IJNRD.ORG ISSN : 2456-4184
INTERNATIONAL JOURNAL OF NOVEL RESEARCH AND DEVELOPMENT (IJNRD) | IJNRD.ORG
An International Open Access, Peer-reviewed, Refereed Journal

How can Polycystic Ovary Syndrome (PCOS) impact fertility in women?

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Abstract

Polycystic Ovary Syndrome or PCOS is very commonly referred to in the medical world as one of the conditions which impacts women of reproductive age greatly. Interestingly, however, it is also a condition for which the diagnostic criteria is greatly debated with many revisions being made through history. Regardless of this, the condition can be very distressing for women as it has several implications. This research paper sets out to discuss the definition and diagnostic criteria, prevalence and clinical features of PCOS. The main aim is to uncover the relationship between PCOS and fertility whilst evaluating the varying infertility treatment options that are available to women who suffer from the condition.

Introduction

As per the literature, what we now know as PCOS was referenced in scientific publications dating back to the 19th century. However, a paper by Stein and Leventhal comprehensively described PCOS for the first time in 1935 (Stein & Leventhal, 1935). In the testing series that they had conducted, a group of patients who had amenorrhea and clinical evidence of androgen excess were found to have the typical polycystic ovarian morphology. As time went on, there have been varied clinical manifestations, complex pathophysiology and many cases of poor diagnosis of PCOS. This has resulted in a fair amount of scientific debate with regards to what truly defines PCOS. In light of this, many institutes attempted to create criterias to enable better diagnosis of the condition. For example, a more widely accepted definition of PCOS was published in the proceedings of a workshop which was held at the National Institute of Health in 1990. As part of this, PCOS was very clearly defined as 'chronic anovulation associated with clinical and or biochemical evidence of androgen excess after the exclusion of other pathologies which could potentially masquerade as PCOS' (Franks, 2006).

Whilst the definition by the National Institute of Health held for many years, certain problems with it started to get noticed. For example, the definition does not include ovarian morphology. Furthermore, it considers anovulation to

be purely chronic which was found to not be the case. Instead, the pattern of anovulatory vaginal bleeding may very well be punctuated by intermittent and/or prolonged episodes of regular ovulatory cycles (Palomba, 2018). As a result of these perceived limitations in the definition, a revised definition was provided jointly by the European Society for Human Reproduction & Embryology and the American Society for Reproductive Medicine at the Rotterdam workshop in 2003. The Rotterdam criteria stated that two out of three conditions must be present in order for PCOS to be diagnosed. The conditions were (1) oligomenorrhea/anovulation, (2) clinical/biochemical hyperandrogenism and (3) polycystic ovaries (more specifically >12 follicles in each ovary measuring 2 to 9 mm) (Broekmans & Fauser, 2006). As per many researchers, this definition took into consideration a broader spectrum of the ways in which PCOS may manifest. Most importantly, however, it recognized and included polycystic ovarian morphology as well as subjects with hirsutism and regular menses.

Since PCOS is a fairly complex condition, it is understandable why the definition and diagnostic criteria for it has created so much debate. After the Rotterdam criteria was created, in 2006, it was The Androgen Excess Society (AES) that decided to further revise the diagnostic criteria. As part of this, the AES stated that in order for PCOS to be present there had to be the specific presence of clinical and/or biochemical hyperandrogenism in combination with either polycystic ovaries or oligo anovulation (Azziz et al., 2006). Whilst the overarching criteria may be fairly similar to that of the Rotterdam criteria, this represented the standardization of diagnosis and helped confront many obstacles which were previously arising. For example, anovulation is an important part of the definition from the very start. However, in early menarche, ovulation does not tend to be regular and thus cannot be considered a definite evidence of PCOS (Vihko & Apter, 1984). Furthermore, within adolescence, transvaginal ultrasonography does not tend to be routinely performed. This has certain restrictions on ovary visualization, therefore, excluding any invasive diagnosis of polycystic ovarian morphology (Khan, 2007). Lastly, there is also reportedly a lack of consensus on the biochemical levels of hyperandrogenism and limited information with regards to what is considered normal levels of androgens in adolescents (Deswal et al., 2020). Therefore, it is not easy to diagnose the androgen abnormality. All the aforementioned, also led the Pediatric Endocrine society to recommend for the guidelines to be altered in a manner which enables differential diagnosis of PCOS in adults and adolescents (Rosenfield, 2015).

