

Abstract:

**Polycystic ovarian disease:**

**AN UPDATE**

Polycystic ovarian syndrome (P.C.O.S.) is a condition characterized by ovaries with multiple small follicles which do not mature to a dominant size leading to ovulation. This is one of the leading causes of infertility. A recent international consensus has emerged on P.C.O.S.. Therefore, the goal of this publication is to review the new diagnostic criteria and therapeutic tools for P.C.O.S., as well as the order in which these therapeutic tools should be used.

**I. Background**

In 1935, Stein and Leventhal first describe this syndrome with 7 initial cases (1). In fact, we can find in the literature several reported cases prior to this publication including one by Achard and Thiers who had already described this clinical entity. They published in a bulletin of "L'Académie de médecine" (Paris) a group of women with severe hirsutism, hyperglycemia and irregular periods in an article titled: «Le diabète des femmes à barbe» (Diabetes in women with beard) in 1921. A series of hypothesis on the adrenal source of hyper androgenism or decrease aromatase activity were suggested and subsequently rejected.

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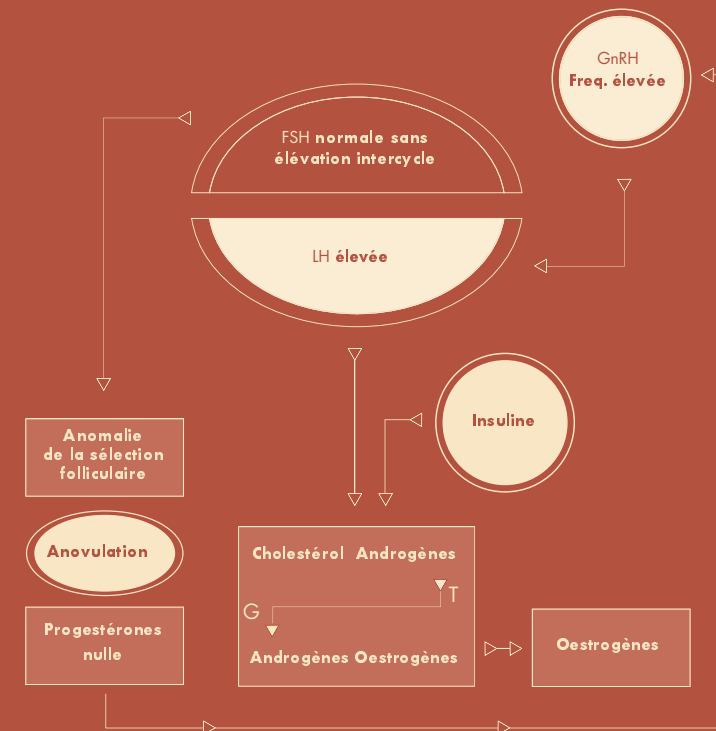
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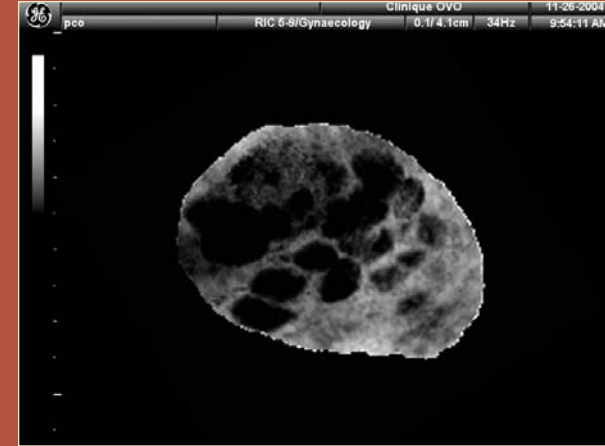
The development of these results, so far, illustrates well the various hypotheses issued to better understand this syndrome.



During the 70's, Dr. Yen suggested that abnormal secretion of LH and FSH from the hypothalamo-pituitary axis was responsible for P.C.O.S. (2). In 1976, Khan showed that abnormal insulin receptors leading to insulin resistance was often present in P.C.O.S. (3). A few years later Burghen and Givens showed that insulin resistance where part of P.C.O.S. (4).

Most of the recent data point to a genetic origin of P.C.O.S.. The exact mode of transmission remains unknown although an autosomal dominant pattern modified by environmental factors has been suggested. Many genetic studies are currently in progress and may help us explain the metabolic ovarian and gonadotropin abnormalities observed in P.C.O.S..

**II. Diagnosis of P.C.O.S**



**Free testosterone = Total testosterone / SHBG x 100**

LH measurement is not clinically useful. Ultrasound criterias for P.C.O.S. include bigger or equal to 12 follicles 2-9mm per ovary +/- ovarian volume bigger than 10ml. Previously described morphological criterias, including sub cortical disposition of follicles, hyper echogenicity and increased vascularity of the ovarian stroma, are not essential to the diagnosis of P.C.O.S..

No clinical test is available for the diagnosis of insulin resistance. Acanthosis nigricans is a physical sign which can be observed quite often in women with insulin resistance (3). In such a case, dark cutaneous lesions in the neck and the axilla are noted. No criteria of insulin resistance is required to make the diagnosis or to decide on the best therapeutic tool for P.C.O.S..

21-hydroxylase deficiency is associated with a 17 hydroxyprogesterone (17OHP) level and an increased androgen production. Its transmission is autosomal recessive. The incidence of being a carrier is 1/50 in the general population, and may lead to sexual ambiguity at birth. When testosterone is high, the 17-hydroxyprogesterone must be measured to make the diagnosis.

