Effect of amlodipine on blood flow of preovulatory follicle in polycystic ovarian patients: A Randomized Controlled Trial

Thesis

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Overview on polycystic ovary syndrome (PCOS)

Polycystic ovary syndrome (PCOS) is one of the most common female endocrine disorders . Among women who present with oligomenorrhea, approximately 87% have PCO and of women with regular menstrual cycles who present with hirsutism, 92% have PCO .It is a complex, heterogeneous disorder of uncertain etiology, but there is strong evidence that it can, to a large degree be classified as a genetic disease **(Fauser et al., 2011).**

Genetic and environmental contributors to hormonal disturbances combine with other factors, including obesity .Ovarian dysfunction and hypothalamic pituitary abnormalities contribute to the etiology of PCOS **(Diamanti et al., 2006).**

Treatments for an adolescent with PCOS include diet and exercise, metformin and oral contraceptive pills. Each of these options has been shown to be effective in improving certain aspects of PCOS and probably the best treatment plan involves some combination of them **(Darren et al., 2004).**

It produces symptoms in approximately 5% to 10% of women of reproductive age 12-45 years old. It is thought to be one of the leading causes of female subfertility **(March et al., 2010)**.

Clomiphene citrate is a first line pharmacological treatment of ovulatory dysfunction associated with PCOS, because it is easily administered, relatively safe, and inexpensive**.** It is a selective estrogen receptor modulator (SERM) that increases production of gonadotropins by inhibiting negative feedback on the hypothalamus. It is used in the form of its citrate to induce ovulation **(Shelly et al., 2008).**

It is known to be both an estrogen agonist and antagonist; however. Its agonist properties manifest only when endogenous estrogen levels are extremely low**.** Its administration leads to depletion of estrogen receptors at the

level of the pituitary and hypothalamus, interrupting the negative feedback that estrogen normally produces. As a result GnRH secretion is improved and stimulates pituitary production of follicle-stimulating hormone (FSH), which in turn drives follicular growth and maturation with emergence of 1 or more dominant follicles **(Schorge et al., 2008).**

In the case of polycystic ovaries, however, the ovaries are larger than normal, and there are a series of undeveloped follicles that appear in clumps, somewhat like a bunch of grapes. **(Fauser et al.,2011).**

However, when the cysts cause a hormonal imbalance, a pattern of symptoms may develop. This pattern of symptoms is called a syndrome. These symptoms are the difference between suffering from polycystic ovary syndrome and from polycystic ovaries **(Warner et al., 2012).**

So you can have polycystic ovaries without having PCOS. However, nearly all women with PCOS will have polycystic ovaries. Polycystic Ovary Syndrome is the name given to a metabolic condition in which a woman will have polycystic ovaries, along with a certain pattern of other symptoms that reflect imbalances in reproductive and other hormones **(Warner et al., 2012).**

❖ Definition:

To maintain uniformity and lessen ambiguity, three major diagnostic criteria for PCOD have been proposed (Table 1). The first arose from the proceedings of a National Institutes of Health (NIH)/ National Institute of Child Health and Human Development (NICHD) sponsored conference in 1990 (i.e., the NIH 1990 criteria)**(Zawadski and Duanif, 1992).**

The second criteria were proposed by an expert conference sponsored by the European Society for Human Reproduction and Embryology (ESHRE) and the American Society for Reproductive Medicine (ASRM) in 2003 in Rotterdam. **(The Rotterdam ESHRE/ASRM, 2004**).

The most recent criteria was defined by a task force of the Androgen Excess Society (AES) in 2006 **(AES, 2006).**

Table (1): Criteria for defining PCOS **(Trivax and Azziz 2007) :-**

NIH 1990 : To include all the following: • Clinical hyperandrogenism and/or hyerandrogenemia • Chronic anovulation • Exclusion of related disorders
ESHRE/ASRM (Rotterdam) 2003: To include two of the following. in addition to exclusion of related disorders: • Oligo-anovulation • Hyperandrogenism and/or hyerandrogenemia • Exclusion of related disorders
AES 2006 : To include two of the following: • Hyperandrogenism (hirsutism and/or hyerandrogenemia) • Ovarian dysfunction (oligo-anovulation and/or polycystic ovaries) • Exclusion of related disorders

- hyperandrogenism (clinical and/or biochemical), ovarian dysfunction (oligo-anovulation and/or polycystic ovaries), and the exclusion of related disorders **(Palomba et al., 2010).**