The remainder of this research paper aims to discuss the prevalence of the condition on a global scale whilst also analyzing the varying clinical features of the characteristics of PCOS. In order to answer the research question, '**How can Polycystic Ovary Syndrome (PCOS) impact fertility in women?',** the latter half of this paper considers the varying health problems that women with PCOS can face and how the condition alters the normal ovulation cycle making the chances of infertility higher. In light of the same, there is also an overview and evaluation of the varying infertility treatment options available to women.

The prevalence of PCOS

As a result of the diagnostic criteria remaining unclear, it may be assumed that the full extent of the prevalence of PCOS is still not known. However, based on several studies that have been conducted to test the prevalence of the condition in specific geographic locations, the overall prevalence of PCOS has been found to range between 2% and 26% (Azziz et al., 2004). There are several reasons for this relatively large range. Firstly, research suggests that many environmental factors tend to play an important role in the occurrence of PCOS. For example, socioeconomic levels, medical care access, health and education as well as the prevalence of influential risk factors can create large disparities geographically (Bozdag et al., 2016). Secondly, even studies that are conducted within the same countries may display strikingly different conclusions since researchers tend to use varying diagnostic criterias in their testing.

In India, for example, it took several years for PCOS and its prevalence to come to the forefront in medical literature (Deswal et al., 2020). In order to overcome this, several studies were conducted between the years 2010 to 2014 and have reported a varied prevalence rate ranging between 6% and 48%. With regards to the specific studies, one of the first Indian case-control studies was published by Ganie et al. (2010) and made use of the Rotterdam criteria. After conducting the testing in 1766 chronic lymphocytic thyroiditis (CLT) patients, the study concluded a relatively high prevalence rate of 46.8%. There have been many other studies conducted wherein further factors such as the age of the subjects have been controlled. For example, in 2011, Nidhi et al. conducted a study with 460 girls who were attending college in South India and were aged between 15-18. The study concluded on a prevalence rate of 9.17%. On the other hand, a more recent study in 2017 by Choudhary et al. found a 41% prevalence rate of PCOS when testing 170 women with irregular menstrual cycles using the NIH criteria. Interestingly, further research uncovered that the discrepancies in the prevalence rates are not only limited to geographic factors but may also extend further into the ethnicity. In 2017, Ding et al. conducted a meta-analysis wherein the prevalence of PCOS across varied ethnic groups was reviewed. The conclusions that were made stated that overall Caucasian females are less likely to develop PCOS when compared with non-white female population and middle easterns.

In line with the aforementioned findings, the overall prevalence rates of PCOS are very different from one country to another country. China, USA and Iran report some of the lowest prevalence rates of 2.2%, 4.7% and 3% respectively. When considering countries such as Greece, Spain, Palestine and the UK, the rate tends to range anywhere between 5-10%. Higher prevalence rates ranging between 15-20% are found in countries such as Turkey, Australia and Denmark (Deswal et al., 2020).

Clinical features of the PCOS diagnostic criteria

Hyperandrogenism

As established through the varying criterias used to diagnose PCOS, one of the main characteristics of the condition is hyperandrogenism - when the ovaries and adrenals produce excessive androgen. Hyperandrogenism in women tends to present itself through increased levels of testosterone, hirsutism, alopecia and acne. Biochemically, hyperandrogenism is defined by heightened concentrations of testosterone as well as other calculated parameters of androgen excess such as free androgen index (FAI) and free testosterone (FT) (Ashraf et al., 2019). In line with this, the Rotterdam criteria establishes that the detection of hyperandrogenism in women with PCOS should be done by testing the circulating free testosterone (cFT) or through the employment of FAI measurements (The Rotterdam ESHRE/ASRM sponsored PCOS consensus workshop group, 2004). Furthermore, the presence of other androgens such as androstenedione and dehydroepiandrosterone could prove helpful in the biochemical diagnosis of hyperandrogenism (Salley et al., 2007).

Of the clinical features of hyperandrogenism, the most common is *hirsutism* or the excessive terminal hair growth in male pattern distribution in women (Witchel et al., 2019). This essentially represents the way in which the local androgen concentrations, circulating androgen concentrations and sensitivity of the hair follicles to androgens interact. In order to test for hirsutism, a semi-subjective Ferriman-Gallwey scoring system is used and a score of ≥4 to 6 is normally indicative of the presence of the condition (Teede et al., 2018). Interestingly, Yildiz et al. (2010) found that the concentration of circulating androgen does not impact the severity of hirsutism but instead genetic and ethnic variations do.

