MINI REVIEW

The Enigma of PCOS.

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INTRODUCTION

Polycystic ovary syndrome (PCOS), a reproductive disorder which is common among women due to elevated male hormone (androgen levels) and prolonged menstrual cycles leading to complications for which the exact cause is a mystery till date. Factors responsible for PCOS are excess insulin, low grade inflammation, excess androgens and sometime heredity that can be a major cause for which genetic analysis may have some significant role in depicting the exact mechanism. Uncountable numbers of theories and hypothesis have been developed since the discovery of PCOS but many controversies still persists due to lack of clinical evidences. This Meta review focuses on unravelling the mechanism through genetic-genomic strategies in which whole genome and whole exome sequencings with targeted gene panels approaches may have a significant conclusion and strategies to decipher the genes responsible for PCOS. Rather focusing on the uni-directional diagnostic approaches, a unifying strategies combining both diagnostic and genetic techniques can be applied that will have increased impact in understanding the etiology of PCOS.

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a disease rather it’s a combination or collection of different conditions which may stimulate the disease [7]. The famous genetic theory and evidence from animal models supports the fact that pcos has developmental origins [8]. There is huge similarity seen between both reproductive and metabolic phenotype in prenatand androgemised animals like sheep and monkeys, and also in women with PCOS, supporting the fact that developmental programming plays an important role in aetiology of PCOS [9]. The dual function of androgen production and reception by human fetal ovary allows androgen to show its effects during fetal period and also in other key developmental windows of life. The onset of puberty and the period have recorded symptoms similar to that occurring in PCOS, like weight gain and these evidences highly supports PCOS having developmental origin, study also suggest that girls in adolescence suffering from androgen excess due to congenital adrenal hyperplasia have shown more distinctive feature of PCOS [10].

An elevated level of leuteinizing hormone (LH) and follicle stimulating hormone (FSH) are an important characteristics of PCOS which disregulate the controls of the development and release of eggs in the ovary in response to stimulation by gonadotroin. The ratio used to indicate abnormal gonadotropin secretion is normally 2–3/1 delineates fast GnRH appear to favor LH secretion, and slow GnRH pulses favor FSH secretion which depicts that regulation of gonadotropin is essential for the menstrual cycle. Inconsistency in regulation of gonadotropin leads to formation of small cysts and poor egg development and inability to ovulate often leads to absence of menstrual periods.

As medicine progressed new theories came into existence one of which was the one of which was the Intrauterine theory. According to this theory androgen exposure during intrauterine life or neonatal period results in alteration of fetal ovaries [11] or can cause congenital masculinization of hypothalamus [12] which helps us to explain PCOS hyperandrogenism [13]; where as some of the studies suggest that various mechanisms occurring during childhood and puberty are responsible for this disease. For example Increase in level of Insulin-Like Growth Factor 1 (IGF1) during infancy, is responsible for ovarian steroidogenesis [14]. Mechanick II hypothesized that PCOS occurs due to abnormal brain development as a result of aberrant puberty [15] whereas Insler in suggested that PCOS occurs due to excess production of androgen during puberty [16]. While Puzigaca et al. was the first one to say that women with PCOS have larger and bulkier ovaries as a result of over androgen production [17]. But then later on it was very interesting to observe that secretion of IGF from ovaries is the main reason or could be the possible cause for both increased insulin resistance and secretion of adrenal androgen. Even after known for such long period genetic theory gave us the idea that PCOS was transmitted in X-linked dominant fashion [18], giving us new insights on studying the heritability of PCOS. 80.5% of women with PCOS and their siblings are affected by having the same genetic origin at the same time in X-linked dominant manner [19] of inheritance. Overall one can say that PCOS has polygenic origin. Recently it was reported that general transcription factor IIA subunit 1 like and luteinizing hormone/choriogonadotropin receptor might serve as biomarkers [20] but on the other hand a study conducted on variants of PCOS suggested that thyroid adenoma-associated protein gene polymorphism and DENN domain-containing protein 1A gene are involved [21]. This supports the fact that PCOS is an inherited disease. One cannot view PCOS as matter of developmental origin or resulting only from intrauterine exposure or an adaptation happening over evolution. We need to determine a more subtle and variable interpretation to understand the physiology of PCOS in order to have a better view regarding when and how to intervene this syndrome. We also need to understand the environmental aspects so that we can modify and then design study to get the best output and have a better understanding of its etiology.

Controversies in Diagnosis

Diagnosis of PCOS was truly based on advice from the specialist as no data from clinical trials were recorded and this was insufficient for correct treatment. This lead to the development of Rotterdam criteria in 2003. Hence in order to diagnose PCOS a women has to fall under these three criteria: i) oligo- or chronic anovulation, ii) clinical and/or biochemical signs of hyperandrogenism and/or iii) polycystic ovaries with the same specification as earlier regarding the exclusion of other androgen excess and anovulatory infertility etiologies. The revision of this criteria resulted in addition of ultrasonography of the ovaries. Due to this, it was implied that now PCOS may be diagnosed without any biochemical or clinical symptoms of hyperandrogenism. PCOS was studied by two groups of medical community, gynecologists and endocrinologist. The gynecologist followed the 2003 Rotterdam criteria but the endocrinologists were not satisfied and hence it lead to development of another set of criteria. Finally in 2006 Androgen Excess Society made a statement that PCOS should be, first of all, considered a “disorder of androgen excess or hyperandrogenism”, at the same time nothing that a minority considered the possibility that there may be forms of PCOS without any evidence of hyperandrogenism [21]. In simple terms the 2006 AES guidelines states that in order to diagnose PCOS the following two criteria are as followed: i) hirsutism and/or hyperandrogenemia, and ii) oligo-anovulation and/or polycystic ovaries after the exclusion of other etiologies of anovulatory infertility and androgen excess.