In this definition, the experts re-established hyperandrogenism as the key to PCOS diagnosis. Biochemical evaluations should look for supporting evidence of PCOS (hyperandrogenism and IR) and rule out the other disorders **(Okoroafor and Jungheim, 2012).**

- A total testosterone is likely to be more reliable than a free testosterone**.** As testosterone values may be normal in PCOS. Oral contraceptives will lower total testosterone, and interpretation in this setting is difficult (3 months off oral contraceptives is best to get a "true" testosterone value). Most testosterone values in PCOS will be ≤150 ng/dL .Testosterone values of ≥200 ng/dL warrant consideration of an ovarian or adrenal tumor **(Derksen et al., 1994).**
- Dehydro-epiandrosterone-sulfate (DHEA-S): DHEA-S values may be normal or slightly elevated in PCOS. DHEA-S values≥800µg/dL warrant consideration of an adrenal tumor **(Derksen et al., 1994).**
- Prolactin: Mild hyperprolactinemia has been reported in 5% to30% of patients with PCOS**.** Prolactin is generally only 50% above the upper limit of normal furthermore; hyperprolactinemia is most often transient, with perhaps only 3% to 7% of hyperprolactinemic PCOS patients having persistently elevated prolactin levels **(Bracero and Zacur, 2001).** Thus, it is now felt that PCOS and hyperprolactinemia are independent disorders. If normalization on re-sampling does not occur, then an assessment for other causes should be undertaken (including pituitary magnetic resonance imaging). Patients with prolactinomas may have polycystic ovaries on ultrasound **(Franks, 1995).**

- 17-hydroxyprogesterone: A morning, fasting, unstimulated level of <200ng/dL in the follicular phase reliably excludes late-onset 21-hydroxylase deficiency. Further evaluation of levels ≥200 ng/dL involves adrenocorticotropic hormone (ACTH)-stimulation with an intravenous 250 μg dose and a 30 minute value (stimulated values ≥1,000 ng/dL confirm the diagnosis).
- Luteinizing hormone/follicle stimulating hormone (LH/FSH) ratio: A ratio ≥2.0 is suggestive of PCOS but is not highly sensitive or specific. Gonadotropin levels are affected by oral contraceptives **(Michael and Sheehan, 2004).**

❖ Prevalence:

Although polycystic ovaries can be found in approximately 20% of the female population, they are not necessarily associated with the typical symptoms, which may be expressed at some time during the fertile life span when provoked by, for example, weight gain or insulin resistance. PCOS is associated with 75% of all an ovulatory disorders causing infertility, with 90% of women with oligomenorrhea, more than 90% with hirsutism and more than 80% with persistent acne **(Homburg et al, 2008).**

❖ Etiology and pathogenesis:-

PCOS is a common, complex genetic disorder. Common diseases such as schizophrenia, asthma, and type 2 diabetes, as well as PCOS, have a complex, multifactorial genes, not just one gene, interact with environmental factors to produce disease **(Goodarzi and Azziz,2006).**

1-Hereditary Factors:

The exact etiology of PCOS is unknown There is, however, increasing evidence for genetic factors. The syndrome clusters in families, and prevalence rates in first degree relatives are five to six times higher than in general population **(Amato and Simpson, 2004).**

Not only is PCOS itself a heritable condition but also within PCOS insulin resistance and insulin secretion appear to be under significant genetic control. Among sisters of women with PCOS or hyperandrogenism with regular menses had lower insulin sensitivity than unaffected sisters, assessed by fasting insulin and glucose measurements **(Goodarzi and Azziz, 2006).**

