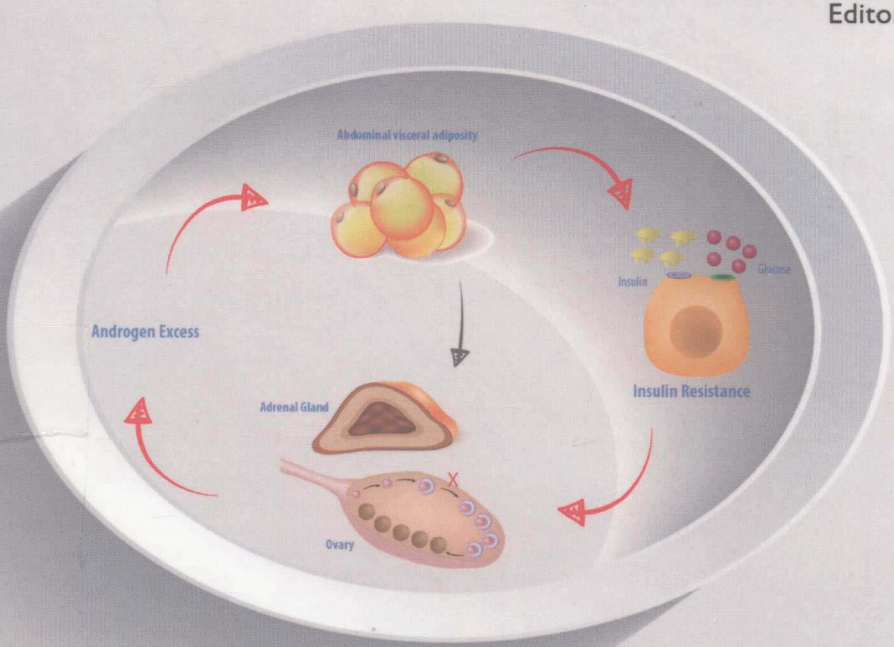
Polycystic Ovary Syndrome (PCOS)

Clinical Aspects, Potential Complications and Dietary Management

Bruce Cobbs
Editor



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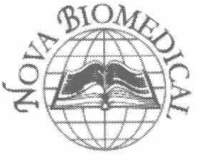

New York

Library of Congress Cataloging-in-Publication Data

Library of Congress Control Number: 2016947966
ISBN: 978-1-63485-924-0

Published by Nova Science Publishers, Inc. † New York

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PREFACE

Polycystic Ovary Syndrome (PCOS) is known as a common gynaecologic and endocrinology disease with multiple short and long-term consequences. It is one of the most common causes for hyperandrogenism and anovulation (therefore hirsutism, acne, menstrual dysfunction and infertility); increases the risk for metabolic syndrome, Type 2 diabetes and, still debated, cardiovascular disease. It represents a substantial psychological, social and economic burden for women's reproductive life span. In this book, Chapter One reviews the aetiology and pathogenesis of the Polycystic Ovary Syndrome, with the objective to set the ground for future research that could help elucidate which patients have risk of developing the disorder and what triggers this risk, so strategies to prevent it could be found. Chapter Two focuses on the most recent studies about PCOS and the current models of its genetic pathogenesis. In addition, it emphasizes the significance of genetic factors and the possibility of developing plausible candidate gene families for diagnosis and to improve therapeutic approaches for PCOS treatment. Chapter Three evaluates the available therapeutic strategies for the treatment of women with PCOS also focusing on diet in order to assess the possible impact on the clinical effects associated with it. Chapter Four reviews the most recent data regarding useful and promising adjuvant therapies in PCOS and its mechanisms of action, in order to expand its use on those patients who do not respond to conventional management. Chapter Five focuses on current existing markers of Insulin resistance (IR).

Chapter 1 - Polycystic Ovary Syndrome (PCOS) is known as a common gynaecologic and endocrinology disease with multiple short and long-term consequences. It is one of the most common causes for hyperandrogenism and anovulation (therefore hirsutism, acne, menstrual dysfunction and infertility);

increases the risk for metabolic syndrome, type 2 diabetes and, still debated, cardiovascular disease; and represents a substantial psychological, social and economic burden for women's reproductive life span.

