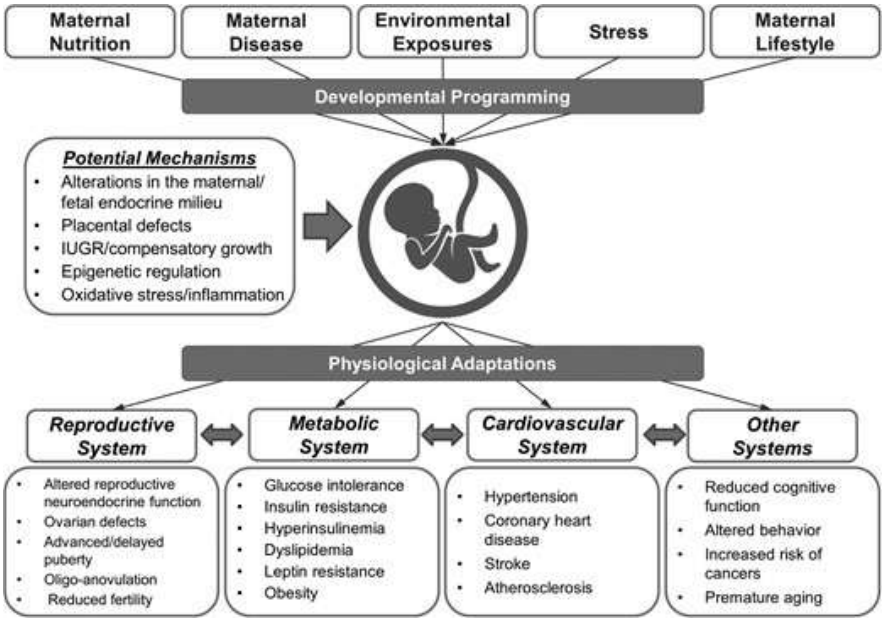

Figure 2. Role of developmental programming in the pathogenesis of PCOS [9]

The presence of abundant androgen during pregnancy may increase the risk of PCOS. Risk of PCOS could be elevated during pregnancy by excess the level if androgen that is result in developmental programming could be happened in patients with T2DM and IR [9]. Experimental studies showed that the increase level of insulin, visceral obesity in childhood, clinical feature like metabolic and reproductive features in female patients could be happened due to increase level of androgen within intrauterine growth of the fetus could be a main cause of [9,10].

Environmental factors associated with PCOS

The environmental causes act as stimuli motivates the clinical features and endocrine activity that consider a specific signs and symptoms of PCOS, these environmental factors have strongly associated with PCOS and can be divided into prenatal factors (fetal developmental program), postnatal factors (obesity, diet, drugs or toxins) [11].

The evidence of the effect of the life style of patients can affect the progression of PCOS and support the role of environmental elements in etiology. The main and initial treatment for PCOS is to reduce body weight in obese women; moreover, losing 2-5% of one's body weight can lower insulin levels, free androgen and certain metabolic syndrome like dyslipidemia [12].

According to some researches that have been reported that decrease in rapid eye movement sleep stage time and increased risk for Obstructive sleep apnea (OSA) in PCOS patients [13-15]. The increased occurrence of OSA may be attributed to alerted reproductive hormone production (high androgen and low estrogen levels, for example) [16]. Also, it was indicated that chronic oligo-anovulatory cycles in PCOS was associated with low estradiol-to-testosterone ratio [17]. The inhibition of hypothalamic positive feedback to estradiol (E2) can disturb the development of the follicle, ovulation defect, granulose cell apoptosis, all these conditions can be related to IR [18,19].

Genetic factors associated with PCOS

Genetic inheritance of PCOS supported by aggregation the disease in certain families and affect first degree relatives. The risk of developing PCOS has been shown to be raised

twice in which, women with monozygotic twin's sisters when they reached the reproductive age group [20].

There are hundred copies of genes variants have been the important cause in pathogenesis and are responsible in signs. Assessment and evaluations for the gene that have been associated with (hyperandrogenism, IR, metabolic and inflammatory markers, and obesity) have been identified for the specific number of people as having PCOS symptoms [21].

DENN domain containing 1A (DENNDIA), a gene that code for quinine modulator associated with a variety of tissue abnormality, as well as, failure in the function of the ovaries, hypothalamus, pituitary, and adrenal glands, also an associated with tissue-specific insulin responses, type II diabetes and obesity. And another thyroid adenoma gene "THADA" linked to dyslipidemia, hyperandrogenism, morphology of polycystic ovaries, luteinizing hormone (LH) level excess, and abnormalities of glucose metabolism, is found in the PCOS population [22].

