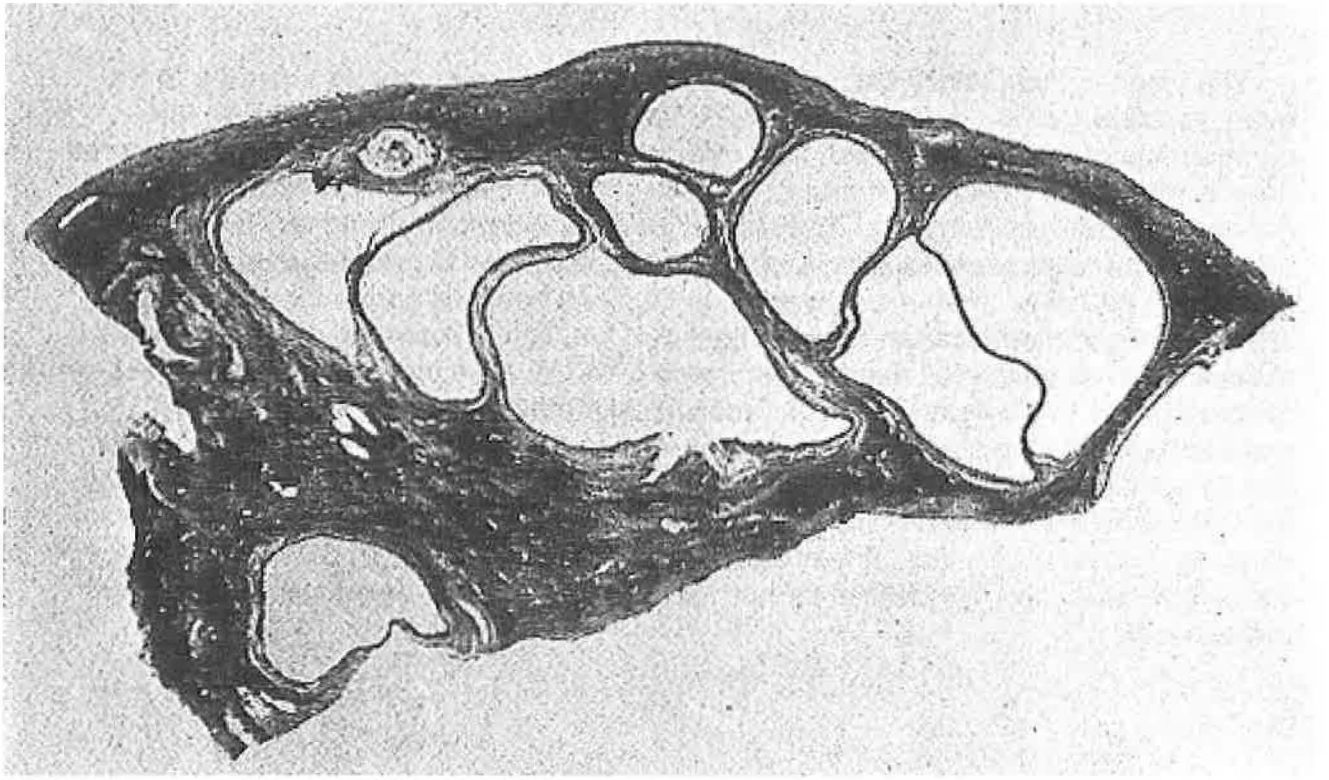
POLYCYSTIC OVARIAN SYNDROME: WHAT IS IT AND WHO'S TO BLAME?



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The Hammes laboratory studies how steroidogenesis and steroid signaling in the ovary regulate ovarian development and function. The laboratory focuses on three components of this system: First, they use frog and mouse models of steroid-triggered oocyte maturation (meiotic resumption) to study transcription-independent, or nongenomic, steroid signaling. The laboratory has made many important discoveries regarding the roles of androgens, androgen receptors, and G proteins in regulating the maturation process. They are interested in studying how this nongenomic androgen signaling might affect ovarian development and function in diseases of androgen excess, such as polycystic ovarian syndrome (PCOS). Second, the laboratory uses mouse models to characterize the intracellular signaling pathways triggered by gonadotropins during steroidogenesis, focusing on potential signaling molecules that can be specifically targeted to reduce ovarian androgen production in PCOS. Finally, the laboratory is interested in understanding ovarian follicle development, and is studying a novel GATA-like protein that is expressed in granulosa cells, may regulate steroidogenesis, and is essential for normal embryonic follicle development and germ cell survival.

