Examining Fertility in Polycystic Ovarian Syndrome

Interplay of Hormones

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Introduction to PCOS
Polycystic ovary syndrome (PCOS) is a condition consisting of ovulatory dysfunction and hyperandrogenism, defined as excess activity of testosterone and related androgen hormones. PCOS affects approximately 10% of women of reproductive age, and is a common cause of infertility. However, women with PCOS often suffer from more subtle disturbances in other hormone axes as well, such as thyroid and adrenal systems. This article will explore the role of these systems in infertility associated with PCOS. We start with a description of the problems underlying PCOS as well as lifestyle-based therapies, which ought to be the front-line therapy for all women with PCOS.

PCOS is one of the most common causes of infertility, characterized by ovulatory dysfunction and hyperandrogenism. Features of PCOS include hirsutism, anovulation (lack of ovulation), polycystic ovaries which show arrested follicular maturation, obesity, and insulin resistance. Androgens or excess testosterone appear to inhibit negative feedback of estrogens and progesterone. Most women with PCOS have higher LH and lower FSH levels, also leading to anovulation. Obesity and insulin resistance directly and indirectly increase estrogen levels, which is converted to testosterone and worsens anovulation.[1]

Lifestyle change alone, and in combination with pharmacological ovulation induction such as clomiphene citrate or metformin, is generally considered the first-line treatment for the management of infertile anovulatory women with PCOS. A 2014 meta-analysis found that use of lifestyle interventions (diet and exercise) compared to usual care alone resulted in significant improvements in the following hormones: FSH, SHBG, testosterone, androstenedione, and hirsuitism score.[2] Another study found that an isocaloric diet (no change in total calories consumed), but which was low-glycemic,
improved insulin sensitivity in women with PCOS.\[^3\]\ A low-glycemic (GI) diet refers to a dietary pattern emphasizing foods that are not quickly metabolized to sugar upon consumption; for instance, brown rice and old-fashioned oatmeal are lower glycemic compared to bread or other products containing flour such as muffins or crackers. Another study examined the effect that timing of food intake has on insulin sensitivity among lean women with PCOS.\[^4\]\ This study showed that consuming a larger breakfast and a smaller dinner resulted in significantly better insulin sensitivity, compared to a diet where breakfast was small and dinner was larger. There was a parallel decrease in free testosterone and 17-hydroxyprogesterone and increase in SHBG associated with the breakfast-dominant diet. Finally, exercise has been shown to improve insulin sensitivity and assist with weight loss in women with PCOS.\[^5\]\

**Role of Thyroid Dysfunction**

Thyroid disorders are well-known to interfere with human reproductive physiology. The hormones involved in regulating thyroid function include thyrotropin-releasing hormone (TRH), produced in the hypothalamus; thyroid-stimulating hormone (TSH), produced by the pituitary gland; and the two thyroid hormones known as T\(_4\) (thyroxine) and T\(_3\) (triiodothyronine). These hormones are synthesized from iodine and tyrosine, and T\(_4\) may be converted to T\(_3\), which is the stronger of the two. Thyroid function can be affected by exposure to environmental toxins, genetics, stress, nutrient deficiencies, autoimmune disorders, infections, and imbalances in other hormones such as cortisol. Many women experience various types of thyroid imbalances that can have an impact on fertility, including overt hypothyroidism as well as subclinical hypothyroidism, hyperthyroidism, and autoimmune thyroid disorders. Blood tests can be completed in order to assess thyroid health, and include an assessment of TSH, T\(_4\), T\(_3\), and thyroid antibodies. It has been shown that menstrual abnormalities were found in 68% of people with thyroid irregularity as compared to 12% in the control group.\[^6\]\