The study of the chromosomes structure (changes in non-coding sequences) has been included in one of the approaches in survey of hereditary mutations in PCOS. The decrease in telomere length in regarding with aging, this alteration can be one of the changes that can be superimposed the vascular disease, increase the cholesterol level and T2DM ([23]. Comparing women with and without PCOS at various periods of life in specific studies demonstrated that a reduction in telomere length plays a crucial role in the pathogenesis of PCOS, also, early detection the differences in telomere length are of benefit in early diagnosis women with PCOS and can be prevent risk of certain metabolic complications [24,25].

Another explanation for the genetic role in PCOS called target of temperature3 (TOT3), which is located at 16q12.1 has been associated with DNA modification, another mutation occurs in insulin receptor gene (INSR) located at 19p13.3 has been associated with IR, beside zinc finger protein 217 gene (ZNF217) which is located at 20q13.2, mutation of this gene is linked to telomere disruption [26,27].

Hormonal factors

- ***Hyperandrogenism:*** This term can be defined as certain changes that happened in the normal ovarian function which results in increase of androgen production [28], also, it may be result from adrenal dysfunction and lesser influence from fatty tissues. Hyperandrogenism can be confirmed by calculating the levels of total serum testosterone, sex hormone binding globulin (SHBG), 17-hydroxy progesterone, and free androgen index [29]. Most women with PCOS have high levels of LH and low follicle stimulating hormone (FSH) during their menstrual phase that promotes the production of androgen which delays the development of the follicles and the low level of FSH encourages the growth of small follicles [30].
- ***IR***: is the inability of a cell to respond well to insulin either to a normal or increased level of insulin [31,32]. This defect leads to metabolic abnormalities in PCOS. Those patients are more commonly to develop glucose intolerance, and ovulatory dysfunction [32].
- Insulin acts directly on thecal cells with LH to enhance androgen production and by acting indirectly reduces the production of SHBG and insulin like growth factor-1 (IGF-1). Furthermore, elevated levels of androgen to produce free fatty acid, which contributes to IR [33,34] (Figure 3).

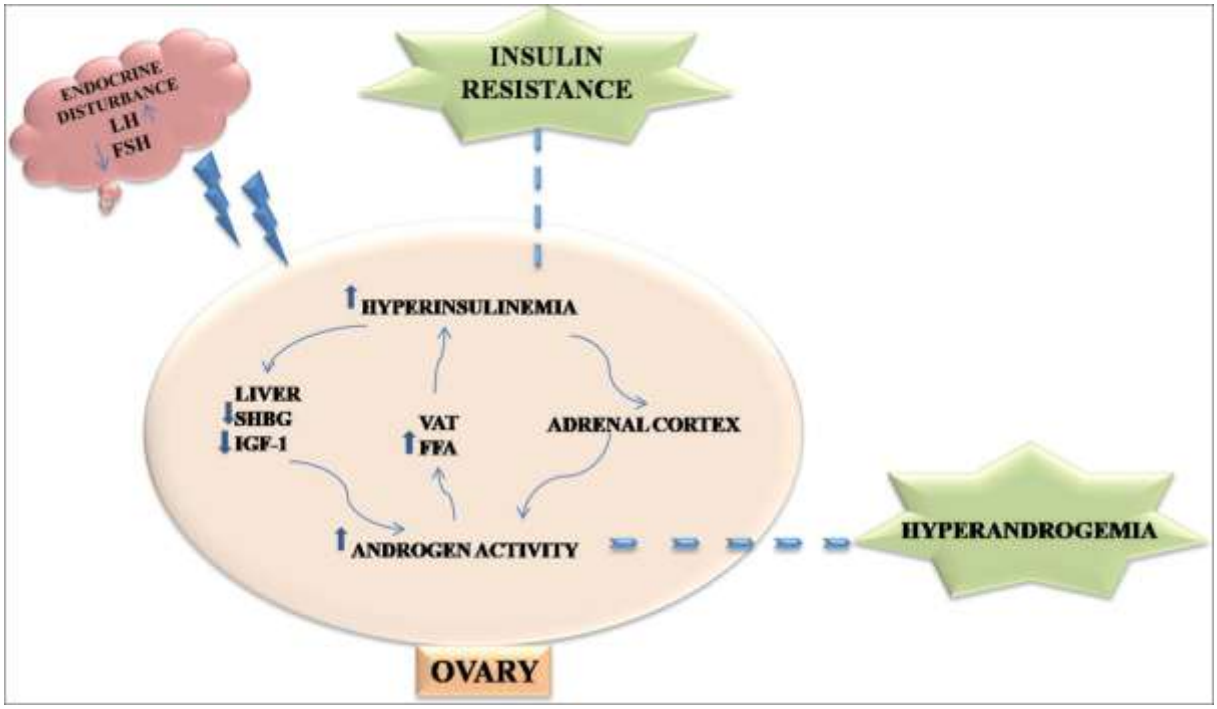

Figure 3. The hyperinsulinemia and hyperandrogenemia for PCOS development [34]