Despite being described more than 80 years ago, its etiology remains unclear. In the past decade, evidence has been accumulated supporting the central role of insulin resistance and/or compensatory hyperinsulinemia in the PCOS pathogenesis. It also has been demonstrated that insulin resistance and subsequent hyperinsulinemia contribute both directly and indirectly to hyperandrogenism development.

Nonetheless, PCOS is thought to be the result of the interaction between predisposing genetic variants with environmental factors and strongly depends on ethnicity. There is some evidence that it may partly depend on genetic factors and that it is more likely to be polygenic or oligogenic than a single gene defect.

Several research groups have suggested that the origin of PCOS lies in foetal life and involves the foetal programming of metabolic/endocrine axes, especially carbohydrate metabolism and adrenal secretion. For example, girls born small for gestational age, an indirect index of exposure to stressful intrauterine conditions, manifest a high incidence of PCOS in adolescence.

Perhaps, the most important feature is the existence of a vicious circle where the insulin resistance leads to hyperandrogenism, which in turn results in obesity and greater insulin resistance thus, closing the circle.

It is the purpose of this chapter, to review the aetiology and pathogenesis of the Polycystic Ovary Syndrome, with the objective to set the ground for future research that could help us to elucidate which patients have risk of developing the disorder and what triggers this risk, so the authors could find some strategies to prevent it.

Chapter 2 - Polycystic ovary syndrome (PCOS) is a common female endocrine disorder that often results in infertility. It is a complex, heterogeneous trait of uncertain etiology, but there is strong evidence that it is influenced by both genetic and environmental factors. Recently, numerous studies have been performed as the role of genetic factors involved in metabolic disorders, sex hormones, and inflammation has become more widely accepted. In the past few years, the authors have tried to identify several novel genes and proteins relevant to PCOS, involved in angiogenesis, insulin signaling, and inflammation. Of these, genes of *tumor necrosis factor (TNF-α), leptin receptor (LEPR), adiponectin, monocyte chemoattractant protein-1 (MCP-1), follicle stimulating hormone receptor (FSHR), and insulin receptor (INSR)* are linked to the chronic inflammation and insulin signaling

pathway. Pre-genome wide association study (GWAS) has been a very powerful tool for identifying the pathogenesis of PCOS, even though most of the strongest associations are for loci rather than functional variants. A trend towards large-scale GWAS has succeeded in identifying many additional novel PCOS loci. Most of the PCOS-associated regions are shared with other diseases or symptoms, as well as with metabolism, inflammation or insulin signaling-related traits, or cancer. Moreover, susceptibility genes for early diagnosis of PCOS are anticipated to offer the prevention of long-term risk of obesity, cardiovascular disease, and type 2 diabetes mellitus (T2DM) as well. Furthermore, advanced new technical approaches such as GWAS and next generation sequencing (NGS) will provide new opportunities in the molecular analysis of PCOS, which can, in the long term, lead to the development of new therapeutic treatments for the disorder. To date, very little was known about the etiology of PCOS, and the mechanisms by which this disorder develops are still unclear. Having identified compelling genetic signals, the functional analyses of these should be assessed to see how the associated alleles regulate gene or protein function. Furthermore, structural variations and epigenetic signatures are also likely to contribute to the genetic background of this disorder. In pursuit of understanding the genetic mechanisms of complex traits, risk prediction models should be established, in order to develop minimally invasive methods of diagnosis and to achieve effective targeted therapy. Alternatively, molecular markers that identify a female population who are just developing the disorder at pubarche would benefit from earlier intervention of the disease, as diagnosing PCOS is particularly problematic among female population lacking even expert consensus.

In conclusion, GWAS methodology and potential functional mechanisms are becoming crucial in investigating genetic association with PCOS. Undoubtedly, GWAS has succeeded in identifying many additional novel PCOS loci. Genes and related pathways involved in PCOS have not been completely identified yet. More importantly, a rational strategy for genetic investigation of PCOS is essential and studies should avoid small sample duplication. Moreover, elucidating the exact functions of these genes or gene products would shed light on the pathogenesis of PCOS and facilitate the development of efficient therapeutics for PCOS.