To begin with, hypothyroidism can cause infertility by preventing ovulation. Other symptoms associated with hypothyroidism that indicate the existence of a problem can include constipation, heavier periods, weight gain, changes in appetite, lethargy, and depression. Oravek & Hlavacka provided evidence of the presence of TSH and T\(_3\) receptors in the ovary, and that these had an effect of egg maturation.\[^7\]\ Hypothyroidism can contribute to ovulatory dysfunction, lowering egg quality and the
chance of successful fertilization, as well as causing poor development of the corpus luteum, which is responsible for progesterone production.[8] Since progesterone is responsible for fostering implantation of the blastocyst into the uterine wall, low levels can contribute to early miscarriage or failure of implantation. Decreased levels of thyroid hormone also increase prolactin levels, shortening the second half of the cycle and exacerbating decreased progesterone levels.[8] Interestingly, not only women with overt hypothyroidism (TSH > 5.0), but women with subclinical hypothyroidism (defined as a TSH level great than 2.5) were also found to become pregnant less frequently.[8] With treatment of thyroid imbalance, however, menstrual disturbances improve and fertility can be restored.[9]

Autoimmune diseases are the most common cause of hypothyroidism. Therefore systematic screening of TSH, free T\textsubscript{4} as well as antithyroid antibodies such as thyroid peroxidase (TPO) should be considered.[10] Where appropriate, use of thyroid hormone supplementation should be obtained through one’s family doctor to correct deficiencies. Complementary therapies to enhance thyroid function include use of guggul (Commiphora mukul), blue flag root (Iris versicolor), and seaweeds such as bladderwrack (Fucus vesiculosus), which are all naturally occurring plants that aid in the treatment of hypothyroidism. These herbs work via different mechanisms so they can be used synergistically to support the thyroid, particularly in cases of Hashimoto’s thyroiditis (an autoimmune disease causing hypothyroidism). Fucus vesiculosus (100–500 mg/d) provides iodine and upregulates iodine-processing hormones; Commiphora mukul (80–900 mg/d) enhances peripheral conversion of T\textsubscript{4} to T\textsubscript{3}; Iris versicolor (400–2400 mg/d) provides glandular stimulation and detoxification. Zinc and selenium are trace minerals that have been shown to be crucial in the conversion of T\textsubscript{4} to T\textsubscript{3}.[11] Stress reduction and regular exercise also help improve the sensitivity of cells to thyroid hormone.

**Adrenal Function and Fertility**

Adrenal is another important gland in the body that contributes to fertility. The adrenal glands sit on top of the kidneys, and release hormones in response to stress and/or inflammation. More specifically, the hypothalamic–pituitary–
adrenal (HPA) axis converges on the adrenal glands. The hypothalamus releases CRH (corticotropin-releasing hormone), which stimulates the pituitary gland to release ACTH (adrenocorticotropic hormone), which in turn stimulates the adrenal glands to produce various steroid hormones, most notably cortisol and dehydroepiandrosterone sulfate (DHEA sulfate or DHEAS). Cortisol is also popularly known as the “stress hormone.” DHEAS is an androgen hormone that may be elevated in PCOS.

The adrenal glands consist of an outer layer, the adrenal cortex, and an inner layer, known as the adrenal medulla. The adrenal cortex is devoted to the production of corticosteroid and androgen hormones. Specific cortical cells produce particular hormones, including aldosterone, cortisol, testosterone, and DHEAS; in PCOS, there is increased presence of androgen hormones, so stress or inflammation can further exacerbate hormone imbalance by increasing adrenocortical function.

The adrenal medulla is the core of the adrenal gland and is surrounded by the adrenal cortex. The medulla secretes the catecholamine hormones such as epinephrine and norepinephrine. These hormones are the major hormones underlying the fight-or-flight response, and are structurally derived from the amino acid tyrosine. Tyrosine is the same amino acid as is used in the synthesis of $T_3$ and $T_4$.

Exposure to stress can impact hormones in part through the adrenal gland. Under high levels of stress, the increased release of epinephrine (aka adrenalin) inhibits the secretion of progesterone. Imbalances of estrogen and progesterone can influence menstrual cycles and ovulation. High amounts of emotional stress increase cortisol, which decreases the body’s main sex hormones, and inhibits ovulation and sexual activity. Cortisol levels are affected by inflammation, poor sleep, emotional stress, and being immunocompromised; over time, this can lead to burnout or “adrenal fatigue.”