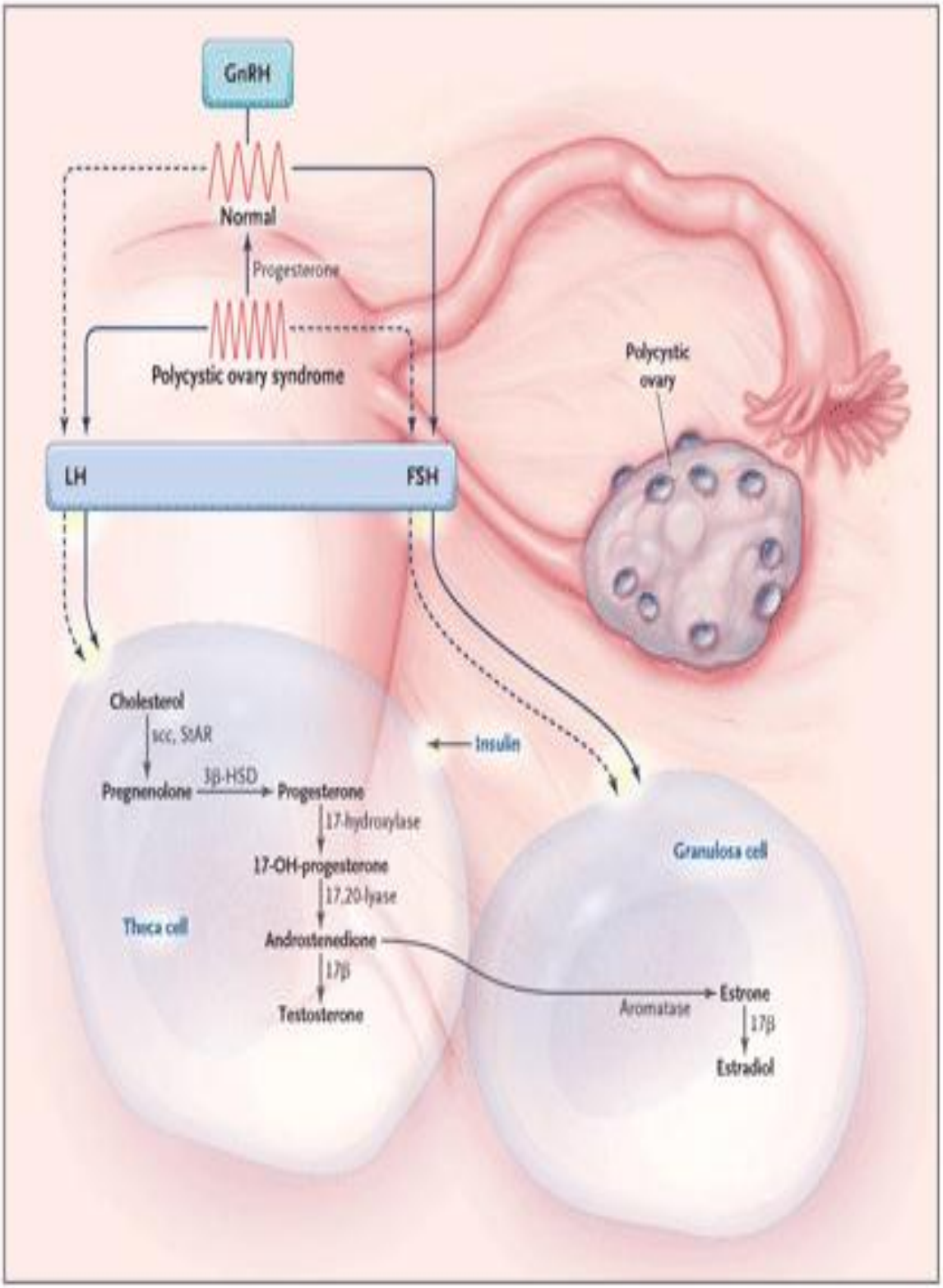
2-Environmental Factors:

While the majority of cases appear to be genetically transmitted, the environmental factors can be involved as PCOS may also be acquired by exposure to excess androgens at anytime during the fertile years. Intra uterine exposure of a female fetus to an excess of androgens is an etiological hypothesis finding increasing favor **(Bruns, 2005).**

Carmina and Lobo (2004) investigated the prevalence of psychological stress and its possible relationship to various hormonal parameters. They hypothesized that psychological stress and neurotransmitter levels may be linked to some of the hormonal derangement including inappropriate gonadotrophins secretion and elevated adrenal androgen levels in women with PCOS.

3-Endocrinological and Metabolic Factors:

PCOS involves overproduction of ovarian androgens leading to a heterogeneous range of symptoms including hirsutism, acne, anovulation and infertility. Hyperinsulinaemia exacerbated by obesity is often a key feature **(Homburg et al., 2008).**



Figure(1): - Hypothalamic-pituitary ovarian axis and the role of insulin in PCOS. The increased frequency of hypothalamic gonadotrophin releasing (**Ehrmann et al,.2008)**

Although the etiology of PCOS is unknown, 3 main hypotheses have been proposed in 2005 by Polycystic Ovary syndrome Writing Committee **(Setji and Brown, 2007)**

A. Hypothalamic-pitutary axis abnormalities cause abnormal secretion of gonadotrophic releasing hormone and luetinizing hormone, resulting in increased ovarian androgen production.
B. Insulin resistance drives the metabolic and reproductive abnormalities in PCOS.
C. An enzymatic defect of ovarian (adrenal) steroidegenesis favors excess androgen production.

