Reproductive System Outcome Among Patients with Polycystic Ovarian Syndrome

Enrico Carmina, MD

KEYWORDS

• PCOS • AMH • Ovulatory PCOS • Fertility • Hyperandrogenism • Insulin resistance • Infertility • Ovarian function

KEY POINTS

- Polycystic ovarian syndrome (PCOS) is a heterogeneous disorder and the anovulatory phenotype, although the most common in patients who are referred to specialized clinics, may not be the most common in general population.
- The association of a derangement of early follicle development and increased insulin level seems to be the main mechanism determining anovulation.
- Because of the role of increased insulin levels in anovulation of women with PCOS, lifestyle represents the first step in any treatment of anovulation in this disorder.
- Changes in ovarian function during later reproductive adult age may be particularly beneficial in women affected by PCOS determining appearance of normal ovulatory cycles and fertility.
- Menopausal age is probably delayed in women with PCOS but long-term follow-up studies are needed to confirm this hypothesis.

REPRODUCTIVE OUTCOME IN POLYCYSTIC OVARY SYNDROME: ANOVULATORY AND OVULATORY PATIENTS

For many years it was believed that polycystic ovary syndrome (PCOS) is characterized by irregular menses and infertility. In the early 1990s the National Institutes of Health definition of PCOS included chronic anovulation as a cardinal symptom of the disorder.[1] However, in the following years several studies indicated that many patients could present a very similar disorder but normal ovulatory cycles.[2–4] Finally, Rotterdam and Androgen Excess definitions of the syndrome acknowledged that ovulatory patients are also part of PCOS.[5,6]

It is now well understood that PCOS may present with different clinical patterns[7–9] and that the anovulatory phenotype, although the most common in patients who are

The author has nothing to disclose.
Reproductive Endocrinology Unit, Department of Mother and Child Health, University of Palermo, Via delle Croci 47, Palermo 90139, Italy
E-mail address: enrico.carmina@ae-society.org

Endocrinol Metab Clin N Am 44 (2015) 787–797
http://dx.doi.org/10.1016/j.ecl.2015.07.006 **endo.theclinics.com**
0889-8529/15/$ – see front matter

referred to specialized clinics,[10,11] may not be the most common in the general population.[12–14] The few epidemiologic studies that have tried to assess the prevalence of PCOS in the general population have found that ovulatory patients with PCOS are as common[12] or more common[13,14] than anovulatory patients with PCOS. Of course, many ovulatory patients are not cured or are not referred to clinics specialized in infertility or in PCOS treatment.

All this information reopens an old question: what is the mechanism of anovulation in PCOS? Why are some patients with PCOS ovulatory, whereas others are anovulatory? A major difficulty in answering this question results from the limited understanding of pathophysiology of PCOS. Although the main elements of the syndrome have been characterized, the causes and the pathophysiologic mechanisms remain largely undetermined. New information coming from genome-wide association studies has confirmed that in most cases PCOS depends on a particular genetic background with some gene polymorphisms (DENND1A, THADA, luteinizing hormone [LH] receptor) being particularly common.[15–17] How this genetic background determines the syndrome is still unclear but initial data suggest that these gene polymorphisms may be based on two main elements of the syndrome: increased ovarian androgen production and derangement of early follicle development.[18–20] No sufficient information exists about the relationship of this genetic background with the ovulatory or anovulatory status, although the large Chinese genome-wide association studies have been performed in patients diagnosed according to Rotterdam criteria and therefore also include ovulatory patients.[15]

MECHANISMS OF ANOVULATION IN POLYCYSTIC OVARY SYNDROME

Most available data suggest that anovulation in PCOS is not the consequence of increased androgen ovarian secretion. Although patients with the classic National Institutes of Health anovulatory phenotype tend to have higher androgen levels than patients with the hyperandrogenic ovulatory phenotype,[21,22] high androgen levels may be found in patients with no PCOS without determining anovulation.[22,23]

It has been suggested that the arrest of antral follicle growth and anovulation are the consequence of the derangement of early follicle development.[24] It has been shown that granulosa cells cultured from follicles derived from anovulatory women with PCOS are hyperresponsive to follicle-stimulating hormone (FSH) in terms of estradiol production.[25,26] When granulosa cells from ovulatory patients with PCOS were evaluated, these cells behaved normally in terms of estradiol response to FSH and responded to LH only when taken from a larger dominant follicle.[27] On the contrary, granulosa cells taken from anovulatory PCOS tended to be hyperresponsive to FSH and in some instances responded to LH also when these cells were taken from small (3–4 mm) follicles.[27] The inappropriate response in small follicles to LH could result in terminal differentiation of the granulosa cells and thence in premature arrest of follicle growth.[24] Because in the same studies there was a large heterogeneity in the behavior of studied follicles of anovulatory women, with granulosa cells of some follicles responding normally to LH,[27] mathematical models have been developed suggesting that in a heterogeneous population of small follicles, if a group of follicles is relatively more mature, anovulatory arrest develops.[24]

However, it is unlikely that the derangement of early follicle development is the only cause of chronic anovulation in PCOS. Genetic studies have been unable to differentiate between ovulatory and anovulatory patients with PCOS.[28] Importantly, most anovulatory women with PCOS become ovulatory when they lose weight, and an increase of body weight may transform an ovulatory woman with PCOS into an anovulatory patient