Developmental programming by increase the glucocorticoid

The correct growth of the fetus, which is regulated by the equilibrium between anabolic and catabolic process, depends on the functional maturation and differentiation of fetal organs. Diet restriction, disease of the mother and placental dysfunction are the main cause of fetal hypoxia leads to growth retardation results from the catabolic process will be predominate. Small gestational age fetus newborn consequence, which in centralization, a process that reduces the blood supply of the fetus to vital organs (heart, brain, and adrenal glands). As a result of the hyperactivity of hypothalamus-pituitary-adrenal (HPA) axis, there is an increase in the production of glucocorticoids, which causes epigenetic changes [35].

The developmental programming results from increase glucocorticoid, clinically appear at late stage of life delayed by the causes and etiology that have many factors in its pathogenesis of most disease of the heart and metabolic disease [36].

Developmental programming by androgen excess

The increase in adrenal androgen levels has the potential to influence gene expression., this may cause changes in and have an impact on the metabolic, reproductive, and developmental phenotypes of PCOS, also other conditions like obesity, DM, weight gain during pregnancy are ominous sign for large baby, children are associated with affect hyperandrogenism [37] (Figure 4).

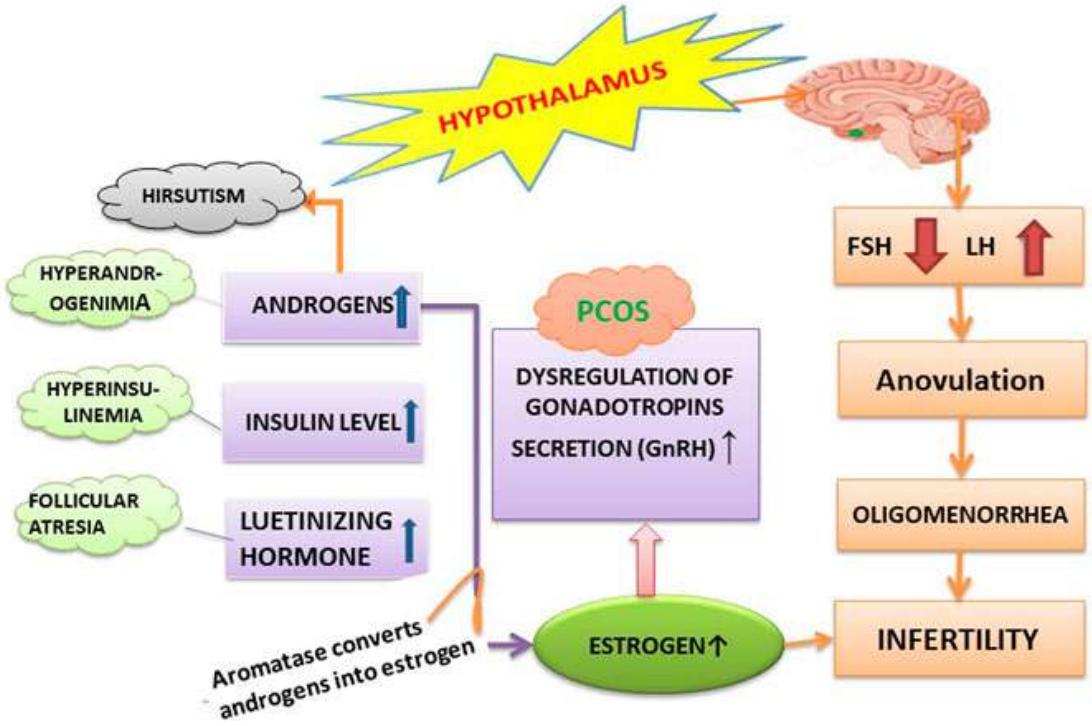

Figure 4. Pathogenesis of PCOS [8]

Clinical manifestations of PCOS

PCOS symptoms and developmental programming: children and adolescents

The compensatory growth usually affects 90% of small weight gain babies has been linked to significant weight gain and growth throughout the first two years of life, this change has been associated increase the level of insulin, central obesity [36].

During the peripubertal period, the damage to adipose tissue causing augmented levels of leptin that in relation of overproduction of LH and the overgrowth of the associated with increased level of androgen. Hence, PCOS is more likely to occur in most women who have an anovulatory cycles also notice that these women are more frequently who were born small for gestational age [38]. In addition, another cause, which increasing level of ovarian androgens that insulin acts on via IGF-1 on the ovarian theca [37-39].