A. Hypothalamic-pituitary axis

LH hypersecretion is a characteristic hallmark of PCOS.LH is secreted in a pulsatile manner. Women with PCOS have an increase in both the LH pulse frequency and amplitude, resulting in increased 24-hour secretion **(Tsilchorozidou et al., 2004).**

The increase in LH secretion is thought to occur as a result of the increase in frequency of hypothalamic GnRH pulses. Increased LH, in turn, leads to an increase in androgen production by the theca cells within the ovary **(Ehrmann et al., 2005).**

By whatever mechanism, the relative increase in pituitary secretion of luteinizing hormone leads to an increase in androgen production by ovarian theca cells. Increased efficiency in the conversion of androgenic precursors in theca cells leads to enhanced production of androstenedione, which is then converted by 17β-hydroxysteroid dehydrogenase (17β-HSD) to form testosterone or aromatized by aromatase enzyme to form estrone.

Within the granulosa cell, estrone is then convened into estradiol by (17β-HSD). Insulin acts synergistically with luteinizing hormone to enhance androgen production. Insulin also inhibits hepatic synthesis of sex hormone-binding globulin, the key circulating protein that binds to testosterone and thus increases the proportion of testosterone that circulates in the unbound, biologically available or free state. Testosterone inhibits and estrogen stimulates hepatic synthesis of sex hormone-binding globulin **(Ehrmann et al., 2005).**

B. Obesity and insulin resistance:

While obesity and insulin resistance are not necessary features of PCOS, they are common and play a role in pathogenesis of many cases. The frequency of obesity in women with anovulation and polycystic ovaries ranged from 35% to 60% **(Rosenfield et al., 2008) .**

Overweight women with PCOS are more likely to be anovulatory and to have symptoms of androgen excess. Furthermore, obesity affects reproductive outcome in response to induction of ovulation **(Balen et al., 2006)**

The mechanism of the effects of obesity on reproductive function is complex, but hyperinsulineamia and/or insulin resistance appear to play an important part **(Tsilchorozidou et al., 2004).**

Insulin resistance, defined as reduced glucose response to a given amount of insulin, is a characteristic metabolic disturbance associated with PCOS. Both obese and non-obese women with PCOS have a higher incidence of insulin resistance and hyperinsulinemia than age matched controls; however, obese women with PCOS have significantly decreased insulin sensitivity compared with non-obese women who have PCOS **(King et al., 2006).**

