

Early Origins of Polycystic Ovary Syndrome: Hypotheses May Change without Notice

Francis de Zegher and Lourdes Ibáñez

Department of Woman and Child (F.d.Z.), University of Leuven, 3000 Leuven, Belgium; and Pediatric and Adolescent Endocrinology (L.I.), Hospital Sant Joan de Deu, University of Barcelona, 08950 Barcelona, Spain

Polycystic ovary syndrome (PCOS) is an evolving concept, as illustrated by its consecutive definitions. In 2004, the definition of PCOS in women changed from the classic National Institutes of Health (NIH) definition (clinical and/or biochemical androgen excess plus oligoovulation, with exclusion of specific etiologies such as hyperprolactinemia and 21-hydroxylase deficiency) (1) to the more inclusive Rotterdam definition (any two of the following three criteria, after similar exclusions: clinical and/or biochemical androgen excess, oligo- or anovulation, and polycystic morphology on ultrasound) (2). In 2009, the Androgen Excess Society launched a new definition that considers PCOS primarily as a disorder of clinical and/or biochemical androgen excess, plus either chronic oligoovulation and/or polycystic ovaries, still with exclusion of specific etiologies (3). The core of the consecutive PCOS populations, however, changed little over the past decades because it continues to consist of women with hyperinsulinemic androgen excess (4–6). This core still constitutes the majority of PCOS women diagnosed by the latest definition, which, just as the earlier definitions, remains to be validated in adolescent girls (3).

A better insight into the (epi-)genetics, early origins, and natural history of hyperinsulinemic androgen excess may sharpen the perspective of PCOS prevention and is therefore a priority in the current research agenda for PCOS.

A Beautiful Hypothesis on the Early Origins of PCOS

Goy and Robinson (7) showed in 1982 that female rhesus monkeys prenatally exposed to an exogenous excess of

androgens had ambiguous genitalia and developed a virilized behavior. Longitudinal follow-up of such monkeys disclosed, particularly in those with adult overweight, the emergence of a PCOS-like phenotype including hyperinsulinemic androgen excess, polycystic ovaries, elevated levels of circulating LH, dyslipidemia, visceral adiposity, and a reduced ovulation rate responsive to insulin sensitization (8). In sheep, a prenatal excess of exogenous androgens was found to lead first to genital virilization and fetal growth restraint, and then to a PCOS-like phenotype, particularly in those sheep who gained a lot of weight postnatally (9). In view of such consistent evidence, the concept of “prenatal androgen excess” gradually became a popular hypothesis on the origins of PCOS. However, doubts on the plausibility of this hypothesis persisted, partly because most women with PCOS do not have ambiguous genitalia and because unborn girls are thought to be protected from maternal androgen excess (if any) by the abundant aromatase activity of the human placenta.

“The Great Tragedy of Science: A Beautiful Hypothesis Slain by an Ugly Fact” (Thomas Huxley, 1894)

In this issue of *JCEM*, Hickey *et al.* (10) report on their first test of the “prenatal androgen excess” hypothesis in the human—a test as beautiful as the challenged hypothesis. These investigators performed a longitudinal study of 244 unselected girls recruited prenatally, along with their mothers, into the Raine cohort that was initiated in 1989 by John Newnham. Their test had enough power to dis-

close convincingly that maternal androgenemia (through pregnancy) and fetal androgenemia (at birth) were *not* elevated in girls who were at age approximately 15 yr diagnosed with PCOS by NIH or Rotterdam criteria. The authors conclude that their findings do not support the hypothesis that maternal androgens, within the normal range for pregnancy, directly program PCOS in the offspring. The “prenatal androgen excess” hypothesis thus seems to have failed its first major test in the human. For many reasons, however, it would be premature to abandon this hypothesis completely. It is still possible that the sampling schedule across pregnancy missed a brief window of maternal or fetal androgen excess. Alternatively, the applied PCOS definitions may not be valid for 15-yr-old adolescents and thus may be misleading. In this context, we emphasize that at least 34% of Hickey’s girls *without* PCOS (by NIH criteria) had menstrual irregularities and that at least 38% of them had a polycystic ovarian morphology. In view of such prevalences of PCOS features in control girls, extreme caution is warranted before conferring a diagnosis of PCOS to an adolescent girl (11, 12). In the absence of validated criteria for adolescent PCOS, the wisest approach may be to apply the most restrictive definition (NIH). Our experience would also humbly endorse any consensus that further restricts the diagnosis of PCOS to those girls who are at least 2 yr beyond menarche and who have androgen excess by both clinical and biochemical norms.

