IVF PHOENIX

PCOS: An Absolute or Relative Deficiency of FSH.

Introductions and definition of PCOS. (excerpted from UpToDate) **INTRODUCTION** — The polycystic ovary syndrome (PCOS) is an important cause of both menstrual irregularity and androgen excess in women. When fully expressed (hirsutism, irregular menstrual cycles, obesity, and a classic ovarian morphology), PCOS can be readily diagnosed. However, there has been considerable controversy about specific diagnostic criteria when not all of these classic features are evident [1].

The diagnosis of PCOS will be reviewed here. The epidemiology and pathogenesis, clinical manifestations and treatment of PCOS are described in detail separately. (See "Epidemiology and pathogenesis of the polycystic ovary syndrome in adults" and "Clinical manifestations of polycystic ovary syndrome in adults" and "Treatment of polycystic ovary syndrome in adults".)

DIAGNOSTIC CRITERIA — Several professional groups have proposed diagnostic criteria for PCOS, using the criteria of ovulatory dysfunction, hyperandrogenism, polycystic ovaries, and exclusion of other disorders in varying combinations.

NIH consensus criteria — After considerable debate at a 1990 National Institutes of Health Conference on PCOS, minimal criteria for diagnosing PCOS were proposed [2]:

- Menstrual irregularity due to oligo- or anovulation
- Evidence of hyperandrogenism, whether clinical (hirsutism, acne, or male pattern balding) or biochemical (high serum androgen concentrations)
- Exclusion of other causes of hyperandrogenism and menstrual irregularity, such as congenital adrenal hyperplasia, androgen-secreting tumors, and hyperprolactinemia.

Rotterdam criteria — Revised diagnostic criteria have been proposed based upon a 2003 consensus meeting held in Rotterdam (European Society of Human Reproduction and Embryology/American Society of Reproductive Medicine consensus workshop group) [3]. These criteria encompass a broader spectrum of phenotypes considered to represent PCOS. In the revised criteria, two out of three of the following are required to make the diagnosis:

- Oligo- and/or anovulation
- Clinical and/or biochemical signs of hyperandrogenism
- Polycystic ovaries (by ultrasound)

In addition, other etiologies (congenital adrenal hyperplasias, androgen-secreting tumors, Cushing's syndrome) must be excluded.

The ultrasound criteria for polycystic ovaries (PCO) have evolved since the first description in 1986. The current criteria (used for the Rotterdam criteria), considered to have sufficient specificity and sensitivity to define PCO are the presence of 12 or more follicles in each ovary measuring 2 to 9 mm in diameter and/or increased ovarian volume (>10 mL; calculated using the formula 0.5 x length x width x

thickness). It was suggested that follicle distribution and an increase in stromal echogenicity and volume be eliminated as diagnostic criteria.

The transvaginal approach should be used. Women with the ultrasound appearance of PCO in the absence of oligo/amenorrhea or hyperandrogenism should not be considered to have PCOS.

AES criteria — Because of the continuing controversy regarding the definition of PCOS, the Androgen Excess Society (AES) proposed that PCOS should be diagnosed by the presence of three features: a) androgen excess (clinical and/or biochemical hyperandrogenism), b) ovarian dysfunction (oligo-anovulation and/or polycystic ovarian morphology), and c) exclusion of other androgen excess or ovulatory disorders (table 1) [4]. This definition then recognizes one additional phenotype above that noted by the NIH 1990 criteria, namely that of women with polycystic ovaries, hyperandrogenism, and apparently normal ovulation. In contrast to the Rotterdam criteria, the AES task force agreed that there were insufficient data to define women with ovulatory dysfunction and polycystic ovaries, but without any evidence of hyperandrogenism, as having PCOS.

The NIH criteria allow for a clinical diagnosis without the use of an imaging study. In addition, the NIH criteria require the presence of irregular menses, while the other criteria do not. Therefore, the Rotterdam and AES criteria encompass a broader spectrum of phenotypes considered to represent PCOS.

We continue to use the NIH criteria to make the diagnosis of PCOS. The current Rotterdam ultrasound criteria for the diagnosis of polycystic ovaries are precise, but often loosely applied. From a practical perspective, unless one is working with an experienced ultrasonographer, these criteria may be difficult to document.

