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Management of Polycystic Ovarian Syndrome: Looking Beyond the Ovaries

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The Pathology Behind Polycystic Ovarian Syndrome

There is something remiss in the name polycystic ovarian syndrome (PCOS). It bears the word ovary; however, the ovary is an innocent bystander of a more sinister pathology. The name belies the nature of a disease that is a complex metabolic and reproductive syndrome with sequelae extending beyond ovarian dysfunction.

PCOS is a chronic, life-long illness that affects approximately 1.4 million Canadians.[1] Its inception is thought to begin in utero. Factors such as elevated levels of maternal anti-Müllerian hormone (AMH), endocrine disruptors, growth restriction, and maternal androgen excess generate epigenetic changes that have a life-long, transgenerational impact on the fetus.[2]

Despite its name, PCOS is not just about the ovary. As we are learning more about the disease, it is becoming clear that insulin resistance, rather than a primary ovarian pathology, is the key contributing factor in its pathogenesis. Poor lifestyle choices exacerbate the condition. Insulin plays a key role in androgen production by augmenting luteinizing hormone (LH) stimulation of the ovarian theca cells, and adrenal androgen production. Insulin inhibits the hepatic synthesis of sex hormone-binding globulin, effectively increasing free androgen circulation.

Diagnostic Criteria for Polycystic Ovary Syndrome			
Rotterdam Criteria	**Two (2) of clinical and/or biochemical hyperandrogenism, oligo- or anovulation, or polycystic ovaries on ultrasound**		
Hyperandrogenism (HA) (Clinical* and/or Biochemical)	Elevated Calculated free testosterone	Free androgen	calculated bioavailable testosterone
Oligo-ovulation or anovulation (OM)	>1 to >3 years postmenarche: **<21 or >45 days**	3 yyears postmenarche to perimenopause: **<21 or >35 days or <8 cycles per year**	1 year postmenarche: **>90 days for any one cycle**
Polycystic ovarian morphology features (PCOM)	Transvaginal is the preferred approach only for women >8 years from menarche.	Transducers with a **frequency bandwidth that includes 8 MHz**	follicle number **per ovary of ≥20 and/or** an **ovarian volume ≥10 ml** on either ovary

Table 1. The Rotterdam Criteria.[4]

*Using the Modified Ferriman-Gallwey system

Consequently, elevated insulin levels lead to gonadotropin imbalances (LH>FSH) which result in ovulatory dysfunction and hyperandrogenism.[3]

Diagnosing Polycystic Ovarian Syndrome

Based on the Rotterdam criteria, there are four PCOS phenotypes that rely on permutations of three criteria: **1)** hyperandrogenism (clinical or biochemical), **2)** irregular cycles, and **3)** polycystic ovarian morphology as observed on ultrasound. The Rotterdam criteria is distinct from other PCOS criteria, because the diagnosis can be made even in the absence of hyperandrogenism or ovulatory dysfunction. Owing to its simplicity, the Rotterdam criteria is the most utilized criterion for diagnosing PCOS worldwide.[2] The Rotterdam criteria are presented in **Table 1**.

Diagnosing PCOS differs for adolescents. First, the definition of oligomenorrhea depends on how remote one is from menarche. Because of the immaturity of the hypothalamic-pituitary-ovarian axis, the absence of menses for up to 90 days remains within the bounds of normal in the year following menarche. Within 1–3 years from menarche, amenorrhea with an interval of up to 45 days is considered normal. However, in women who are 3 years post-menarche, an amenorrhea with an interval of more than 35 days is considered prolonged.

Polycystic ovarian (PCO) morphology is defined as an ovary with ≥20 follicles and/or an ovarian volume of ≥10 mL as seen on ultrasound (8 mHz bandwidth). In adolescents, the diagnosis does not depend on ovarian morphology. Instead, the diagnosis mainly considers the presence of hyperandrogenism and oligomenorrhea. In addition, ultrasound is generally only useful 8 years after menarche.[4]

An accurate measure of biochemical hyperandrogenism uses either calculated free testosterone, free androgen index (FAI), or calculated bioavailable testosterone. One challenge is the limited availability of high-quality assays for these measures. Alternatively, androstenedione or dehydroepandrostenedione sulfate (DHEAS) may be used as measures of biochemical hyperandrogenism. Clinically, hirsutism is a reliable marker for hyperandrogenism, and the Modified Ferriman-Gallwey scoring system is one of the most common methods of assessment. While the published cut-off score for hirsutism is >7, this value varies depending on ethnicity, with east