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I. Introduction

In 1934, Irving Stein and Michael Leventhal presented an article entitled "Amenorrhea Associated with Bilateral Polycystic Ovaries" at a meeting of the Central Association of Obstetrics and Gynecology. In this presentation, they described seven cases of reproductive age women who presented with irregular menses and bilaterally enlarged and cystic ovaries by physical exam. Several of these patients had been treated with "estrogenic hormone" with limited success. Interestingly, Stein and Leventhal performed wedge-resections in all of these patients, and every one began cycling normally again. In fact, two of the seven patients even became pregnant. They concluded that "mechanical crowding of the cortex by cysts interferes with the progress of normal graafian follicles to the surface of the ovary," thus resulting in amenorrhea and infertility.

More than 70 years later, we have learned a great deal more about the disease now known as "Polycystic Ovarian Syndrome," and have come to find that it is one of the most common causes of infertility in women, with an incidence of 5-10% in reproductive age women. In addition, we now know that a great many of these patients have obesity and insulin resistance, as well as other components of the metabolic syndrome. In this review we will briefly discuss the definition of PCOS, followed by a longer discussion regarding the pathophysiology of PCOS, and how insulin resistance and ovarian dysfunction can be seen hand in hand. Finally, we will discuss the current treatment options for PCOS.

II. Diagnosis

A. 1990 NIH Consensus Conference – PCOS must include all of the following:
   1. Hyperandrogenemia – either with laboratory values or with symptoms.
   2. Oligomenorrhea – periods less frequent than every 35 days, or 10 per year.
   3. The exclusion of related disorders

B. Homburg 2002 – Women with more than one of these need an ultrasound:
   1. Menstrual Disturbance
   2. Hirsutism
   3. Acne
   4. Anovulation and infertility

If the ultrasound shows polycystic ovaries, then the diagnosis is made. If not, one of the following is needed:

1. Elevated testosterone
2. Elevated LH
3. Insulin resistance (glucose:insulin ratio <4.5).

C. Rotterdam Criteria (2003) – In addition to excluding other causes, two of the following are needed:
   1. Oligo- or anovulation
   2. Clinical or biochemical signs of hyperandrogenemia
   3. Polycystic Ovaries (Presence of >12 follicles of 2-9 mm diameter and/or an ovarian volume >10 cm^3).

D. Modified NIH Criteria – Need all of the following:
   1. Androgen excess (clinical or biochemical)
   2. Ovarian dysfunction (oligo/anovulation or polycystic ovaries)
   3. Exclusion of other causes

III. Heritability of PCOS

A. When studying women with PCOS, 35% of premenopausal mothers and 40% of sisters had PCOS. In the general population, the incidence is only 5-10%.

B. In general, approximately 50% of women with PCOS also have insulin resistance, although this number is rising with the obesity epidemic.

C. In looking at women with both PCOS and insulin resistance, hyperinsulinemia was found in 69% of family members. Thus, there may be some genetic linkage between insulin resistance and PCOS. However, it is difficult to rule out obesity as a common etiology for both.

IV. The Normal Hypothalamic/Pituitary/Gonadal Axis

A. The hypothalamus secretes GnRH in a pulsatile fashion. The faster these pulsations, the more stimulation of gonadotropin release (LH and FSH) from the pituitary.

B. LH and FSH are secreted from the pituitary. Specifically, LH is also secreted in a pulsatile fashion that matches that of GnRH secretion. Thus, the faster GnRH is released from the hypothalamus, the faster LH is released from the pituitary.

