Toward Adolescent Prevention of Adult Anovulation in Polycystic Ovary Syndrome

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3.1 Definition, Origins, and Diagnosis of Adolescent PCOS

Recent changes in the paradigm of adolescent polycystic ovary syndrome (PCOS) are summarized in Table 3.1 [1].

Adolescent PCOS is defined by the co-presence of irregular menses (as proxy for oligo-anovulation) and androgen excess (clinical + biochemical evidence) at least 2 years after menarche, and by the exclusion of disorders such as an androgen-secreting tumor; ovarian morphology is not a criterion [2].

Worldwide, PCOS is the most prevalent endocrinopathy of adolescent girls (≈10%), and its prevalence is rising since, in essence, adolescent PCOS is the outcome of a mismatch between a relatively energy-sparing (epi)genetic background and a relatively energy-rich environment [3]. In any variant of such a mismatch, there is a chronic need to store more fat than is safely feasible in subcutaneous adipose tissue, and the lipid excess ends up being stored in ectopic depots, notably in liver and viscera (= hepato-visceral fat excess, or central obesity). Adolescent PCOS is typically driven by an ensemble including central obesity, insulin resistance, LH hypersecretion, and low concentrations of circulating high-molecular-weight (HMW) adiponectin, which is a key adipokine with insulin-sensitizing properties [2–4].

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Table 3.1 Adolescent PCOS: a changing paradigm

	Past	Present
The essence of PCOS	Highly heritable disorder of the hypothalamic-pituitary-ovarian axis	Mismatch disorder in obesogenic world: Absolute or relative excess of subc fat leads to ectopic adiposity and insulin resistance, on a background of genetic susceptibility (involving >19 genes)
Sequence	PCOS → fat excess	Fat excess → PCOS
Forerunners	Early androgen excess?	Upward mismatch between BW Z-score and subsequent BMI Z-score → early adrenarche/pubarche, → early puberty/menarche
Clinical presentation	Hirsutism, severe acne/seborrhea, irregular menses	
Diagnostic criteria • Androgen excess • Oligo-amenorrhea • Polycystic ovaries (US)	Presence of any 2 of the 3 criteria	Presence of the 2 upper criteria

Subc subcutaneous, *BMI* body mass index, *BW* birth weight, *US* ultrasound
Adapted from [1]

Adolescent PCOS is commonly heralded by an upward Z-score change from weight-at-birth to body mass index (BMI)-in-childhood; weight-at-birth tends to be below average in non-obese PCOS, but not in obese PCOS girls [5]. The magnitude of this Z-score increment is partly driven by genetic variants that control appetite and/or BMI [6]. A higher Z-score increment associates with more insulin resistance and with more central adiposity in childhood [7], and also with a faster maturation toward pubarche and menarche [8, 9].

Oligo-anovulation may result from an adaptive neuroendocrine response to a deficit of central fat (as in athletic amenorrhea) [10], or to an excess of central fat (as in obese PCOS and non-obese PCOS) [11, 12], and there is genetic variation in the hypothalamo-pituitary responsiveness to central adiposity. Girls genetically attuned to the harshest environments are nowadays the most vulnerable to develop PCOS under circumstances of physical inactivity and/or nutritional abundance [13, 14].

3.2 Treatment of Adolescent PCOS: Lifestyle, Estro-Progestagen, SPIOMET

There is still no EMA/FDA-approved treatment for adolescent PCOS. Given the crucial role of central fat excess, the prime aim should be a preferential loss of central fat. Such a loss can revert the entire PCOS phenotype, and it can be achieved with sustained lifestyle measures that involve multiple factors including diet, exercise, sleep, and biorhythm, all within an environment that may remain stubbornly obesogenic [15].

Failure to sustain these lifestyle measures is frequent, and the standard approach is then to add an oral estro-progestagen contraceptive [2, 16]. This adjunct silences the gonadotropic axis, reduces the androgen excess [in part via a pharmacological increment of circulating sex-hormone-binding globulin (SHBG)], and leads to regular and

anovulatory pseudo-menses [2, 16], but it does not solve the core (or central-fat) problem, and thus channels the adolescent girl toward a post-treatment rebound of androgen excess and oligo-anovulation, in other words, toward adult PCOS [12].

Alternative adjuncts could aim at enhancing the effects of lifestyle measures, by switching fat from ectopic to eutopic depots, and/or by stimulating brown adipose tissue (BAT) activity, thereby increasing energy expenditure. A first example of such an alternative adjunct could be SPIOMET, which is a fixed low-dose combination of three old and safe generics that act through different pathways: spironolactone (only 50 mg/day), pioglitazone (only 7.5 mg/day), and metformin (only 850 mg/day).