PCOS symptoms and developmental programming: reproductive age

Women who exhibit the clinical symptoms of PCOS are at increased risk for acquiring it. at reproductive age are commonly associated with raised level of insulin and androgen, people who are required to have a high complication rate, such as restriction of fetus growth during intrauterine life, also those women are more commonly to have high incidence of anovulatory cycles [38]. Another group of patents showing other clinical features, that appear after the age of 40 in the general people in regarding with PCOS patients, therefore visceral obesity is more common in the daughters of hyperandrogenic women, increase cholesterol level, these appearances and traits may serve as early clinical indicators of dyslipidemia, metabolic syndrome, and type 2 diabetes associated with PCOS [32].

PCOS symptoms and developmental programming: menopause

Cardiovascular illness is more prevalent and susceptible in younger age group than menopause- and older age to have PCOS as a result of initial aggravating to the hazards to the effect of oxidative and inflammatory settings, because of early exposure to risk factors in inflammatory and oxidative states, these facts clarify by that the cardiac disease have many factors in etiology and the possible risk of affect the women in different age group [39]. Moreover, the atherogenic effect in females of reproductive age, with an increase in insulin levels, endocrine glands abnormality may increase the chance incidence of arterial thrombosis during menopause, in women with PCOS, all of these variables show an important influence in the progress of heart and arterial disease [40].

Diagnosis

Blood tests can measure hormone levels, fasting cholesterol and triglyceride levels. Ultrasound can assess the structure of the ovaries and the thickness of the lining of uterus [39].

Rotterdam diagnostic criteria (2003) for PCOS

Two out of the following three after exclusion of other hyperandrogenic disorders:

- Oligo- or anovulation
- Clinical and/or biochemical signs of hyperandrogenism
- Ultrasonographic evidence of polycystic ovaries (Figure 5) [41]

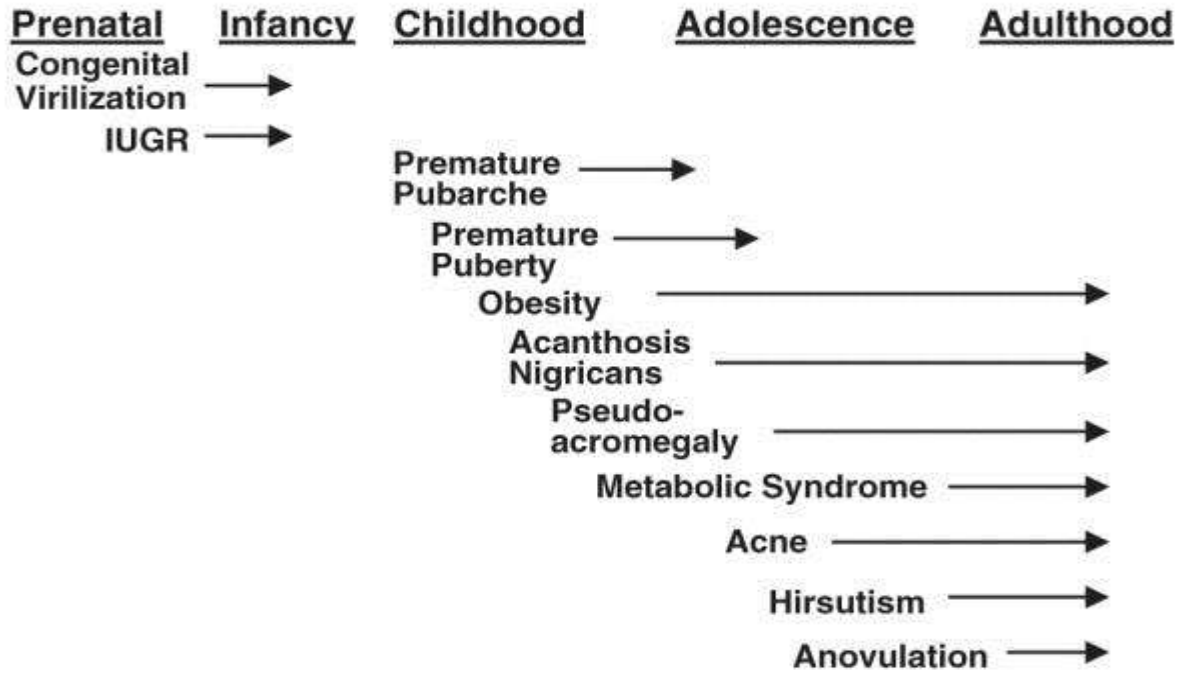

Figure 5. Presentation of PCOS [41]

Conclusion

PCOS is a heterogeneous complex metabolic disorder triggered by inheritable genetic and environmental risk factors. There is no specific gene that have been identified with clear clinical significance but it can be concluded that women with PCOS have two major genetic alteration in androgen and insulin action with variable gene polymorphism.

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Correspondence to Dr. Rawaa G. Farhood
E-mail: dr.rawaaghali123@gmail.com

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