A consensus conference sponsored by the ESHRE and the ASRM, was held in Rotterdam in May 2004. In order to standardize the definition of P.C.O.S.(5), the following criteria's were agreed upon:

- **Oligo or anovulation**
- **Clinical or laboratory Hyper androgenism**
- **Ultrasonographic appearance of polycystic ovaries**

Two of these criterias were sufficient to make the diagnosis of P.C.O.S. after the exclusion of 21-hydroxylase deficiency or virilizing tumor of the ovaries or adrenals.

The diagnosis of hyper androgenism is made mainly by the presence of hirsutism. When there is no hirsutism, the free testosterone must be measured.

**III. Treatment TO INDUCE OVULATION**

**1. INSULIN SENSITIZING AGENTS**

We should always encourage P.C.O.S. patients to lose weight and to exercise since even a small weight loss can reestablish ovulation or increase the sensitivity to ovulation inducing agents. But it is often easier to prescribe Metformin than to change the life habits of the patient.

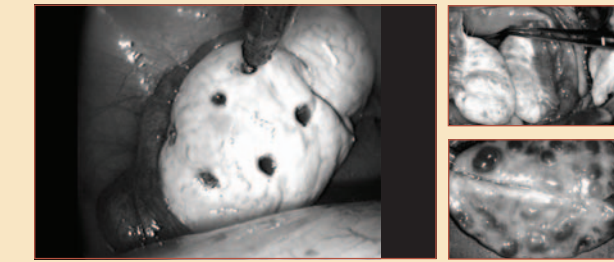
Insulin resistance can be present in normal weight P.C.O.S. patients. The higher insulin level predisposes to diabetes and cardiovascular disease. Insulin sensitizing agents have been showed to be effective.

The most widely used treatment is Metformin at a dose of 500 mg T.I.D.. It is recommended to increase the dosage progressively over a few weeks in order to decrease gastric side effects. Certain patients will respond to higher dosage (850 mg T.I.D.). The use of Metformin will reestablish regular cyclicality in 68 to 91% of cases.(6,7)

**2. OVARIAN STIMULATION**

Ovarian stimulation with Clomiphene citrate (CC) remains for many, the first line of treatment in order to induce ovulation in P.C.O.S..This treatment is simple and relatively inexpensive leading to an ovulation rate between 57% and 91%, and a pregnancy rate between 27% and 40%. Approximately 50% of pregnancies are achieved during the first 3 cycles of treatment.

When insulin sensitizing agents are used as first line of treatment and anovulation persists after 3 months, Clomiphene citrate should be added. This will lead to a 75% ovulation rate and a 55% pregnancy rate (8). If anovulation persists, low dose of FSH (super ovulation) can be used, but care must be taken (low dose) in order to prevent multiple follicular development.



**3. OVARIAN DRILLING**

This treatment has replaced the historical treatment of ovarian wedge resection. It is used mainly with Clomiphene resistant patients. This treatment modality has the advantage of normalizing the hormonal environment with an 80% ovulation rate, without the risk of hyper stimulation syndrome and multiple pregnancies (9). This technique has the unfortunate risk of creating pelvic adhesions.

**4. IN VITRO FERTILIZATION**

In vitro fertilization is a treatment tool which is used following the failure of less invasive treatment modalities. It offers a lower risk of multiple births by replacing only a small number of embryos, compared to super ovulation (5.0).

The major risk of IVF with P.C.O.S. patients is the risk of hyper stimulation syndrome (OHSS). This is increased in P.C.O.S. like ovaries on ultrasound even with women who don't have P.C.O.S.. Therefore, lower dose of FSH should be used with these patients.

In cases when too many follicles are being stimulated, a reduction in medication "step down" or arrest of medication (coasting) for a few days should be done in order to reduce the risk of OHSS. The use of GnRH antagonists could also reduce the risk of OHSS.

**5. IN VITRO MATURATION**

This method helps to prevent hyper stimulation syndrome but so far the implantation rate reported remains well below those reported in classic IVF.

**IV. Long term prognosis of P.C.O.S.**

The long term prognosis of P.C.O.S. is linked to the increase in cardiovascular diseases, insulin resistance and obesity. It is very important to recognize the metabolic syndrome which is associated with an increase cardiovascular risk.

**"DEFINITION OF METABOLIC SYNDROME"** Presence of at least 3 of the following criterias:

- **Central obesity** (waist bigger or equal to 88 cm)
- **Arterial hypertension:** systolic bigger or equal to 130 diastolic bigger or equal to 85
- **Hypertriglyceridemia** Low HDL : bigger than 0.5 gr/L
- **Elevated glycemia :** "Fasting sugar" 1.26gr/L
- **2 hours sugar** 1.99 gr/L

Cardiovascular risk has only been showed to be elevated with P.C.O.S. patients over 55 years of age. Gestational diabetes and type II diabetes is increased 3 fold: Preeclampsia, dyslipidemia and endometrial cancer are also increased. The use of insulin sensitizing agents may also be used with P.C.O.S. patients outside the infertility context in order to reduce the long term complications of the metabolic syndrome.

**V. Conclusion**

P.C.O.S. is the most frequent endocrine disorder in reproductive age women affecting between 5 and 10% of the population. It is characterized by follicular development arrest at between 8-9 mm. The pathophysiology of anovulation in P.C.O.S. leading to infertility is not yet fully understood. Recognition of the metabolic syndrome plays an important role in the long term prognosis of these patients.

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