Chapter 3 - Polycystic Ovary Syndrome (PCOS) is one of the most common female endocrine disorders affecting 6-15% of women in reproductive age. This syndrome involves the hypothalamus, the pituitary gland, the ovaries and the adrenal gland. Women with PCOS show chronic anovulation, hyperandrogenism and insulin resistance. It is the main cause of

infertility and it is characterized by menstrual dysfunction and metabolic disorders. Both hyperandrogenism and hyperinsulinemia play a pivotal role in the pathogenesis of PCOS. Dyslipidemia and insulin resistance, that occur in this syndrome, also cause an increase in cardiovascular risk.

Many years of studies and researches allowed us to outline a fairly exhaustive picture about the etiology of PCOS, and many steps forward have been made regarding the diagnosis of this syndrome, but there is still no certainty related to the therapy.

Certainly lifestyle management is a first - line treatment in PCOS: a proper diet, important also to obtain a correct BMI, may help in reducing insulin resistance and in restoring ovulatory cycles.

Inositol(s) – present in many foods, especially fruits and beans – plays a central role in important metabolic pathways which, in case of malfunction, is involved in the onset and development of PCOS. As proof of this, it was demonstrated that two stereoisomers belonging to inositol(s), myo-inositol (MI), and D-chiro-inositol (DCI), can improve several pathologic conditions related to PCOS. In plants, the inositol family is generally represented in the form of hexaphosphate, and phytic acid or its salts (phytates). A current diet is often poor of these substances; indeed, in the last decades the content of phytates was considerably reduced in food, because of their strong chelating effect.

Also other dietary molecules, such as omega-3 fatty acid eicosapentaenoic acid (EPA), were found useful for improving some pathologic conditions of PCOS. Currently, the dietary intake of women with PCOS is unclear and there is no research assessing dietary patterns of women with and without PCOS. The endocrine disorders may be managed by specific strategies employing sequential or combined pharmacological and non-pharmacological treatment. The authors know how important is the use of insulin-sensitizing compounds as putative treatments to solve the hyperinsulinemia-induced dysfunction of the ovarian response to endogenous gonadotropins. In this way, it is possible to reestablish menstrual cyclicity and ovulation, increasing the chance of a spontaneous pregnancy. Therefore, insulin - sensitizing drugs such as metformin and thiazolidines are therapeutic options, although some side effects limit their use for PCOS patients. MI and DCI act as insulin sensitizing drugs too. DCI is involved in mediating insulin activity chiefly in non - ovarian tissues, and MI displays specific effects on the ovary, mainly by the modulation of FSH - signaling and glucose metabolism. Moreover, MI may also enhance the ovarian steroidogenic function. Recent studies have shown

that the best approach to PCOS therapy with inositol(s) is associating MI and DCI at the 40:1 ratio.

Our analysis aims to evaluate the available therapeutic strategies for the treatment of women with PCOS also focusing on diet in order to assess the possible impact on the clinical effects associated to it.

Chapter 4 - The aetiology of the Polycystic Ovary Syndrome remains unclear. There is also controversy regarding the diagnostic criteria and discussion around the variability of the phenotypes. This lack of agreement has conducted the treatment to focus only into the symptoms and most evident features like infertility or obesity.

Primary approach is based on improving the insulin resistance through diet, weight lose and exercise. When this fails, insulin sensitizers could have a role. Another strategy includes assisted reproduction techniques (ART) in women who are infertile or the use of oral contraceptives to regulate the menstrual cycle. It can be necessary to administer anti-androgens depending on the severity of the hyperandrogenism. There is also the need to bariatric surgery in case of morbid obesity and the presence of metabolic syndrome.

Complementary medicine (CM) has been emerging in recent years as an alternative and coadjutant to conventional medical management. Evidence has shown that CM may have a role in the treatment of women with PCOS demonstrating benefits in the endocrine, cardio-metabolic and reproductive complications of the syndrome.

Chapter 5 - Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders affecting 5-10% of women in reproductive age. The importance of this syndrome lies in the magnitude of comorbidities associated: infertility, metabolic dysfunction, cardio-vascular diseases (CVD), psychological and oncological complications.