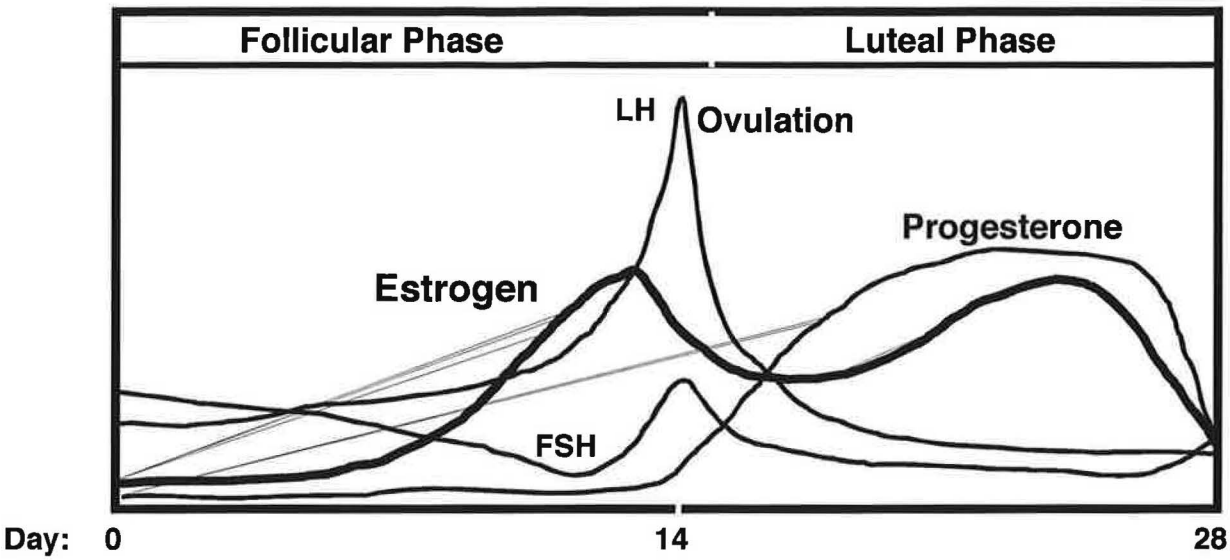

Figure 1

C. FSH stimulates follicle growth and estrogen production
    1. FSH is secreted during the very early follicular stage of the cycle
    2. FSH receptors are located primarily on granulosa cells.
    3. FSH stimulates granulosa cell expansion, resulting in follicle growth
    4. FSH stimulates LH receptor expression in theca and mural granulosa cells.
    5. Low but steady levels of LH stimulate androgen production in follicles, which promotes follicle growth and possibly the selection of dominant follicles.
    6. FSH also stimulates expression of aromatase, which converts the aforementioned androgens to estrogens. Thus, LH and FSH promote estradiol production from follicles.
    7. As follicles grow, they secrete inhibin, which suppresses FSH secretion from the pituitary late in the follicular phase.
    8. Just prior to ovulation, estradiol secretion from the ovary surges and then rapidly falls (as aromatase levels drop from the loss of FSH), leading to a rapid increase in GnRH pulsatility and a subsequent increase in LH release from the pituitary. FSH also rises with this surge.

D. LH stimulates progesterone production and ovulation
    1. LH activates its receptors in theca and mural granulosa cells, resulting in elevated progesterone secretion in follicles.
    2. Progesterone levels rise coincident with the LH surge, and this rise is necessary for normal ovulation.
    3. After ovulation, progesterone secretion from the corpus luteum results in a further rise in serum progesterone.

4. Progesterone inhibits pulsatile GnRH secretion, which leads to decreased gonadotropin release and a subsequent drop in follicle growth and steroid production.
5. As the corpus luteum degenerates at the end of the luteal phase, progesterone levels drop, GnRH pulsatility rises, and the cycle begins again.