Asians having a lower cut-off score compared to South Asian and Middle Eastern women. Another reliable clinical marker of hyperandrogenism is androgenetic alopecia. Take note that female pattern hair loss is characterized by anterior hairline sparing, which differs from male pattern hair loss that occurs at the vertex and frontotemporal regions.[5]

There is emerging evidence that Anti-Müllerian Hormone (AMH) can be used as a marker for PCOS. AMH levels for PCOS are generally higher (>3.8 ng/mL), however, cut-off values have not been standardized.[6]

Considering that the sequelae of unchecked hyperglycemia are potentially life-threatening, there is a need to screen for insulin dysfunction. In women with PCOS, glycemic status should be reassessed every one to three years. The gold standard for diagnosing insulin resistance is the glucose clamp. This method relies on dynamic testing after a glucose load. Because dynamic testing is cumbersome and viable alternatives exist, its use has largely been relegated to research.[4,7] The Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) is a popular diagnostic test. Unfortunately, its mainstream use is limited by a lack of standardization among different centres. The 75g Oral Glucose Tolerance Test (OGTT) is a reliable method of testing because of its availability, practicality, and standardization.[8] Fasting insulin is also useful because it has been shown to correlate well with other metabolic parameters.[9]

The following routine screening for women with PCOS is recommended: cardiovascular disease risk, endometrial pathology (hyperplasia or cancer), obstructive sleep apnea, and mental health disorders. Cardiovascular disease screening is advised every 6–12 months and should include the following: determination of body mass index (BMI), waist circumference, blood pressure, lipid profile, and an evaluation of lifestyle risk factors such as smoking and sedentary behaviours. A detailed menstrual history should be directed toward ruling out abnormal uterine bleeding or prolonged amenorrhea—both of which are suggestive of unopposed estrogen on the endometrium. Obesity is another risk factor for endometrial cancer that should be documented on the first visit. If these risk factors are present, an endometrial biopsy may be warranted, particularly in women who are over the age of 40 years.[10] Another important risk factor for cardiovascular disease is obstructive sleep apnea. Screening is recommended in women with PCOS because they are more likely to develop obstructive sleep apnea. The Berlin Questionnaire is a practical method of screening those at risk of obstructive sleep apnea, and if positive, the patient should be referred for specialist care. In addition, anxiety, depression, psychosexual disorders, and eating disorders are significantly more common in women with PCOS and, likewise, must be screened for at the first visit.[4]

Therapeutic strategies

PCOS may not have manifested as a disease in the past. It may be an ancestral adaptive response to an environment where food scarcity and fear of predation kept humans mobile and lean. Our ancestral past set the stage for evolution favouring the promotion of traits of PCOS. Lower conception rates due to infrequent ovulation and sustained high levels of AMH allowed for better child spacing and a longer reproductive career. Enhanced energy storage and insulin resistance provided stable glucose levels in times of starvation. Increased physical activity counteracted the elevated blood glucose levels caused by insulin insensitivity. Hyperandrogenism fostered increased muscle mass and aggressiveness that were advantages for ancient survival.[11] Unfortunately, the modern environment has engendered maladaptation to the survival benefit of insulin resistance, resulting in a “devolution” into the pathology known as PCOS today.

The impact of lifestyle interventions on the reproductive endocrine profile are not as intuitive as their established benefit on the metabolic profile. One prospective study looked at women with PCOS who underwent a lifestyle regimen in addition to their usual care. Overall, lifestyle intervention showed statistical improvements on the levels of follicle-stimulating hormone (FSH), sex hormone binding globulin (SHBG), FAI, and clinical improvement in hirsutism.[12]

As ubiquitous as the term “lifestyle intervention” is, precise recommendations for diet and exercise are difficult to find. Various diets (Keto diet, intermittent fasting, the Atkin’s diet, among others) have been recommended for women with PCOS, and most are considered effective for short-term weight loss—the commonality among them being hypocaloric intake (1500 kCal/day or a 500 kCal/day deficit). To maintain long-term adherence to an eating

plan with a healthy balance, a good strategy is to include nutritionists in the care team. Regarding exercise regimens, there is likewise no specific recommendation. Instead, women with PCOS are advised to perform moderate intensity exercise for at least 150 minutes/week. Brisk walking for 30 minutes, 5 times a week is a practical example of such a regimen.[4]