Hickey’s data may be the beginning of the end for one hypothesis, but they may also be the end of the beginning for another. Indeed, 56% of Hickey’s adolescents with PCOS (by NIH criteria) were overweight, and 25% were even obese; the body mass index (BMI) Z-score of the total PCOS subgroup averaged +1.05 with a SD of 0.80. These numbers imply that more than 90% of Hickey’s adolescents with PCOS have a BMI Z-score above 0.00. In other words, PCOS is about 10-fold more prevalent in girls with a BMI above than below the average. In Hickey’s cohort, BMI was the most discerning factor between girls with and without PCOS.

**“Facts Are Stubborn Things, and Whatever May Be Our Wishes, Our Inclinations, or the Dictates of Our Passion, They Cannot Alter the State of Facts and Evidence”
(John Adams, 1770)**

The link between adolescent PCOS and overweight is not limited to Hickey’s cohort in Australia. In *JCEM*’s most recent papers on PCOS in young American patients *unselected for obesity*, the average BMI values were 35.5 kg/m² at a mean age of 19.6 yr (13) and 33.9 kg/m² at 16.1

yr, the latter corresponding to a median BMI-for-age percentile of 98 (14). Thus, in adolescents, there appears to be a stubborn link between overweight/obesity and the phenotype nowadays labeled as PCOS. If the current PCOS definitions continue to be applied to adolescents, then most girls with so-called PCOS may in essence have no more than an ovarian epiphenomenon of their overweight, and presumably, this epiphenomenon is largely mediated by hyperinsulinemic insulin resistance and/or its correlates (14). This reasoning would also explain why the best therapy for adolescents with obesity/PCOS is lifestyle intervention rather than any of the conventional PCOS medications (15).

“Facts Do Not Cease to Exist Because They Are Ignored” (Aldous Huxley, 1927)

Although there is little doubt that overweight/obese girls are currently the largest subgroup of adolescents with PCOS, some small—and sometimes ignored—subgroups may also contribute to the elucidation of the early origins of PCOS.

One such subgroup is formed by female patients with a genetic lipodystrophy. Most women with a congenital generalized lipodystrophy (for example, due to an *AGPAT2* or *BSCL2* mutation) have long been known to develop hyperinsulinemic androgen excess, often with polycystic ovaries; more recently, a substantial fraction (up to 54%) of women with a partial lipodystrophy (for example, due to a *LMNA* mutation) was also shown to have features of PCOS (16, 17).

Another subgroup consists of girls with a combined history of low birthweight and precocious pubarche (appearance of pubic hair before age 8 yr, not to be confounded with precocious puberty), most of whom experience menarche before age 12 yr and develop hyperinsulinemic androgen excess (18). Low birthweight and advanced menarche are also known to confer risk for glucose intolerance in women with PCOS (19).

These small subgroups share a key feature in early life, namely a reduction in the expansion of sc adipose tissue. Regardless of their genetic or environmental origins, these early reductions are thought to diminish the subsequent capacity to store lipids sc (20–22).

Such nonobese adolescents with PCOS respond, without lowering body weight, to interventions with metformin (23), pioglitazone (24), or their combination with flutamide (24, 25). Metformin therapy, when started before puberty and given across puberty, may even prevent the development of PCOS in low-birthweight girls with precocious pubarche (26).