The complexity and heterogeneity of this syndrome gives us a clinical division of four types of phenotypes namely: Phenotype A or the classic PCOS which includes polycystic ovaries, hyperandrogenism and oligo-anovulation, Phenotype B i.e. hyperandrogenic anovulation which includes hyperandrogenism with oligo-anovulation, Phenotype C (i.e. ovulatory PCOS) which includes polycystic ovaries (e.g. without ovulatory dysfunction) and hyperandrogenism, n Phenotype D (i.e. non-hyperandrogenic PCOS) including polycystic ovaries and oligo-anovulation. No data exist regarding the range of normal androgen levels in women, nor any data is available on which androgen should be measured in order to diagnose PCOS till date. This makes the presence of hyperandrogenism debatable and one would also need biochemical criteria for androgen to make the diagnosis [22]. Increase in high serum levels of testosterone both total and free is used as the classic definition for hyperandrogenism but some of the research have contrasting results and according to them decrease in sex hormone-binding globulin (SHBG) levels, and increase in free testosterone concentration and DHEA concentrations, are the currently most evocative reason for hyperandrogenism [23,24]. The biggest debatable topic exists regarding the method of measurement.
to be used for assessment of androgen in women. Recent studies provide information on 11-oxygenated androgens who possessed the most desirable characteristic for diagnosing PCOS [25]. There is need of specification in relation to method, criteria and functions when it comes to diagnosis of PCOS, moreover it is not necessary that irregularity of menses could be the only criteria for diagnosing PCOS. Rotterdam criteria is used as the basis for diagnosing PCOS in which the total number follicle (e.g. 12 or more follicles seen in the ovary measuring from 2 to 9 mm in diameter) or increased in ovarian volume is used for measurement (i.e. volume more than 10 cm³). Until a study conducted in 2007 suggested that more than 50% of healthy women have 12 or more follicles per ovary [26] and hence this provide us with explanation of specialist considering polycystic ovary only when the number of follicles exceeds 20/ovary.

**Controversies in Treatment**

All treatment discovered till date for PCOS focuses on treating its effect rather than addressing the cause, for example anovulation, oligomenorrhea, hyperandrogenism and metabolic changes. According to any research conducted throughout world suggest that change in lifestyle can be used as the primary therapy for treating PCOS especially for overweight and obese women facing metabolic complications [27]. The changes involve reduction in weight and body mass index by 5% to 10% initially followed by long term weight loss of up to 15% to 20%, eliminating carbs from diet having a balanced diet and reducing waist circumference till 88 cm or less [28]. These small lifestyle changes are considered very effective and simple in terms of treatment and result in improving sensitivity towards insulin, it also result in reduction of metabolic syndrome and type II diabetes [29]. Studies have shown that losing weight have many beneficial effect in fertility [30]. Even evidence from pharmacological research have shown excellent results when it comes to losing weight as it also helps in decreasing risk of cardiovascular disease [31] but it was also observed that few drugs ended up in increasing risk of cardiovascular events and were removed from market. Further advancement in medicine lead to development of bariatric surgery and in some studies it was found that bariatric surgery was found to be associated with betterment or complete removal of type II diabetes, hypertension, hyperlipidemia and obstructive sleep apnea [32] whereas some of the studies also reported of getting rid of PCOS symptoms even facial hirsutism, hyperandrogenism, anovulation or menstrual irregularity. Treatment regarding fertility in PCOS can be achieved via many techniques. The first line of treatment for fertility involves restoration of ovulation which can be achieved by weight loss and have been reported highly successful in previous research papers [33]. Use of Metformin is highly common when a pregnancy is not successful. Metformin is the most common and famous insulin sensitizing drug and its helps in reducing weight followed by regular menses [34]. The controversies surrounding this drug resulted in generation of clinical trial. In 2009 after a huge meta-analysis of the most prominent clinical trials it was concluded metformin results in significant weight loss in comparison to that of placebo but no significant change were seen in case of patients on diet or on patients enrolled in life changing program [35]. Studies also showed that administration of metformin results in successful induction of ovulation in women with PCOS [36]. Another drug similar to metformin is Clomiphene citrate which has proven to be successful in inducing ovulation in 57% of cases with much higher pregnancy rate. The association between these two drugs is frequently encountered but are found to irrelevant and no difference is seen between the pregnancy rates after or before clomiphene citrate plus metformin [37].

**Unravelling the Mechanism Through Genetic-Genomic Strategies**

Systematic bioinformatics approaches has unravelled the mechanism of PCOS as reported by Panda et al. [38] gave an insight to the genetic aspects of PCOS in which they reported several genes such as CYP11A1, CYP17A1, CYP19, HSD17B1, HSD17B2, STAR DENND1A,FSHB [39], that are responsible for the disease causing events (Figures 1A-1D with CYP11A1, FSHB, STAR and CYP19A1 variants from COSMIC, Pediatric, Clinvar). Recent developments in genome wide studies may unveil the understanding through mutational hotspots identified through sequencing approaches. In Figures 1A-1D, the aforementioned gene mutations has been depicted using Protein Paint [40] which can be taken as a reference for the purpose of genome wide studies. Genetic-genomics approaches have enabled considerable progress on elucidating the etiology of PCOS [39]. Next-generation sequencing enables researchers to identify rare genetic variants contributing to PCOS as well as to map the genetic variants. The PCOS studies is plagued...
Sequencing strategies should end the bickering over pathophysiological diagnostic approaches, and the emerging NGS data suggest a remarkable degree of progress. Rather focusing on the uni-directional diagnostic approaches, the goal of the researchers is to perform unifying strategies combining both diagnostic and genetic techniques that will have increased impact in understanding the etiology of PCOS.

REFERENCES


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