

## **INTRAUTERINE EVENTS AND RISK OF DEVELOPING PCOS**

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Polycystic ovary syndrome (PCOS) is a common disorder affecting 5-10% of women of reproductive age that often emerges post-menarche and that is hallmarked by androgen excess and a low ovulation rate. Less consistently, PCOS is characterized by hyperinsulinemic insulin resistance, dyslipidemia, increased abdominal adiposity, low-grade inflammation -as judged by a high ratio of neutrophil-over-lymphocyte count, by hypo-adiponectinemia or by high circulating C-reactive protein (CRP), interleukin-6 (IL-6) or transforming growth factor- $\alpha$  (TNF- $\alpha$ ) levels-, and the presence of polycystic ovaries (PCO) on ultrasound. This variant of PCOS may not be a primarily ovarian disease of pubertal onset, but could reflect a systemic disorder with origins in prenatal or prepubertal life.

At least two developmental pathways seem to lead to PCOS. One begins with a normal prenatal growth and continues, via simple obesity, to an absolute fat excess; the other begins with fetal growth restraint, continues in infancy with rapid catch-up of weight, and leads to hyperinsulinemia, low levels of total and high-molecular weight adiponectin, and to relative adiposity and visceral fat excess at the age of 4-6 yr. In late childhood, both pathways may converge to conform "pre-PCOS", a state characterized by hyperinsulinemia, adiposity, low-grade inflammation, amplified adrenarche (with or without precocious pubarche), and early-normal puberty and menarche, which may result in a shorter final stature. Finally, the two pathways diverge again, the "postnatal-overweight" pathway rather leading to PCOS-with-PCO, while the "prenatal-underweight" pathway is more often linked to an adult PCOS phenotype with glucose intolerance and without PCO. Insulin sensitization with metformin in girls with a low birthweight, and a history of precocious pubarche and "pre-PCOS", when started postmenarche, can revert the "pre-PCOS" state, but the benefits are readily lost upon discontinuation of therapy. In contrast, when metformin treatment is started in prepuberty -at age ~8 yr-, and is given across puberty, it delays pubertal onset, slows-down pubertal progression, postpones menarche, reduces total and visceral fat, normalizes the inflammation markers and the endocrine-metabolic profile, and thus holds a potential for heightening final stature and for reverting the development of full-blown PCOS. This normalizing effects seem to persist beyond stopping metformin intake.

In conclusion, markers have been identified along two pathways to PCOS. These markers allow for timely recognition of "pre-PCOS" and for intervention, with overweight-control and/or insulin sensitization. The early origins of PCOS may thus be pivotal in the development of the adult phenotype, and may partly determine the heterogeneity in the clinical presentation.