While high levels of cortisol inhibit reproductive function, so do low levels. Adrenal fatigue is the last stage of a process involving first adrenal hyperfunction as part of the stress response, then maintenance, and finally burnout. During the acute phase of adrenal hyperfunction, there is an adaptation response where the body produces increased levels of cortisol, but is able to rebalance itself. After an extended time of stress, the adrenal glands “burn out,” running out of steam and resources to keep up high levels of hormone production. This is called adrenal fatigue. In this state, the body starts favoring production of stress hormones over sex hormones, and shifts production in favor of these. As a result, conditions such as anovulation, luteal phase defects, PCOS, immune disorders, and thyroid disorders occur. Thus, exposure to various forms of stress, physical and emotional, can result in hormone imbalances that impact reproductive function.
Naturopathic strategies for adrenal fatigue entail the use of adaptogenic herbs that help restore optimal adrenal function. *Rhodiola rosea* is a prime example of an herb has been found to balance the stress-response system and is safe to take during pregnancy. Generally, *Rhodiola* can be dosed at 200–400 mg/d to balance the hypothalamic–pituitary–adrenal axis. In one study, use of 100 mg *Rhodiola* twice daily was found to correct amenorrhea (lack of menses), and restore normal menstrual cycles.[16] There are also a host of other herbs and nutrients utilized by naturopathic doctors to restore proper adrenal function and hormone balance.

**Putting It Together**

The most important part of this discussion about hormones is the extent to which they interact, and how much of an influence each hormone has on the rest of the body. PCOS is a multifactorial condition; there is likewise an array of conventional and complementary therapies available to women to target the multiple aspects of this syndrome.

Front-line natural therapy for PCOS includes an emphasis on diet and lifestyle, including a low glycemic index (GI) diet, exercise, and moderate weight loss if appropriate. These have been shown to improve insulin sensitivity; improve FSH, SHBG, testosterone, and androstenedione levels; and improve hirsuitism. Such changes have been shown to improve pregnancy rates; in one study, there were 10 spontaneous pregnancies among women with PCOS who began a diet and exercise program, and who lost 5% of their initial weight.[17]

Conventional therapies for infertility related to PCOS include clomiphene citrate, metformin, and aromatase inhibitors. Clomiphene citrate is considered a first-line pharmacological therapy that regulates estrogen and FSH levels to improve follicular development, ovulation, and fertility outcomes.[18] Metformin is a drug that helps improve insulin sensitivity, and it has been shown to improve ovulation in this population.[19] Another conventional treatment for PCOS is aromatase inhibitors, which convert testosterone to estrogen. Aromatase inhibitors allow for more FSH production and greater follicle growth, and prevent the development of cysts on the ovaries.[20] From an alternative medicine perspective, diindolylmethane (DIM) improves estrogen metabolism by altering liver function, which increases the rate at which estrogens are metabolized. DIM increases sex hormone-binding globulin (SHBG) that binds to estradiol and testosterone, and thereby manages the bioavailability of sex hormones. This can be extremely beneficial in PCOS.[20]
When treating PCOS, it is important to recognize the different underlying factors. In different women, different causes have more or less relative importance. In some women, the primary issue is simply insulin resistance. Excess testosterone is a side effect of insulin resistance. An endocrinologist will prescribe weight loss with a low glycemic index (GI) diet and exercise, as well as an insulin-sensitizing drug such as metformin. From a complementary perspective, chromium (200–1000 mcg) and magnesium increase insulin sensitivity.[21, 22] Herbs such as licorice (3.5 g with 7.6% glycyrrhizic acid) decrease testosterone, and products such as DIM assist with estrogen metabolism.[23, 20]

Some women with PCOS may be more affected by low adrenal and/or thyroid function, or possibly hormone-disrupting chemicals. Iodine, calcium (1000 mg/d), and vitamin D (100,000 IU/mo) supplementation have been found to help regulate PCOS.[23, 24] Iodine helps to regulate the thyroid, which indirectly helps improve ovulation and progesterone production. Liver detoxification helps to metabolize excess hormones and endocrine-disrupting chemicals. Bioidentical progesterone can be used to downregulate LH secretion in the brain, helping to balance estrogen and progesterone production in the body, and improve ovulation.[25] This example shows the interconnectedness of hormone systems in the body. Women with PCOS often suffer from subtle disturbances in thyroid or adrenal function, as well as the better-characterized problems with estrogen, progesterone, and testosterone. Thorough assessment of these systems, and treatment if needed, is critical in correcting infertility associated with PCOS.

References