There is emerging evidence that serum concentrations of anti-mullerian hormone (AMH) may be useful in the diagnosis of PCOS. In one study, serum concentrations were two to three-fold higher in women with PCOS compared with normal ovulatory women [5]. In addition, the number of small antral follicles detected on transvaginal imaging appears to be correlated with serum AMH concentrations [6]. However, AMH is not currently considered to be a criterion for the diagnosis of PCOS.

Diagnosis vs description: Even though the criteria presume to make a diagnosis, it is more of a description and does not attempt to define what may be driving this syndrome. When one says they saw a car crashed on the side of the road, this is like describing PCOS. It describes what you see, but it does not help you to understand why the accident occurred and how to avoid or prevent it. I am suggesting another approach to understanding PCOS, and it is , **PCOS is the absolute or relative deficiency of FSH.** This approach incorporates the NIH or Rotterdam criteria or AES criteria, as well as allowing one to contemplate the varied exclusion states such as CAH or androgen tumors, etc. It explains poor responders who present as PCOS, when most of the time they are overresponders, and it incorporates those ovulatory, but hyperandrogenic, polyfollicular ovary presenting patients who are not conceiving.

The many faces of PCOS:

- Fat vs Thin
- IR vs normal
- Androgen excess: biochemical vs clinical
- Over-responders vs resistant ovaries.
- Ovulation vs irregular to anovulation

Consider stratifying patients into two groups: Absolute or Relative Deficiency of FSH.

This approach allows one to focus on the action of FSH upon the follicle. It is the follicle and its behavior to FSH that ultimately defines whether ovulation will occur. The ovarian androgens, namely androstendione and testosterone are secondary elements to this FSH disruption. These

androgens can ultimately interfere with FSH levels in circulation, but we have all seen hirsuite ovulatory women, with elevated androgens, who by all criteria should be PCOS. Depending on which PCOS criteria one follows, will define PCOS. Rather than simply try to define PCOS, I seek to understand this pleomorphic disorder and fix the underlying issues and allow these patients to try to normalize follicle action, especially when trying to help them conceive.

Absolute deficiency is low FSH defined as low FSH <5 to 1.5, with normal or elevated LH.

Relative deficiency is normal FSH >5 with normal or elevated LH.

Absolute deficiency with low FSH.

Suppressors of FSH. : obesity with increased estrone feedback and suppression

Elevated A-dione to estrone feedback, most often with high LH and theca cell androgenization.

Elevated DHEA with direct and indirect FSH suppression. One out of 8 PCOS to possibly 1 in 4 have enzyme defect at 3 beta-HSD

Elevated DHEA to Adione to Testosterone to estradiol conversion, with FSH suppression

Pituitary dysfunction : Empty sella, or microadenoma in pituitary directly reducing FSH or increasing LH or ACTH or low GH

Mild hypothalamic dysfunction with low FSH and higher LH pulsatility, driving theca cell androgens, and lower FSH, etc.

Relative deficiency with nomal FSH:

Hormone transmission defects with failure of FSH to reach the target receptor

Capillary occlusive disease from clotting imbalance, vasospasm, sticky platelets.

Thromophillia:

Fibrinolytic defects:

Sticky platelets, secondary to above and activation.

Spasm from 11-deoxycorticosterone from accumulation due to partial enzyme defect.

Spasm due to disorder of arginine metabolism with low nitric oxide formation. Kidney or liver disease or psoriasis or sickle cell dz or hyperhomocysteinemia.

Lack of IGF-1, a permissive hormone, to allow FSH to effect stimulation.

Low GH output, with low IGF-1 in second half of day.

Low GH to IGF-1 conversion: liver disease

FSH receptor defect:

Tend to respond better to endogenous FSH than injectable FSH

Defective FSH:

Tend to respond better to exogenous FSH.

Potential for FSH receptor antibodies.

Antibodies against FSH more so in infertile and ovarian failure

Hum Reprod. 1994 May;9(5):806-11.

Aetiological factors involved in the low response to gonadotrophins in infertile women with normal basal serum follicle stimulating hormone levels.

Pellicer A, Ballester MJ, Serrano MD, Mir A, Serra-Serra V, Remohi J, Bonilla-Musoles FM.

Instituto Valenciano de Infertilidad, Valencia University School of Medicine, Spain.