The Ovarian Axis in PCOS

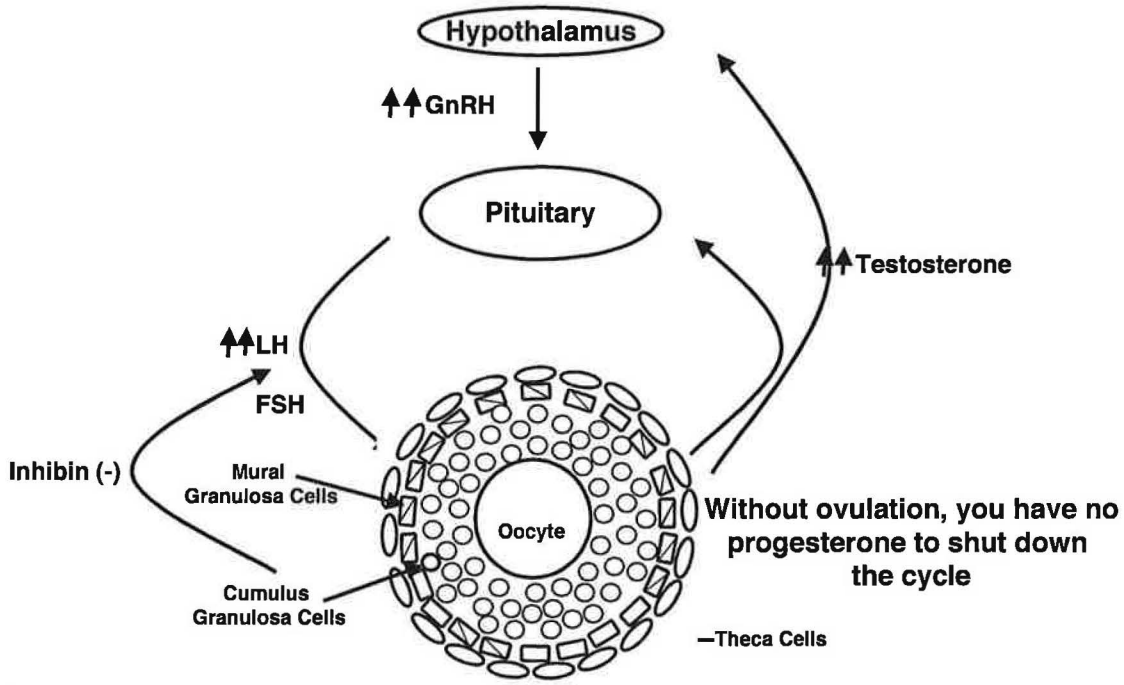

Figure 2

V. The vicious cycle of PCOS

A. In most patients with PCOS, the pulsatile secretion of GnRH is increased. This leads to increased gonadotropin release from the pituitary (LH, and, at the start, possibly FSH).

B. With increased gonadotropin release, follicles grow more rapidly. This results in increased inhibin release, which selectively suppresses FSH. Thus, patients with PCOS almost always have higher LH levels relative to FSH.

C. With high LH and low FSH, androgen production is increased but conversion to estrogens by aromatase is decreased. Thus, testosterone levels rise.

D. Testosterone very likely has direct stimulatory effects on follicle growth
    1. In vitro models demonstrate testosterone-induced follicle growth.
    2. Androgen Receptor null mice have small follicles and decreased fertility

E. Testosterone blocks the inhibitory effects of progesterone on the GnRH pulsatile secretion, and may even stimulate GnRH release. Thus, GnRH secretion increases, which promotes LH secretion from the pituitary, and the cycle continues in a powerful positive feedback loop.

VI. What is the initial cause of this vicious positive feedback loop? There are probably many ways to start this process, but the end result will always be the same.

A. Excess androgens from any source
    1. Congenital Adrenal Hyperplasia
        a. In the absence of 21-hyroxylase, adrenal androgen production is extremely high, even *in-utero*.
        b. Female babies are often born with polycystic ovaries, and develop increased ovarian androgen production later in life. Thus, androgen exposure *in-utero* may initiate a "program leading to PCOS."
        c. Importantly, the incidence of insulin resistance in this population lower than in the total PCOS population, suggesting that insulin resistance is not needed for the development of PCOS.
    2. Aromatase deficiency
        a. These females cannot convert androgens to estrogens; thus, LH and androgen levels are high, just as in PCOS.
        b. These high levels lead to excessive follicle growth, and the aforementioned cycle is perpetuated.
    3. Anabolic Steroid Abuse and Transgender Patients
        a. These women are taking exogenous androgens, which then stimulate GnRH pulsatility and follicle growth. Thus, the vicious cycle is initiated.
    4. Experimental *in utero* exposure of primates, sheep, and mice.
        a. As seen in humans with CAH, females develop PCOS as they go through puberty, with increased ovarian androgen production
        b. Again, this suggests that the androgens i*n utero* may be "programming" the axis toward PCOS. Once the cycle has begun, it will perpetuate, even in the absence of the original insult.
        c. Many of these females animals also develop obesity and glucose intolerance or insulin resistance, suggesting that hyperandrogenemia may contribute to the development of insulin resistance in PCOS.