Spironolactone has been used for >50 years as a mixed anti-androgen and anti-mineralocorticoid, and has recently been identified as a potent activator of BAT [17, 18], and thus as a potential driver of energy expenditure. There are no major safety concerns when spironolactone is dosed at only 50 mg/d (≤1 mg/kg/day) in adolescent girls with PCOS [19].

Pioglitazone has been used for >20 years as an anti-diabetes medication, in four- to six-fold higher doses than in SPIOMET. The observation that low-dose pioglitazone (7.5 mg/day) raises the concentrations of circulating HMW adiponectin [20] suggests that such a low dose acts as an inhibitor of cyclin-dependent kinase 5 (CDK5)-mediated phosphorylation of peroxisome proliferator-activated receptor (PPAR)-Y rather than as an activator of PPAR-Y [21], also in the hypothalamus [22]. The uncertainty around a potential risk for bladder cancer in older male patients with diabetes and with long-term, high-dose pioglitazone treatment has recently been cleared: there is no evidence for this risk, which is now considered to have been "a red herring" [23].

Metformin has been known for >20 years to have normalizing effects on the endocrine-metabolic state [24] and on the ovulation rate [25] of adolescent girls with PCOS. Metformin monotherapy failed to reach the market for adolescent PCOS because it proved to be too cheap to be commercially viable [26]. The pharmacokinetics of metformin in girls compare to those in women [27]. Metformin is well tolerated by adolescent girls with PCOS [24, 25], and also by younger girls at high risk of developing PCOS [28].

SPIOMET components have partially overlapping benefits that are essentially present with low doses, and have different side effects that are essentially absent with low doses. Hence, the SPIOMET concept is to aim for the presence of cumulative effectiveness, and for the absence of safety concerns.

3.3 SPIOMET Experience in Adolescent Girls: Limited but Promising

So far, the effects of SPIOMET have only been investigated in two randomized controlled pilot studies (ISRCTN29234515 and ISRCTN11062950) that were based in Barcelona between 2012 and 2019 and were performed in non-obese girls with PCOS and with no need for contraception (total N = 62; mean age 16 year and BMI 24 Kg/m^2; treatment for 1 year; ovulation assessment during the post-treatment year). In these two studies, the effects of SPIOMET were compared to those of an oral contraceptive (OC; ethinylestradiol-levonorgestrel).

Proof-of-concept by ISRCTN29234515 has been reported in 2017 [12] and has recently been confirmed by ISRCTN11062950 [29]. Indeed, pooled results from both studies disclosed that SPIOMET has more normalizing effects than OC, notably on insulin sensitivity, visceral fat, and liver fat (Fig. 3.1); there were a mean threefold (and even a median fivefold) more ovulations post-SPIOMET than post-OC (Fig. 3.2); normovulation was only observed post-SPIOMET; anovulation was >ten-fold more frequent post-OC [29].

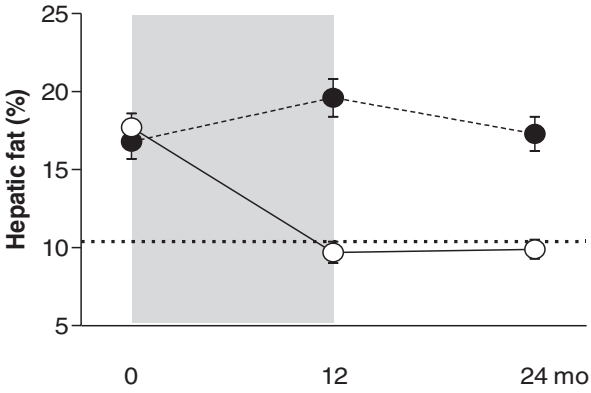

Fig. 3.1 Hepatic fat content (by magnetic resonance imaging) in non-obese adolescent girls with PCOS who were randomized to receive either an oral contraceptive (OC; N = 31; dark circles) for 12 months or a low-dose combination of spironolactone-pioglitazone-metformin (SPIOMET; N = 31; white circles) for 12 months; subsequently, both subgroups were untreated for 12 months. Body weight did not change in either subgroup. The dotted line indicates the average level in healthy control girls of similar age. Results are expressed as mean ± SEM. P < 0.0001 for on-treatment change between subgroups. Modified from Reference 29

