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Original article

Normalizing Ovulation Rate by Preferential Reduction of Hepato-Visceral Fat in Adolescent Girls With Polycystic Ovary Syndrome

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A B S T R A C T

Purpose: Polycystic ovary syndrome (PCOS) is an increasingly prevalent disorder in adolescent girls, commonly presenting with hirsutism/oligomenorrhea, commonly treated with an oral contraceptive (OC), and commonly followed by oligoanovulatory subfertility. We tested whether an intervention targeting the reduction of hepato-visceral adiposity is followed by a higher ovulation rate than OC treatment.

Methods: This randomized, open-label, single-center, pilot proof-of-concept study (12 months on treatment, then 12 months off) was performed in adolescent girls with hirsutism and oligomenorrhea (PCOS by National Institutes of Health; no sexual activity; N = 36; mean age 16 years, body mass index 23.5 kg/m^2; 94% study completion). Compared treatments were OC (ethinylestradiol–levonorgestrel) versus low-dose combination of spironolactone 50 mg/d, pioglitazone 7.5 mg/d, and metformin 850 mg/d (SPIOMET). Primary outcome was post-treatment ovulation rate inferred from menstrual diaries and salivary progesterone (12 + 12 weeks). Secondary outcomes included body composition (dual X-ray absorptiometry), abdominal fat (magnetic resonance imaging), insulinemia (oral glucose tolerance test), and androgenemia (liquid chromatography – tandem mass spectrometry).

Results: SPIOMET was followed by a 2.5-fold higher ovulation rate than OC ($p \leq .001$) and by a 6-fold higher normovulatory fraction (71% vs. 12%; $p \leq .001$); oligoanovulation risk after SPIOMET was 65% lower (95% confidence interval, 40%–89%) than after OC. Higher post-treatment ovulation rates related to more on-treatment loss of hepatic fat ($r^2 = .27$; $p < .005$). Visceral fat and insulinemia normalized only with SPIOMET; androgenemia normalized faster with OC but rebounded more thereafter. Body weight, lean mass, and abdominal subcutaneous fat mass remained stable in both groups.

IMPLICATIONS AND CONTRIBUTION

In adolescent girls with polycystic ovary syndrome, treatment with a low-dose combination of spironolactone–pioglitazone–metformin was accompanied by a reduction of hepato-visceral fat (without loss of weight), was followed by a more normal ovulation rate than standard treatment with an oral contraceptive, and may thus prevent part of later oligoanovulatory subfertility.

Conflicts of Interest: The authors have no conflicts of interest to disclose.
This manuscript is dedicated to the memory of Dr. Melvin M. Grumbach (1925–2016).

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Conclusions: Early SPIOMET treatment for PCOS normalized post-treatment ovulation rates more than OC. Focusing PCOS treatment on early reduction of hepato-visceral fat may prevent part of later oligoanovulatory subfertility.

Oligo-ovulatory androgen excess in women (polycystic ovary syndrome [PCOS] by the National Institutes of Health [NIH] definition) is a prime cause of female subfertility [1,2] and appears to relate to hepatic and visceral adiposity, independently of body mass index (BMI) [3–5]. In adolescent girls, PCOS by NIH is the most common cause of hirsutism (with or without acne and seborrhea) and menstrual irregularity [6,7]. The ovarian androgen excess is thought to originate most often from an absolute or relative excess of fat in subcutaneous adipose tissue and from an ensuing excess of hepatic and visceral fat with elevations of insulinemia and gonadotropin secretion [7–9]. Phenotypic variation is partly accounted by an increasing set of PCOS loci identified by genome-wide association studies [10].

No therapy has been approved by the Food and Drug Administration (FDA) or by the European Medicines Agency (EMA) for PCOS in adolescent girls. Prime recommendation is to reduce body adiposity with lifestyle measures [11,12]. The addition of an oral estroprogestagen contraceptive (OC) is broadly endorsed [1,12,13] and prescribed for an estimated 98% of PCOS girls [14]. An alternative addition for hyperandrogenic girls who are not sexually active is a combination treatment that aims at a reduction of hepatic and visceral fat excess and thus at a further lowering of circulating insulin, gonadotropin, and androgen concentrations [15–18].