Hyperandrogenism

Combined hormonal contraceptives (CHCs) provide non-contraceptive benefits for women with PCOS. When choosing the right CHC, it is helpful to consider its progestin component, since not all progestins are considered equal. Given the metabolic profile of women with PCOS, cardiovascular friendly options (with anti-mineralocorticoid activity, without glucocorticoid activity, and natural estrogen preparations) are preferred. Another factor to be considered is the anti-androgenic component of the CHC. Cyproterone acetate (CPA) was once considered a first-line choice owing to its strong anti-androgenic properties. Unfortunately, CPA is paired with higher levels of ethinyl estradiol which, in turn, can increase the atherogenic and thromboembolic potential. CPA also enhances glucocorticoid activity, making it less cardiovascular-friendly than other CHCs. Third generation CHCs contain low-dose estrogen preparations and are considered safer for obese/overweight women.[13]

Anti-androgens such as spironolactone, finasteride, and flutamide are part of the armamentarium for hyperandrogenism. The use of flutamide, however, is limited because of the potential for liver toxicity. Anti-androgens are not recommended for women seeking fertility because of their potential for teratogenicity. In fact, in women being treated for hyperandrogenism, contraception forms part of the therapeutic goals. This adds another dimension to the importance of CHCs in the treatment of PCOS.[13]

Hyperinsulinemia

The use of metformin in managing PCOS is backed up by robust data. Metformin inhibits gluconeogenesis and promotes peripheral glucose uptake. The overall effect is lower levels of glucose in the bloodstream owing to enhanced cellular uptake. Unfortunately, in some patients, compliance with metformin is limited by its gastrointestinal side effects.[14]

Thiazolidinediones, particularly pioglitazone, can be used in patients with PCOS. Pioglitazone is a peroxisome proliferator-activated receptor gamma (PPAR-γ) agonist that indirectly ameliorates peripheral insulin resistance and reduces androgen synthesis in the ovaries.[15] Glucagon-like peptide 1 (GLP-1) analogs function as an incretin mimetic that directly increases pancreatic insulin secretion in response to food intake. One of the major limitations of GLP-1 is the mode of delivery (injectable). In addition, similar to metformin, GLP-1 causes significant gastrointestinal symptoms. Despite these limitations, the use of GLP-1 has been steadily on the rise due to its marked effectiveness for weight control.[2] (See **Table 2** for information on insulin sensitizers.)

Infertility

Though arguably more important, less attention is given to lifestyle therapy in women wishing to achieve a pregnancy. The periconceptional period is a stage in which environmental endocrine disruptors and other exposures can critically affect the fetus. These are important counselling pearls because the effects are far-reaching and potentially trans-generational. Counselling should also underscore that gestational diabetes mellitus (GDM), pregnancy related hypertension, preterm delivery, and babies who are small and large for gestational age are possible sequelae of PCOS and poor lifestyle choices.

Ovulation induction is the major therapeutic focus in the treatment of women with PCOS. For ovulation induction, letrozole is considered a first-line treatment.[5] It is an aromatase inhibitor that works peripherally; therefore, it mimics the natural tendency of the menstrual cycle for monofollicular development. In contrast, clomiphene citrate, because of its central mechanism of action, induces polyfollicular development. Another advantage of letrozole over clomiphene citrate is its promotion of normal endometrial proliferation. Letrozole may also improve the quality and quantity of the oocytes because the transient build-up of androgens favours improved gonadotropin receptivity. These physiologic advantages have shown clinical implications. Compared to clomiphene citrate, letrozole significantly improves ovulation and live birth rates.[16] Clomiphene citrate is no longer available in Canada.

Use of Insulin-sensitizing agents for Infertile Patients with PCOS			
Insulin-sensitizer	**Dosage**	**Mode of action**	**Issues**
Metfomin	Usual dose: 500 mg TID	Inhibits hepatic gluconeogenesis and promotes skeletal muscle glucose uptake. Helps regulate menses and decreases androgens.	**PROS:** Backed up by existing national and international guidelines due to robust evidence. **CON:** Gastrointestinal side-effects affect tolerbility.
Thiazolidinediones (TZD)	Pioglitazone: 30-45 mg/day	PPAR-γ agonist that ameliorates peripheral insulin resitance indirectly and can decrease androgen synthesis in ovaries.	May cause weight gain, some association with bladder cancer but not backed up by recent data.
Glucagon-like peptide 1 (GLP-1) analogs	Liraglutide SQ 18 µg BID Semaglutide SQ 1 mg/week	Incretin mimetic; increases insulin secretion from the pancreas in response to ingested food. Improves menstrual frequency and hyper-androgenemia in obese women.	**PROS:** Improves glycemic control, insulin resistance and weight loss. **CON:** Injectable medication.
Inositol	Myo Inositol: 2000 mg BID D-Chiro Inositol: 50 mg BID	Acts as a second messanger increasing the cellular uptake of glucose. In the ovary it acts as a second messenger for FSH.	**PROS:** Very favourable safety profile. **CONS:** Evidence is from smaller scale studies.