Other than hirsutism, the second most common clinical feature of hyperandrogenism is *acne*. The reason for this is that heightened testosterone levels favor the production of more potent forms of dihydrotestosterone which in turn increases the production of sebum in the sebaceous glands. This aforementioned ultimately leads to abnormal desquamation in the follicular epithelial cells. It is this accumulation of epithelial cell debris and sebum that gets colonized by the bacterium Propionibacterium acnes which then causes acne (Ayer & Burrows, 2006). In PCOS patients, acne can be present on varying parts of the body with the most common being the face, upper back and neck. However, acne can occur with varying severity as per WHO. For example, whilst mild acne may be present in the form of papules and comedones, severe acne could consist of cysts and scars. With regards to the prevalence of acne in PCOS patients, some studies have estimated that it is between 9.8%-34%. However, once again, ethnicity plays a big role in dictating the prevalence of acne with the highest levels occurring amidst Indio-Asian women and the lowest amidst Pacific islanders (Williamson et al., 2001).

Another manner in which hyperandrogenism clinally appears in patients is through *alopecia* or more specially androgenic alopecia. It has been identified to take place as a result of miniaturization which is when the mature terminal hair present on the scalp region shortens the growth phase and gradually transforms into fewer and finer vellus hair (Sinclair, 1998). When it comes to hair volume, interestingly, the high levels of testosterone create a dual effect wherein women with PCOS tend to witness an increased level of facial hair growth but a reduced level of scalp hair. Whilst the reduction in scalp hair is something that men commonly face, in women, the hair follicle remains alive and thus there are chances of retaining the lost hair through therapy. With regards to how commonly alopecia occurs in PCOS cases, the range varies between 3.2-34.8% (Ashraf et al., 2019). Once again, varying factors including ethnic and genetic may impact these rates.

Polycystic ovary morphology

Another common characteristic of PCOS is the presence of polycystic ovary morphology. This is defined as ovaries that are enlarged with more small peripheral cysts and increased stroma. In order to detect the same, a transvaginal probe and high-resolution technology must be used and there must be ≥20 follicles per ovary as per the Androgen Excess-PCOS Society (Dewailly et al., 2013). However, in reality, the diagnosis of polycystic ovarian morphology is not easy, especially when it comes to adolescents. In adolescent girls, an increased ovarian volume and follicular growth occur due to the increased gonadotropin stimulation which eventually gives rise to the appearance of multifollicular ovaries (Codner et al., 2011). Furthermore, the actual use of transvaginal probes in adolescents is not condoned as a result of the intrusive nature of the same.

Overall diagnosis for PCOS

Most commonly, once a girl starts to show the signs which are suggestive of PCOS (such as those mentioned above), a thorough medical evaluation commences. As part of this, professionals typically conduct physical examinations and blood tests but more importantly start by analyzing the history of the patient as well as their families. In terms of the physical examination, this mainly includes ultrasounds to provide an image and examination of the ovaries, uterus and pelvis. Whilst the ultrasound can be transvaginal or abdominal, the former provides a more clear picture but is only used in sexually active women. Furthermore, blood tests may also be conducted including those that test the thyroid function, prolactin levels, total testosterone and androstenedione concentrations etc. Most of these tests are also used to ensure that any other conditions which may have similar symptoms to PCOS can be excluded as a possibility.

PCOS and infertility

Since PCOS has a range of metabolic and reproductive features including insulin resistance, metabolic abnormalities and hormonal imbalances, for women who have it, the risk of many other medical conditions increases. For example, some of the mental health conditions such as anxiety, mood swings and eating disorders tend to be more common in women with PCOS. However, even some other serious medical conditions may occur more commonly in PCOS patients including infertility, cardiovascular disease and type 2 diabetes (Azziz et al., 2005). Focusing on infertility in particular, studies show that around 90% of women who are suffering from anovulation and seeking treatment for infertility tend to have PCOS - making it one of the most common causes for anovulatory infertility (Teede et al., 2010). Moreover, since the diagnostic criteria for PCOS is still debated in medicine, many times, women tend to go undiagnosed and therefore only learn of the presence of the condition when they seek infertility treatment.

