PCOS: UPDATE ON PATHOGENESIS, DIAGNOSIS AND TREATMENT

PROF. DR. ENRICO CARMINA
Endocrinology Unit, School of Medicine, University of Palermo, Italy

Polycystic Ovary Syndrome is a very heterogeneous disorder that includes several different forms. The clinical heterogeneity depends on different genetic patterns that may determine the syndrome but also on epigenetic and environmental influences. In some patients, the contemporaneous presence of several genetic alterations interesting reproductive and metabolic functions (androgen production, follicle regulation, insulin activity and production) may be sufficient for determining the syndrome. These altered genes may be also rare genes variants that regulate androgen secretion and/or follicle growth. In many other patients, PCOS appears in women who present a genetic risk for developing the syndrome, but the disorder needs some other nongenetic factors, that may be epigenetic (increased AMH and/or androgens during fetal life) or environmental (mainly obesity or exposure to oxidative stress).

Classic diagnosis according Rotterdam guidelines requires a combination of hyperandrogenism, chronic anovulation and polycystic ovaries (at least 2 of 3 of these factors) but increased AMH serum levels may substitute ovarian sonography in patients who present chronic anovulation and/or hyperandrogenism. In any of the Rotterdam phenotypes a metabolic (hyperandrogenism and or chronic anovulation associated to insulin resistance and obesity) or a reproductive (hyperandrogenism and/or chronic anovulation but normal body weight and mild or no insulin resistance) should be distinguished.

Treatment depends on age and clinical problems. Infertility is common and depends on chronic anovulation. Clomiphene (sometimes associated to metformin) may determine ovulation and fertility but, in several patients, PMA is needed. Treatment of obesity with new drugs that mimic intestinal hormones may improve fertility.

Take Home Messages

- PCOS is a complex genetic disorder that is strongly influenced by epigenetic and environmental factors
- Diagnosis requires the finding of at least 2 out of 3 different alterations (hyperandrogenism and/or chronic anovulation and/or polycystic ovaries) but increased AMH may substitute polycystic ovaries in the diagnostic process
- Treatment depends on the age and the wishes of the patient but, in obese patients, new drugs reducing body weight may be necessary before starting a fertility program.

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NEW TREATMENTS OF OBESITY (SEMAGLUTIDE AND TIRZEPATIDE) AND THEIR IMPACT ON FERTILITY

PROF. DR. ENRICO CARMINA
Endocrinology Unit, School of Medicine, University of Palermo, Italy

Obesity is common in patients with PCOS and strongly influences the presentation of the syndrome, the metabolic risks and the response to infertility treatments. For many years, lifestyle modification programs that include diet and physical exercise have been considered the only possible treatment of obesity but long-term results are generally disappointing.

New drugs, semaglutide and tirzepatide, that mimic intestinal hormones (GLP-1 for semaglutide, GLP-1 and GIP for tirzepatide) are determining a complete change in the approach to obese patients who do not respond to lifestyle modification programs but their results on fertility are unclear.

In past 2 years we have treated for at least 6 months 112 overweight or obese PCOS patients with semaglutide and 48 overweight or obese PCOS patients with tirzepatide. Before and during treatment serum pancreatic amylase was measured and, in few patients, treatment was interrupted because a progressive increase of this pancreatic enzyme.

Our large experience and the analysis of the results show:
1. Normalization of body weight in almost all overweight PCOS patients with both drugs with little difference between semaglutide and tirzepatide. In 60% of these patients, reduction of body weight was associated to improvement in menstrual cyclicity and in fertility.
2. Reduction of at least 10% of body weight in 50% of PCOS patients with mild obesity (BMI 30- 34.9) treated with semaglutide and in 60% of patients treated with tirzepatide. Mean and % body weight reduction were larger with tirzepatide than with semaglutide. Improvement in menstrual cyclicity in most responsive patients were observed and response to fertility treatment improved in all responsive patients.
3. Reduction of at least 10% of body weight in 30% of PCOS patients with moderate (BMI 35-39.9) or severe obesity (BMI 40 or more) without main differences between semaglutide and tirzepatide.
4. High doses of both drugs did not improve the results. No significant changes in menstrual cyclicity in responsive patients were observed but response to fertility treatments improved in responsive patients.
In conclusion, new drug treatment of excessive body weight may significantly improve body weight in women with PCOS. Results are better in overweight and in patients with mild obesity than in patients with moderate or severe obesity.

Take Home Messages

- Semaglutide and tirzepatide are an important progress in treatment of excessive body weight
- The response to both drugs is very good in overweight patients with PCOS\
- In PCOS patients with mild obesity results are still good but several patients do not respond to both drugs. In general, reduction of body weight is larger with tirzepatide. All responsive patients show improvement in response to fertility treatments.
- Only one third of patients with moderate or severe obesity present a significant decrease of their body weight with these new drugs but responsive patents respond better to fertility treatments.