Table 2. Insulin Sensitizers.[2,14,15,17]

Future Directions

The inositols are gaining recognition as a therapy for PCOS. In the latest European guideline, Myo-inositol (MI), initially classified as an experimental therapy, is included in the recommendations for the treatment of PCOS.[4] This recommendation is based on clinical evidence for metabolic benefits and some studies have provided evidence for improved ovulation, decreased hirsutism, and weight reduction, all while reporting limited harm. This favourable benefit-to-risk ratio is logical given that inositol is a naturally occurring molecule found ubiquitously in nature. Once considered a B vitamin (Vitamin B8), inositol is found in many plant-based foods. It is also present in animal tissues, and once it was discovered to be copiously produced in the body, inositol was declassified as a vitamin.

The most common biologically active inositols are MI and d-chiro-inositol (DCI). MI, the most abundant isomer, acts as a second messenger to several endocrine signals including insulin, FSH, and thyroid stimulating hormone. Conversely, DCI is produced from MI via a unidirectional, insulin-dependent reaction. With insulin signalling, DCI facilitates glycogen formation thereby reducing the circulating levels of glucose. Simply put, MI promotes glucose uptake, while DCI promotes storage.

Insulin insensitivity, common in women with PCOS, dampens the production of DCI in the peripheral organs. Interestingly, this does not apply to all tissues of the body.[17] Here lies the key to understanding the role of the inositols in regulating critical reproductive endocrine processes.

Overall, DCI levels are reduced in PCOS women, while counterintuitively, there are copious amounts of DCI in their ovarian follicular fluid. This is thought to be due to the ovary, which never becomes insulin resistant—a phenomenon called the "ovarian paradox." In the ovary, MI acts as a second messenger to FSH in the granulosa cells and potentiates the production of estrogen. DCI acts in the theca cells by converting cholesterol to androgens. In the granulosa cells, DCI acts as an aromatase inhibitor. Therefore, with continual insulin stimulation, an androgen build up occurs. The resulting hyperandrogenism likewise affects the FSH receptors in the granulosa cells resulting in a relative decrease in estrogen. The end effect is the arrest of follicular growth, which is observed as polycystic appearing ovaries.[18]

Because the in-vitro fertilization (IVF) process provides us a glimpse of the markers of fertility, it is interesting to observe the effects of inositol supplementation during the stimulation cycle. An early prospective observational study by Chiu et al looked at MI and estradiol levels in follicular fluid and compared the quality of embryos treated with MI. They found that higher levels of follicular MI can be a surrogate marker for embryo quality.[19] Another paper showed that MI lowers usage of gonadotropins, stimulation days, and the risk of ovarian hyperstimulation.[20] In addition, emerging evidence suggests that follicular MI improves clinical pregnancy rates.[21]

Women with PCOS are at risk for GDM, which is fairly common in North America, with a prevalence of approximately 7%.[22] Since MI supplementation is considered safe for pregnant women, several studies have evaluated its effect on women at risk for GDM (strong family history of type 2 DM). The findings demonstrate that MI supplementation at a dosage of 4 g/day significantly decreases the prevalence of GDM. Moreover, supplementation has been shown to improve secondary outcomes such as insulin therapy, prevalence of polyhydramnios, and neonatal hyperglycemia.[23]

Summary

PCOS is a life-long metabolic, and endocrine condition. Hyperandrogenism and insulin resistance jointly contribute to PCOS, which, when unchecked, increases the risk of metabolic disease, cardiovascular disease, mental health issues, and endometrial cancer. Contrary to the simplicity of its name, the pathophysiology of PCOS is complex, and extends well beyond the morphology of the ovary. The treatment approach is therefore multifaceted and anchored to healthy lifestyle choices. Therapy depends on the goals of the patient, and can include treatment of infertility, alleviation of hyperandrogenism, weight loss, and/or good glycemic control. Pharmacologic therapies are available to treat the above symptoms. Finally, nutraceuticals, such as the inositols, are gaining legitimacy as treatment options for PCOS.

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Financial Disclosures

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