But how exactly does PCOS impact the normal ovulation cycle? Well, when a normal menstrual cycle with ovulation is analyzed, several eggs tend to mature in the follicles present in the ovaries. After this, the ripest egg is released into one of the fallopian tubes where it successfully meets with the sperm to begin the reproductive process (Tommy's, 2018). Unfortunately, if a woman has PCOS, this process is not as simple. Instead, women with PCOS tend to have elevated levels of insulin, androgen and luteinizing hormone in combination with reduced levels of follicle-stimulating hormone (Deswal et al., 2020). These imbalances can firstly lead to infrequent or a lack of menstruation which immediately reduce the chances of fertility. Additionally, the underproduction of estrogen and overproduction of androgens including testosterone may lead to the varied clinical features including the presence of polycysts (tiny cysts which appear on the surface of the ovaries). All these factors combined with the lack of development and maturation of the follicles means that there is no ovulation for fertility to occur.

With regards to the evaluation of infertility in women with PCOS, as per the American Society for Reproductive Medicine, this should start after six months of attempting pregnancy without success (Practice Committee of the American Society for Reproductive Medicine, 2013). Once the diagnosis is made, first-line treatment may include non-pharmacological as well as pharmacological measures. The former entails *preconception guidelines* and primarily includes suggestions to facilitate a change in lifestyle post the identification of risk factors including obesity and alcohol and tobacco usage. In fact, a reduction of body weight by only 5% to 10% over the span of six months has shown to improve central obesity, hyperandrogenism and ovulation rates (The Thessaloniki ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2008). Reduction in body weight can also lead to a smoother pregnancy for women with PCOS as it reduces the incidence of many complications which may otherwise occur. On the other hand, the pharmacological measures include *administration of drugs* to induce bifollicular or monofollicular ovulation. Of these drugs, clomiphene citrate (CC) - an estrogen receptor modulator - is the most common and first choice treatment for women suffering from anovulation (Melo et al., 2015).

However, sometimes women with PCOS are found to be resistant to even the maximum dosage of CC. In such scenarios, second-line treatment options such as *laparoscopic ovarian surgery* may be required. As part of this therapeutic modality, laser techniques or monopolar electrocautery may be used to drill into the ovaries with the goal being to create around four to ten punctures as a larger number could favor the development of premature ovarian failure (Balen, 2013). In comparison to the first-line treatments, this one is considered invasive, more costly and more capable of causing complications. That being said, studies analyzing the efficacy of this treatment have found that ovulation rates were between 54 and 76% six months after the procedure and 88% in the twelve months after the procedure. During these periods, the spontaneous pregnancy rate ranged between 28 and 56% and 54 and 70%, respectively (Unlu & Atabekoglu, 2006). There is also a third-line treatment for women suffering from infertility due to PCOS. This is commonly known as *IVF or in vitro fertilization*. At the end of the day, however, the ultimate choice of the most appropriate treatment plan is dictated by several factors including the patient's age, duration of previous treatments, anxiety level of couples as well as the presence of other factors associated with infertility.

Conclusion

PCOS is still a condition which remains highly debated. However, one thing that is inarguable is that the condition is incredibly common amongst women of reproductive age. Fortunately, the increased study of PCOS along with clinical experiments has allowed for some criterias to be formed and guide the diagnosis of it. At today's date, the condition is most commonly characterized by the presence of hyperandrogenism and polycystic ovarian morphology. Whilst the presence of the signs lead to the eventual diagnosis of the condition through varying tests, PCOS does bring with it increased risks of other conditions such as diabetes and infertility.

This paper looked particularly at the relationship between PCOS and fertility to conclude that, on the whole, the extensive alterations that PCOS causes to the normal ovulation cycle does in fact lead to a lack of fertility in several women. However, on the upside, there are clearly many treatment options which can help women overcome these challenges. In fact, the administration of first-line treatments is most commonly the solution with medical studies finding that almost 80 percent of women with PCOS treated with the drug clomiphene citrate successfully ovulate. Furthermore, whilst these complications may be distressing to many women and cause further mental health problems as well as feelings of guilt and failure, it has been strongly recommended that infertility caused by PCOS is viewed as another treatable medical condition as opposed to a reflection of the type of woman one is.

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