B. Insulin-mediated androgen production from the ovary
    1. Interestingly, the follicle seems to remain relatively sensitive to insulin in the setting of insulin resistance and type 2 diabetes.
    2. Insulin signals via the insulin receptor and possibly IGF1 receptors to to promote increased androgen production in the ovary.
    3. Theory of Excessive serine phosphorylation
        a. In insulin resistant PCOS patients, there is some evidence for excessive serine phosphorylation of the insulin receptor, which may regulate its activity
        b. There is also some evidence that CYP17, the enzyme that converts progestins to androgens, might be hyperphosphorylated, which may increase its activity.
        c. The evidence supporting this theory is still relatively weak at this time.
    4. Theory of altered mitogen-activated protein kinase (MAPK) signaling
        a. Evidence suggests that theca cells from patients with PCOS have decreased MAPK signaling.
        b. Decreased MAPK signaling leads to increased CYP17 expression, which leads to increased androgen production.
        c. This decreased MAPK signaling occurs independent of insulin, suggesting that insulin signaling is not the only factor contributing to the increased androgen production in PCOS.

VII. Treatment Options for PCOS – Break the Vicious Positive Feedback Loop

A. Wedge Resection, or Ovarian "Mining"
    1. Used from the time of Stein and Leventhal.
    2. Remove part of the ovary to decrease overall steroid production
    3. Reasonably effective in lowering androgen levels, which breaks the positive feedback loop.
    4. Many women will start cycling normally again.
    5. Some evidence of improved fertility in those patients with large polycystic ovaries, but this may not apply to everybody.
    6. The drawback is that this is an invasive procedure that has not actually been tested in a prospective, controlled trial.

B. Oral Contraceptives
    1. High estrogen and progesterone suppresses GnRH pulsations, thus lowering testosterone production and improving symptoms of hyperandrogenemia.
    2. Can bring back cycling, but obviously not via the hypothalamus.
    3. Can use only progesterone if estrogens contraindicated, as progesterone will still suppress GnRH pulsatile secretion.
    4. Not useful if pregnancy is the desired outcome

C. GnRH Agonists
   1. At first, hyperstimulate the pituitary; however, GnRH receptors are rapidly down-regulated, resulting in decreased gonadotropin release, reduced testosterone, and decreased symptoms of hyperandrogenemia.
   2. Not useful if pregnancy is the desired outcome.
   3. By lowering estrogen levels as well as testosterone, long-term use may lead to osteoporosis.

D. Androgen Receptor Antagonists
   1. Flutamide or Spironolactone
   2. Improve signs of hyperandrogenemia by blocking the androgen receptor in peripheral tissues.
   3. Also block the central stimulatory effects of androgen in the hypothalamus and pituitary. Thus, the antagonists, will suppress testosterone-mediated increases in GnRH pulsatility, which will reduce ovarian androgen production and help break the cycle.
   4. Can help resume normal menstrual cycling, and may increase pregnancy rates.
   5. Improve effects of other treatments, such as metformin (see below).

E. Insulin Sensitizers
   1. Metformin or thiazolidinediones
   2. Improve insulin sensitivity, which results in decreased insulin levels
   3. With decreased insulin levels, the postulate is that one has less insulin-stimulated steroidogenesis in the ovary.
   4. These drugs may also have direct inhibitory effects on steroid production in the ovary.
   5. In several populations, these drugs significantly improve cycling and ovulation. In general, the greater the BMI, the less effective these medications become.
   6. In some studies, these drugs improve fertility, although, again, their efficacy is likely dependent upon the BMI of the patient being treated.
   7. May be less effective in those PCOS patients without significant insulin resistance.

F. Clomiphene Citrate
   1. Used to promote ovulation in patients who desire pregnancy
   2. An estrogen agonist/SERM that triggers LH release from the pituitary. This may due to direct effects or due to blockade and down-regulation of estrogen receptors in the pituitary and hypothalamus, which leads to a strong LH surge.
   3. Improves fertility in many patients.
   4. Perhaps more effective in combination with metformin

G. Aromatase Inhibitors
    1. Block estradiol production in the ovary
    2. The loss of estradiol leads to increased GnRH pulsatility and subsequent LH secretion, resulting in ovulation
    3. Being used more and more as an alternative to clomiphene citrate

H. Problems with Over-stimulation
    1. The major point of ovulation induction us to hyperstimulate the ovary in a controlled fashion.
    2. In PCOS, the ovaries are ALREADY hyperstimulated; thus, one must be careful not to promote overstimulation, or "Ovarian Hyperstimulation Syndrome (OHS)." OHS usually includes an estradiol>4000 pg/ml, Ovarian diameter>12 cm, or > 8 follicles per ovary by ultrasound.

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