Abstract

This study was designed to investigate possible aetiological factors involved in the low response to gonadotrophins in women with normal basal serum follicle stimulating hormone (FSH) concentrations, stimulated for assisted reproduction. Nine of these patients with normal basal serum FSH and 22 normal controls (five of whom had had a normal response to previous gonadotrophin stimulation) were prospectively subjected to: (i) transvaginal pulsed colour Doppler ultrasound evaluation of the vessels surrounding the dominant follicle for blood flow impedance analysis, (ii) the clonidine test to explore the ability of the pituitary to release growth hormone, and (iii) detection of anti-granulosa cell auto-antibodies in blood using an enzyme-linked immunosorbent assay (ELISA). The pulsatility and resistance indices (PI, RI) were significantly ($P < 0.01$) higher in the women with low responses as compared to the controls on days -1 and 0 (day 0 = ovulation). Seven out of the nine low responders were out of the range calculated for normal values after evaluation of the controls. A significant ($P < 0.05$) decrease in the secretion of growth hormone 60-90 min after clonidine ingestion was observed in the low responders as compared to five controls with previous normal response to ovarian stimulation. Six out of the nine low responders showed a negative clonidine test. No increase in anti-granulosa cell auto-antibodies was observed in the low responders as compared to the controls, including normal responders. In conclusion, an abnormal follicular blood flow impedance in the natural cycle may be related to low responses to gonadotrophins in patients with normal serum FSH concentrations.(ABSTRACT TRUNCATED AT 250 WORDS)

PMID: 7929726 [PubMed - indexed for MEDLINE]

Evidence of gonadal and gonadotropin antibodies in women with a suboptimal ovarian response to exogenous gonadotropin.

Meyer WR, Lavy G, DeCherney AH, Visintin I, Economy K, Luborsky JL.

Department of Obstetrics and Gynecology, Yale School of Medicine, New Haven, Connecticut.

Comment in:

- Obstet Gynecol. 1990 Nov;76(5 Pt 1):897-8.

Abstract

Failure to respond to human menopausal gonadotropin (hMG) with adequate ovarian stimulation is associated with a poor prognosis in subsequent cycles in women participating in an in vitro fertilization/embryo transfer program. Sera from 26 menstruating women (mean age 38 +/- 4.3 years) identified as "low responders" with either tubal or male factor infertility, mean baseline FSH values of 11 mIU/mL, and peak serum estradiol levels lower than 300 pg/mL were assessed for specific antibodies to human ovary and gonadotropins. Twenty-five infertile women with tubal or male factor infertility with a good response to hMG served as controls. Ninety-two percent of low responders had antibodies to FSH and 65% had antibodies to LH when assessed by enzyme-linked immunosorbent assay. Similarly, 77% of low responders had ovarian antibodies. No hepatic antibodies were found in the sera of low responders, indicating that the positivity was not a general interaction with cell components. None of the "good responders" had antibodies to gonadotropins or to ovarian or liver tissue. The significant differences in antibodies between the groups supports a possible immunologic cause for low ovarian stimulation response to gonadotropin.

PMID: 2109293 [PubMed - indexed for MEDLINE]

Prog Clin Biol Res. 1982;112 Pt A:111-21.

Immunoglobulin anti FSH receptor in the resistant ovary syndrome.

Charreau EH, Chiauzzi V, Cigorraga S, Escobar ME, Rivarola M.

PMID: 6298822 [PubMed - indexed for MEDLINE]

Fertil Steril. 1984 Nov;42(5):741-4.

Endocrine and immunologic studies in a patient with resistant ovary syndrome.

Talbert LM, Raj MH, Hammond MG, Greer T.

Abstract

A patient with the resistant ovary syndrome is reported. To evaluate the hypothesis that the hypogonadism might be the result of circulating antibodies to gonadotropin receptors or to an abnormal gonadotropin molecule, a series of clinical and laboratory studies was carried out. Administration of human menopausal gonadotropin had no effect on the serum estradiol level. The patient's serum did not affect follicle-stimulating hormone binding to a membrane preparation of monkey testes, suggesting the absence of antibodies to follicle-stimulating hormone receptors, nor did the patient's

serum affect in vitro responsiveness of human granulosa cells to human menopausal gonadotropin. Unresponsiveness to exogenous gonadotropins, combined with anatomically normal follicular apparatus and the absence of serum antibodies to gonadotropin receptors, supports the concept of a gonadotropin receptor or a postreceptor defect.