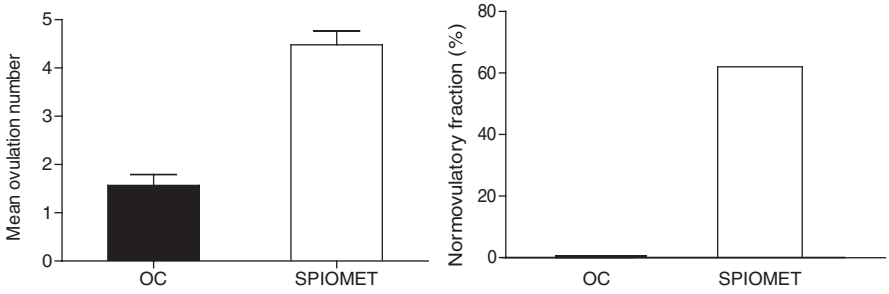

Fig. 3.2 Post-treatment ovulation results in adolescent girls with polycystic ovary syndrome who were randomized to receive an oral contraceptive (OC) or low-dose spironolactone + pioglitazone + metformin (SPIOMET) for 12 months and were subsequently followed for 12 months without treatment. Ovulations were assessed twice over 12 weeks, for a total of 24 weeks, between the study timepoints of 15–18 months (= post-treatment months 3–6) and 21–24 months (= post-treatment months 9–12). Both the ovulation number and the normovulatory fraction (%) were significantly higher ($p < 0.0001$) in girls receiving SPIOMET

3.4 Perspective

Adolescence may provide an early opportunity to normalize the PCOS phenotype, and to prevent subsequent oligo-anovulation, and its consequences and comorbidities (Fig. 3.3).

SPIOMET's efficacy and safety remain to be corroborated by a randomized, double-blind, multicenter study wherein the effects of SPIOMET (in a single tablet) are tested versus placebo, versus pioglitazone, and versus pioglitazone-plus-spironolactone, all on a background of standardized lifestyle measures, in larger study populations that are more diverse in genetic background and that span broader ranges of age and BMI.

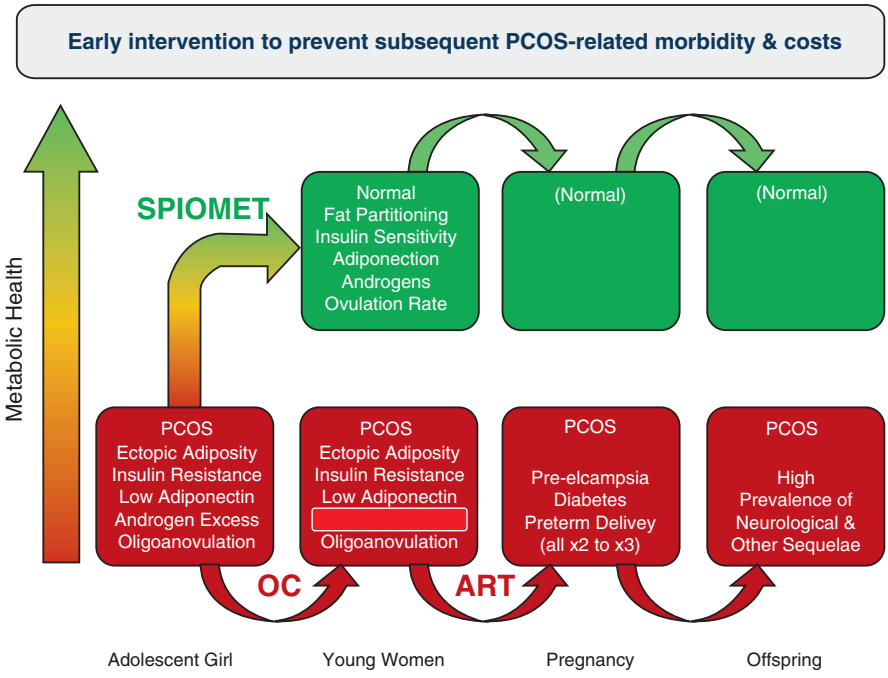

Fig. 3.3 Summary of how early SPIOMET treatment may prevent or reduce subsequent PCOS-related morbidity and costs. Adolescent girls with PCOS are rather unhealthy (= on the low/red side along the metabolic-health spectrum), and lifestyle measures are recommended for most of these girls, particularly when obese. Pharmacological treatment with an oral contraceptive (OC) reduces the androgen excess but fails to improve other markers of metabolic health. Post-OC oligo-anovulation may require the use of assisted reproductive technology (ART) in order to achieve a pregnancy. In turn, ART-induced pregnancies in women with PCOS are accompanied by a doubling-to-tripling of major complications, and followed by a higher prevalence of sequelae in the offspring. In contrast, pharmacological intervention with SPIOMET in adolescent girls with PCOS improves their metabolic health and leads to the virtual disappearance of the entire PCOS phenotype. The anticipation that there will be fewer complications in spontaneous post-SPIOMET pregnancies than in post-OC/ART pregnancies remains to be corroborated in future studies

The primary endpoint of clinical relevance could be ovulation rate, but this is cumbersome to assess in adolescent girls [12]. Circulating microRNA-451a, either alone [30], or together with fasting insulinemia [29], are simple candidate proxies to gauge the normalization of the underpinning PCOS condition. Indeed, circulating microRNA-451a was recently identified as a biomarker that associates closely to androgen excess, insulin resistance, hepato-visceral adiposity, and ovulation rate in adolescent girls with PCOS [30].

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