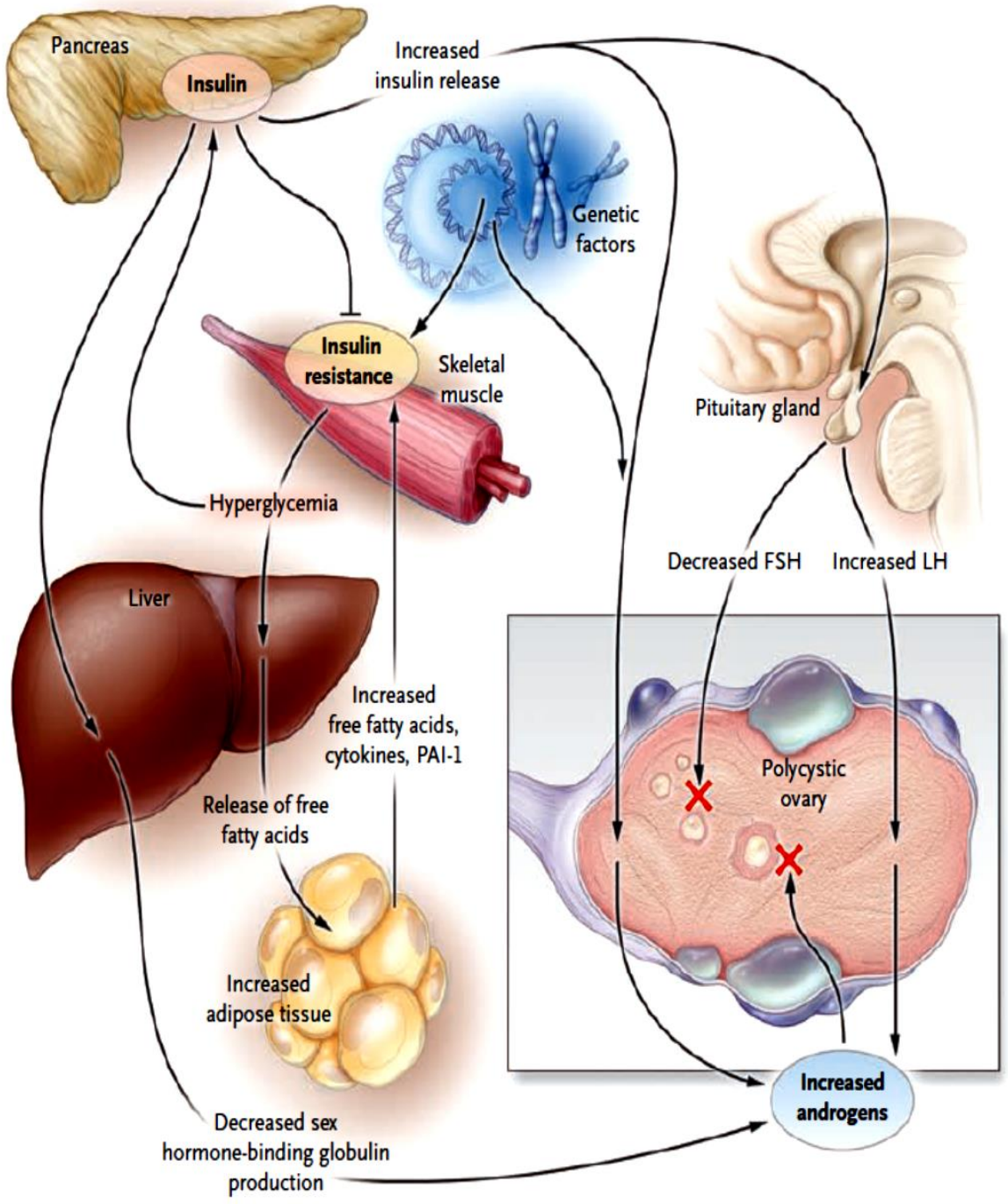


Figure 1. Pathophysiological Characteristics of the Polycystic Ovary Syndrome (PCOS).

Insulin resistance results in a compensatory hyperinsulinemia, which stimulates ovarian androgen production in an ovary genetically predisposed to PCOS. Arrest of follicular development (red "X") and anovulation could be caused by the abnormal secretion of gonadotropins such as follicle-stimulating hormone (FSH) or luteinizing hormone (LH) (perhaps induced by hyperinsulinemia), intraovarian androgen excess, direct effects of insulin, or a combination of these factors. Insulin resistance, in concert with genetic factors, may also lead to hyperglycemia and an adverse profile of cardiovascular risk factors. PAI-1 denotes plasminogen-activator inhibitor type 1.

Figure (2):- Obesity, Insulin Resistance and hyperinsulinemia **(Nestler et al.,2008).**

C. Androgen Excess:

PCOS is the most common cause of excess androgen production. It is also the most common hormonal disturbance which can underlie hirsutism (over half of cases) **(Ehrmann et al., 2008).**

Increasing evidence indicates that hyperandrogenism results from intrinsic dysfunction of the ovaries and adrenal glands. The neuroendocrine dysfunction, manifest most often as elevated levels of luteinizing hormone, seems increasingly likely to be the consequence of moderate androgen excess interfering with female hormone negative feedback, rather than the cause **(Rosenfield et al., 2008).**

The most likely primary factor driving the increase in testosterone secretion in PCOS is an increase in ovarian enzymatic activity involved in the synthesis of testosterone precursors **(Hill et al., 2003).**

Gonadotrophin-dependent functional ovarian hyperandrogenism is the major source of the hyprandrogenemia in the majority of PCOS cases. The increase in LH, together with hyperinsulinemia, leads to an increase in androgen production by ovarian theca cells **(Tsilchorozidou et al., 2004).**

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In summary, endocrine and metabolic factors appear to have an influence on the development of anovulation in women with PCOS, but these factors do not exclude the possibility of an intrinsic abnormality of folliculogenesis in PCOS **(Barber et at., 2007).**

❖ Pathology:

An important fact is that the polycystic ovary is a sign, not a disease. Macroscopically, ovaries in women with PCOS are 2 to 5 times the normal size. A cross-section of the surface of the ovary discloses a white, thickened cortex with multiple cysts that are typically less than a centimeter in diameter. Microscopically, the superficial cortex is fibrotic and hypocellular and may contain prominent increase in the number of follicles with luteinized theca interna, The stroma may contain luteinized stromal cells **(Kocak et al., 2002).**