PMID: 6092154 [PubMed - indexed for MEDLINE]

Polycystic Ovarian Syndrome: Absolute or relative FSH deficiency. Permissive role of GH/IGF-1 and hormone transmission defect.

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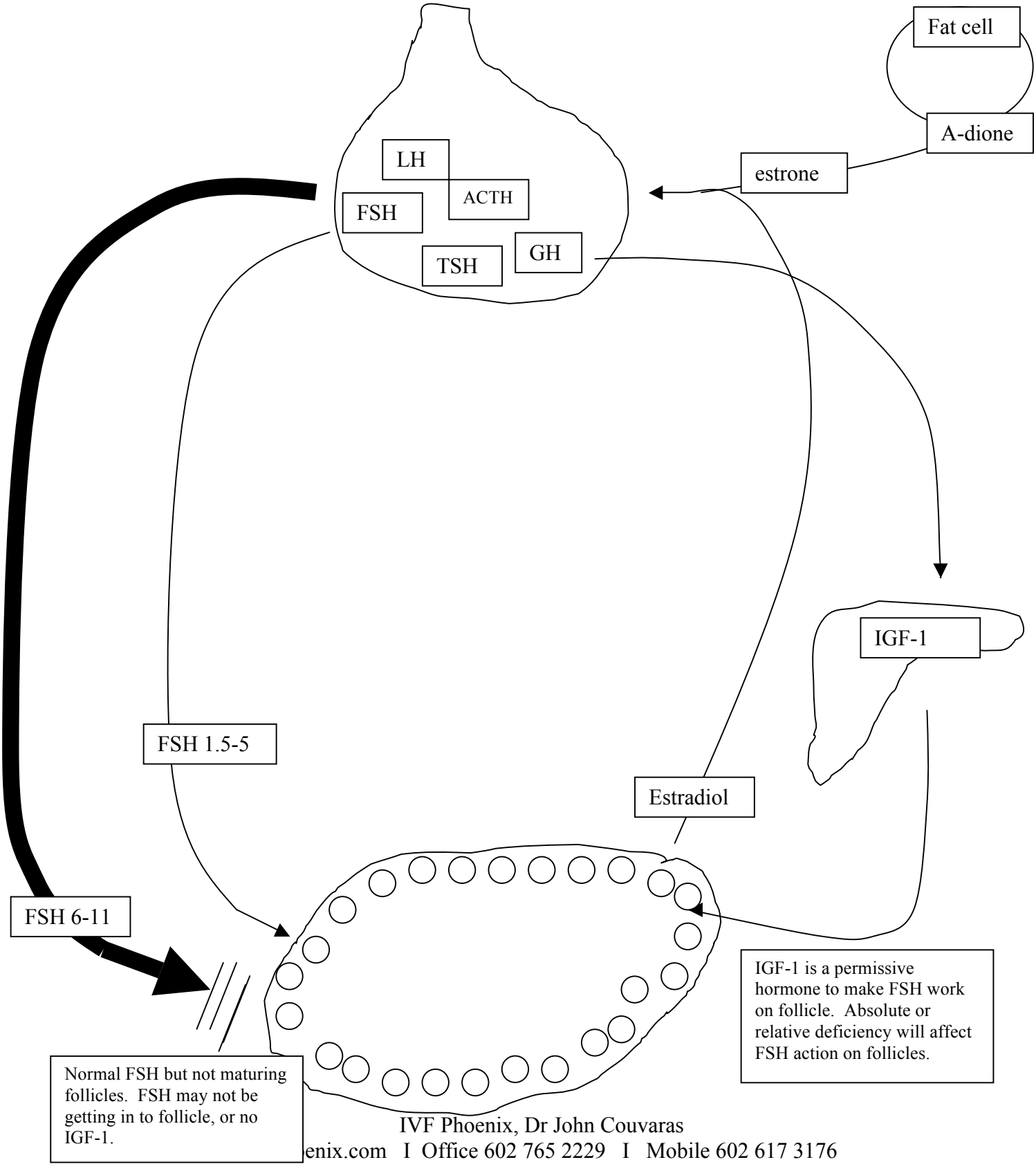

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