It is unknown whether the use of an OC or other medications influences post-treatment ovulation rates. We report a first randomized study comparing ovulation rates after treatment with an OC versus treatment with a low-dose combination of spironolactone–pioglitazone–metformin (SPIOMET) in adolescent girls with hirsutism and oligomenorrhea and with no need for contraception.

Methods

Study design and population

Table 1 summarizes the design of this randomized, single-center, open-label, pilot proof-of-concept study over 24 months.

The study population consisted of 36 Catalan girls meeting the four inclusion criteria of hirsutism (score >8 on Ferriman–Gallwey scale), oligomenorrhea (menstrual intervals >45 days), gynecological age (or time span postmenarche) >2.0 years, and absence of sexual activity (no need for contraception).

The girls were recruited in the Adolescent Endocrinology Unit of Sant Joan de Déu University Hospital, Barcelona, Spain, between January 2013 and May 2014 (CONSORT flow diagram; Supplementary Figure 1). Recruitment was biased against overweight/obesity because, in our setting, overweight/obese adolescent girls are primarily referred to the Adolescent Obesity Unit rather than to the Adolescent Endocrinology Unit.

Exclusion criteria were 21-hydroxylase deficiency (as judged by 17-OH-progesteronemia ≥200 ng/dL in the follicular phase or after 2 months of amenorrhea); glucose intolerance or diabetes mellitus; evidence of thyroid, liver, or kidney dysfunction; hyperprolactinemia; any prior use of medication affecting gonadal or adrenal function, or carbohydrate or lipid metabolism [17].

Table 1
Study design

Study months	0	6	12	18	24
OC or SPIOMET intake (0–12 mo)[a]		√	√		
Clinical and circulating markers[b]	√	√	√	√	√
DXA, abdominal MRI, cIMT	√	√	√	√	√
Oral glucose tolerance test	√		√		√
Ovulation assessment[c]				√	√

BMI = body mass index; cIMT = carotid intima-media thickness; DXA = dual X-ray absorptiometry; mo = months; MRI = magnetic resonance imaging (hepatic and visceral fat).

[a] OC, oral contraceptive; SPIOMET, low-dose spironolactone–pioglitazone–metformin; 1:1 randomization with stratification for age and BMI.

[b] Morning blood sampling in fasting state, in early follicular phase.

[c] By weekly salivary progesterone over the 12 weeks prior to the study visit, in combination with a menstrual diary over the same 12 weeks + 2 subsequent weeks.

End points

The primary end point was post-treatment ovulation rate. Secondary outcomes were hirsutism and acne scores, body composition, abdominal fat partitioning (subcutaneous, visceral, and hepatic fat), carotid intima-media thickness, circulating insulin, testosterone, androstenedione, C-reactive protein (CRP), lipids, and high-molecular-weight (HMW) adiponectin.

Study registration and ethics

The study was registered as ISRCTN29234515 and conducted after approval by the Institutional Review Board of Sant Joan de Déu University Hospital, after written consent by parents, and after assent by each of the study girls, including of the healthy controls who allowed to derive indicative values. Updates of the original study registration reflect changes that occurred since August 2012, notably in the diagnosis of adolescent PCOS [6], in the study duration (extension of the post-treatment time span from 6 to 12 months, after obtaining an extension of funding), and in the measurement of circulating androgens (switch to liquid chromatography–tandem mass spectrometry).

Randomization and study medications

Mediterranean diet and regular exercise were recommended to all girls. Randomization (1:1) for study medication was web based (http://www.SealedEnvelope.com), using random permuted blocks, with strata for age (<16.0 or ≥16.0 years) and BMI (<24.0 or ≥24.0 kg/m^2). Girls were randomly assigned to