Excess androgens probably play a key role in the etiology of the abnormal ovarian morphology. Androgens encourage the development of primary follicles with arrest of growth to the stage of preantral and small antral follicles, and, in the presence of excess androgens, this process is accelerated compared with the normal ovary **(Homburg 2008).**

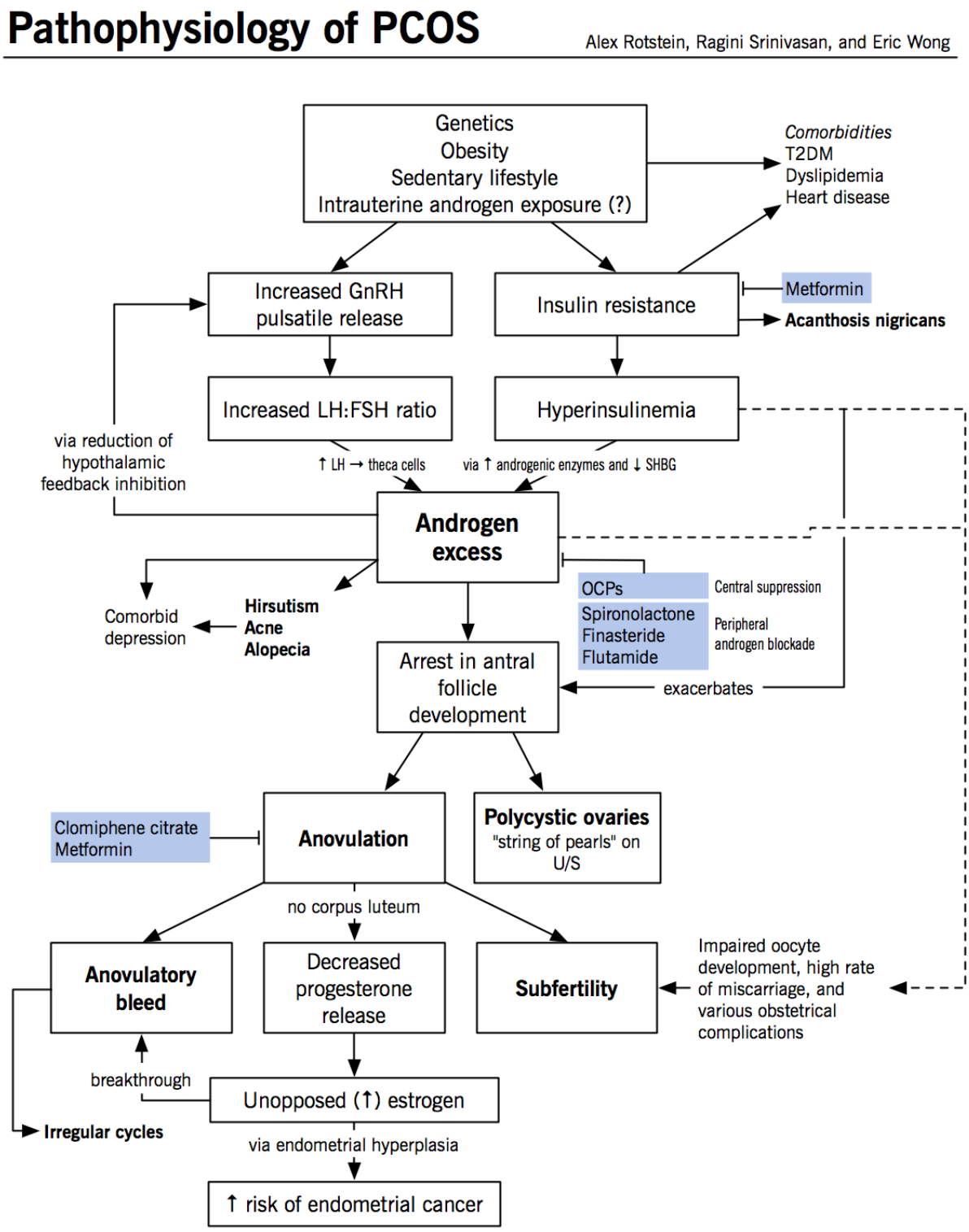

Figure (3):- Pathophysiology of PCOS (http://www.pathophys.org/)