Insulin resistance (IR) is a prominent feature of PCOS with a prevalence of 35-80%. Without an adequate management, IR with its compensatory hyperinsulinemia contributes directly to reproductive dysfunction in PCOS women. On the other hand, epidemiological data show compelling evidence that PCOS is associated with increased risk of impaired glucose tolerance (IGT), gestational diabetes mellitus (GDM) and type 2 diabetes (T2D). Furthermore, metabolic dysfunction leads to magnified risk for CVD with aging in women with PCOS. Indeed, severity of IR in PCOS women is associated to the amount of abdominal obesity even in lean PCOS women.

Given this severe implications, it is important to diagnose and treat insulin resistance as early as possible.

Looking at the current available literature on PCOS, it appears that this syndrome is mostly found in women from western countries or from developed countries. Few studies are available in Sub-Saharan African women with PCOS. Nevertheless, this syndrome exists and is commonly found in the daily medical practice. Furthermore, on the road, many women are seen with beard or moustache, or android adiposity. Sub-Saharan African women with PCOS are used to see a doctor mostly for infertility or when other complication occurs. This fact emphasized that the PCOS is unknown for many black Sub-Saharan African women.

A study conducted in Congolese women with PCOS shows that almost one of two women with PCOS is insulin resistant. And this feature is independent from overweight and obesity. Considering this fact and its burden, there is a need of an accurate marker for early detection and assessment of IR in Sub-Saharan African PCOS women.

Many markers exist and have been proposed. But quantitative assessment of insulin resistance in clinical practice remains a big challenge. The gold standard method for assessing insulin sensitivity is the hyperinsulinemic euglycemic glucose clamp. However, it is not used routinely because of the complexity of its procedure. Consequently, there has been an urgent need of surrogate markers of IR which are more applicable in large population-based epidemiological investigations. Despite this, many of them are either difficult to apply in routinely clinical practice, either useless for PCOS women.

This review focuses on current existing markers of IR. In depth knowledge of these markers will help to discover which can be an easy-to-detect marker that can be used efficiently for assessing IR in Sub-Saharan African women with PCOS.

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In: Polycystic Ovary Syndrome (PCOS) ISBN: 978-1-63485-924-0
Editor: Bruce Cobbs

Chapter 1

PCOS AETIOLOGY: CURRENT RESEARCH AND FUTURE STRATEGIES OF STUDY

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ABSTRACT

Polycystic Ovary Syndrome (PCOS) is known as a common gynaecologic and endocrinology disease with multiple short and long-term consequences [1-4]. It is one of the most common causes for hyperandrogenism and anovulation (therefore hirsutism, acne, menstrual dysfunction and infertility) [3]; increases the risk for metabolic syndrome, type 2 diabetes and, still debated, cardiovascular disease [5]; and

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represents a substantial psychological, social and economic burden for women's reproductive life span [1].

Despite being described more than 80 years ago, its etiology remains unclear. In the past decade, evidence has been accumulated supporting the central role of insulin resistance and/or compensatory hyperinsulinemia in the PCOS pathogenesis [6, 7]. It also has been demonstrated that insulin resistance and subsequent hyperinsulinemia contribute both directly and indirectly to hyperandrogenism development [8, 9].

Nonetheless, PCOS is thought to be the result of the interaction between predisposing genetic variants with environmental factors and strongly depends on ethnicity. There is some evidence that it may partly depend on genetic factors [10] and that it is more likely to be polygenic or oligogenic than a single gene defect [11, 12].

Several research groups have suggested that the origin of PCOS lies in foetal life and involves the foetal programming of metabolic/endocrine axes, especially carbohydrate metabolism and adrenal secretion [10, 13-16]. For example, girls born small for gestational age, an indirect index of exposure to stressful intrauterine conditions, manifest a high incidence of PCOS in adolescence [17].

Perhaps, the most important feature is the existence of a vicious circle where the insulin resistance leads to hyperandrogenism, which in turn results in obesity and greater insulin resistance thus, closing the circle.

It is the purpose of this chapter, to review the aetiology and pathogenesis of the Polycystic Ovary Syndrome, with the objective to set the ground for future research that could help us to elucidate which patients have risk of developing the disorder and what triggers this risk, so we could find some strategies to prevent it.