Toward a Next Hypothesis (To Be Slain) on the Early Origins of PCOS

The “adipose tissue expandability” hypothesis, recently proposed by Virtue and Vidal-Puig (27), allows the reconciliation of available evidence on hyperinsulinemic androgen excess. This hypothesis builds further on the concept of adipose tissue dysfunction, which explains the apparent paradox that insulin resistance may occur not only in obesity but also when there is a deficit of adipose tissue (20). The essence of the hypothesis is that sc adipose tissue has a limited capacity to increase its mass safely. This capacity is individually determined by a wide range of environmental and genetic factors. When sc adipocytes start to be overfilled, a lipotoxic state emerges. Lipotoxicity is characterized by dyslipidemia, an unfavorable adipocytokine profile, and lipid deposition in non-sc adipose tissue and in nonadipose organs such as liver, muscle, or pancreas. Lipotoxicity has adverse effects on metabolism, most notably on insulin action. According to this concept then, metabolic health is maintained as long as the adipose depot can accommodate the caloric supply safely, that is, without causing lipotoxicity. The concept thus implies that there is an individual setpoint beyond which further lipid storage is rapidly accompanied by insulin resistance and its correlates. Hyperinsulinemic androgen excess may commonly be driven by the exhaustion of the capacity to expand sc adipose tissue in a metabolically safe way (22).

Obesity ensuing from a chronically positive imbalance between energy intake and output can exhaust a normal capacity to store fat and lead to metabolic complications, including insulin resistance and androgen excess, and thus PCOS. This is the proposed explanation for the robust links between obesity, hyperinsulinemia, and hyperandrogenemia in women, links already established in prepuberty and persisting through puberty into adulthood (28). In the adipose tissue expandability concept of obesity/PCOS, any therapeutic weight loss should be tailored individually, the aim being a reduction until weight falls within a woman’s maximal fuel storage capacity. To gauge the latter, markers such as fasting glucose, insulin, lipids, C-reactive protein, neutrophil count, and high-molecular-weight adiponectin may be useful, but they remain to be validated in adolescents and women with PCOS.

The adipose tissue expandability hypothesis also offers a rationale for how obese women may escape from developing androgen excess, *i.e.* they seem to have an enlarged capacity to store fat sc. For example, a Caucasian background confers more sc capacity for fat storage than a South Asian or Far Eastern origin; accordingly, Indian, Chinese, and Japanese women tend to develop hyperinsulinemic androgen excess and polycystic ovaries in re-

sponse to less overweight than Caucasian women (reviewed in Ref. 22).

Human newborns, especially the girls, are the most adipose of all mammalian newborns, and more than 90% of their adipose tissue is located sc; even baby seals have a much lower level of sc adiposity (reviewed in Ref. 22). An accelerated expansion of adipose tissue before birth and in early infancy confers protection against obesity-linked insulin resistance in adulthood (29), perhaps by augmenting the recruitment of sc adipocytes or their individual capacity to store fat. In countries like India, Pakistan, and Bangladesh, where still about one fourth of the girls have a birthweight below 2.5 kg, an increment of weight gain in early life may be among the most effective approaches to prevent disorders like PCOS in later life.

Given that testosterone and dihydrotestosterone are potent inhibitors of adipogenic differentiation of preadipocytes into adipocytes (30), one of the pathways whereby a prenatal excess of exogenous androgens may result in a PCOS-like phenotype in some female mammals could be via the reduction of sc adipogenesis within a critical window of early development.

Conclusion

A simple extension of the adipose tissue expandability hypothesis allows us to bring the pathogenesis of major — not all — PCOS variants together under the same umbrella, namely under the exhaustion of the sc storage of fat. This unifying hypothesis can also harbor the seemingly conflicting evidence that a prenatal excess of exogenous androgens may induce a PCOS-like phenotype in experimental models, but that human PCOS is not commonly preceded by maternal/fetal androgen excess, as elegantly shown by Hickey *et al.* in this issue of *JCEM*.

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Address all correspondence and requests for reprints to: Lourdes Ibáñez, Pediatric and Adolescent Endocrinology, Hospital Sant Joan de Deu, University of Barcelona, Barcelona, Spain. E-mail: francis.dezegher@uzleuven.be or libanez@hsjdbcn.org.

F.d.Z. and L.I. are Senior Clinical Investigators of the Fund for Scientific Research (Flanders, Belgium) and Centro de Investigación Biomédica en Red de Diabetes y Enfermedades Metabólicas Asociadas, Instituto de Salud Carlos III (Spain).

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