PCOS: An heterogeneous condition with multiple faces for multiple doctors

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In this issue of EJE, you will find an exhaustive review of the polycystic ovary syndrome (PCOS), an European Endocrine perspective, written by the European Society of Endocrinology taskforce, led by Renato Pasquali (1), in collaboration with European leading experts. This remarkable perspective presents the multiple faces of this very frequent and complex syndrome as well as diagnostic tools and treatment options.

The disease has been coined after the classical description by Irving Stein and Michael Leventhal in 1935, but this condition has been known since antiquity (2, 3). We now all agree on how to define this heterogeneous condition (establishment by the Rotterdam consensus conference in 2003 (4, 5) and recently confirmed by the NIH in the USA in 2012 (6)). PCOS is also frequently associated with metabolic dysfunction that may induce an increased cardiovascular (CV) disease risk (7), although disease endpoints are not well documented as yet (8).

Supposedly PCOS is responsible for both infertility and increased CV risk. Is it not amazing that this condition has not yet disappeared! This is probably due to the fact that the PCOS phenotype and severity of the disease vary considerably. Moreover, the phenotype varies throughout life and at certain times in life; when excess weight is controlled, the disease may become silent.

The second puzzle remains the underlying disease mechanisms. Evidence is accumulating that the expression of the disease is under genetic control (presumably as an autosomal dominant disease) (9). Genes implicated in androgen synthesis within the ovary may be involved in this, such as DENND1A as recently suggested (10). However, gene–environment interactions definitely share the responsibility (11). Importantly, excess weight and insulin resistance are also clearly

implicated, although to variable degrees. Insulin *per se*, through IGF1R signaling or through classical insulin receptor signaling, can enhance androgen secretion and induce multifollicular development. This has also been elegantly shown in women with an extreme form of insulin resistance (12, 13).

At the end of the day, when the pathophysiology becomes clearer involving androgen excess within the ovary, along with high insulin action on the theca cells, two outstanding questions remain to be answered:

- 1 What are the genes involved? As discussed earlier, DENND1A is clearly one of the candidates, but PCOS is indeed a multigenic disease. Modern genetics, such as genome-wide association study and more recently next generation sequencing, is clearly bringing important novel information as shown by various investigators in recent years (14, 15). Genes implicated in adipose tissue function may also be involved. On top of this genetic background, environment (i.e. body weight) and endocrine disruptors may be held responsible for the aggravation of the latent disease.
- 2 The second question remains the metabolic risk, obvious in some studies, but probably less obvious in others. This discrepancy may be related to study design imperfections and the variable degree of CV risk depending on lipoprotein levels, glycemic control, blood pressure, and obviously excess weight.

What Pasquali *et al.* are brilliantly clearly describing is the multiple presentations of the disease, explaining that the bleeding problems and infertility frequently associated with oligo- or amenorrhea as observed by gynecologists, and the complaints related to hyperandrogenemia in women with PCOS as observed by many endocrinologists,

are representing the wide and diverse spectrum of the same disease. Finally, physicians involved in diabetes and obesity probably meet a lot of these patients too.

It is clear that pediatricians, infertility specialists, endocrinologists, and specialists in obesity and metabolic syndrome should combine their efforts and recognize the proteiform presentation of PCOS and bring clinical care to these women throughout their life. It is also clear that general practitioners should be encouraged to read this position paper, which may help them in providing adequate care to affected women. Whether or not the name, which is now attached to the ovarian morphology, should be changed to another acronym implicating the metabolic risk is an ancillary question as long as the pathology and wide scope of clinical implications are recognized and patient care designed accordingly regardless of the initial complaint of the woman and background of the treating physician.

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