Keywords: polycystic ovary syndrome, PCOS aetiology, PCOS pathology, PCOS origin

1. PCOS: Starting Point

Polycystic Ovary Syndrome (PCOS) is considered the most common endocrinopathy of women of reproductive age [18] and its cost to the public healthcare system in the United States of America (USA) has been estimated in about 4 billion dollar annually [1]. There is no similar data available for Europe, but clinicians do not underestimate its importance and impact on women's health [19].

It is considered as the most common cause for hyperandrogenism and anovulation [3] with its aesthetic, metabolic and reproductive features such as hirsutism, acne, menstrual dysfunction and infertility. PCOS patients have been associated with a high risk for developing obesity, metabolic syndrome, type 2 diabetes and, still debated, cardiovascular disease [5].

The prevalence of PCOS varies from 4% to 26% according to different authors, populations and because of different diagnostic criteria used in those studies [20-24].

In order to set a starting point and discuss about the aetiology, we have briefly summarized some of the basic concepts regarding PCOS in the next paragraphs.

1.1. PCOS: Diagnostic Criteria

Three major diagnostic criteria have been proposed to identify women with PCOS: I) National Institute of Health (NIH) expert conference in 1990 [25]; II) Expert conference of the European Society for Human Reproduction and Embryology (ESHRE) and the American Society for Reproductive Medicine (ASRM) in Rotterdam, 2003 [26, 27]; and III) Androgen Excess PCOS Society (AEPCOS) in 2006 [28] (see Table 1).

Table 1. Diagnostic Criteria for PCOS

Signs and Symptoms*	NIH (1990)	Rotterdam (2003)	AES (2006)
Hyperandrogenism+	R	NR	R
Oligo or anovulation	R	NR	NR
Polycystic Ovaries	-	NR	NR

R: Required.

NR: Not Required.

* Exclude other pathology.

+ Hirsutism or chemical hyperandrogenemia.

Each one of these criteria has strengths and weaknesses. It has been said that the NIH 1990 criteria represent the core of PCOS patients. Meanwhile, the Rotterdam 2003 and AES 2006 criteria broaden the NIH 1990 definition by expanding the possible phenotypes for this syndrome [28, 29].

The lack of consensus has implications over the prevalence, changing the estimation according to which diagnostic criteria is used. Nonetheless, there

are two classic reports regarding prevalence that are still cited in European Caucasian population: Diamanti-Kandarakis et al. [30], report a prevalence of 6.77% in the Greek population (13 women of 192); meanwhile, Asuncion et al. [21], demonstrate a 6.5% prevalence in blood donors from Spain (10 women of 154). A recent paper by our group found a raise in the prevalence for Spanish population by more than two fold from what Asuncion et al. [21] previously reported. We also made a comparison between the three diagnostic criteria, this is important since, as we discuss below, the Rotterdam criteria is the one currently used by general international consensus.

Recently, in December 2012, the NIH organized an evidence-based methodology workshop in order to discuss and identify future research priorities regarding PCOS [31]. The panel was asked to clarify the benefits and drawbacks of different diagnostic criteria; causes, predictors and long-term consequences of PCOS; and, optimal prevention and treatment strategies. The NIH Experts Panel recommended the maintenance of the broad diagnostic criteria of Rotterdam [26, 27], but focused on the need for specific identification of the phenotype of each patient.

A more recent consensus was published recently were international associations and task force groups highlighted the most important clinical issues about PCOS reassuring the use of the Rotterdam criteria for its diagnosis [32]. Interestingly, there is also an agreement on the number of follicles considered for the evaluation of ovarian morphology increasing the threshold count of small ovarian follicles to 25 per ovary [33]. However, this concept is valid only with the use of ultrasound vaginal probes with a frequency of at least 8 mHz, if this is not possible, the ovarian size must be assessed (threshold of 10 mL) [32].

1.2. PCOS: Phenotypes

By using the possible combinations of the Rotterdam criteria [26, 27], there are four phenotypes identified: **A)** hyperandrogenism (clinical or biochemical) and chronic anovulation (**H-CA**); **B)** hyperandrogenism and polycystic ovaries on ultrasound (PCOm) with ovulatory cycles (**H-PCOm**); **C)** CA and PCOm without hyperandrogenism (**CA-PCOm**); and **D)** hyperandrogenism, CA and PCOm (**H-CA-PCOm**) (see Table 2).