Accepted Article

Article type : Correspondence

Corresponding Author Email ID: libanez@sjdhospitalbarcelona.org

Letter to the Editor

Tackling NAFLD in adolescent PCOS:

reducing liver fat to mimick weight loss

Francis de Zegher [1]

Lourdes Ibáñez [2,3]

[1] Department of Development & Regeneration, University of Leuven, 3000 Leuven, Belgium

[2] Endocrinology Department, Pediatric Research Institute Sant Joan de Déu, University of Barcelona, 08950 Esplugues, Barcelona, Spain; [3] Centro de Investigación Biomédica en Red de Diabetes y Enfermedades Metabólicas Asociadas (CIBERDEM), ISCIII, 28029, Madrid, Spain

Adolescent girls with Polycystic Ovary Syndrome (PCOS) fit in at least two of the target populations wherein Wegermann *et al* propose to tackle NAFLD [1]. Diagnostic features of adolescent PCOS are androgen excess (clinical and biochemical) and menstrual irregularity, but ectopic lipid accumulation in the liver is emerging as a key pathogenic mechanism, apparently driven by a mismatch between (reduced)

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/HEP.31592

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prenatal weight gain and (augmented) postnatal weight gain [2]. The latter mismatch implies that adolescents with PCOS may have NAFLD without being overweight or obese, particularly in regions as South Asia [3], where prenatal weight gain and subcutaneous adipogenesis tend to be low [2]. For those adolescents, it is notoriously difficult to achieve a sustained loss of body weight. In 1998, this fact prompted a search for weight-loss-mimicking interventions in non-obese adolescents with PCOS [4]. Two decades later, this search has led to a low-dose combination of generics (SPIOMET), consisting of spironolactone (50 mg/d, to activate brown adipose tissue, as judged by circulating CXCL14), pioglitazone (7.5 mg/d, to double circulating high-molecular-weight adiponectin) and metformin (850 mg/d, to triple the circulating concentrations of appetite-attenuating GDF15) [5]. In the absence of weight loss, SPIOMET intake was associated with a marked reduction of hepatic fat and with a disappearance of PCOS features, including a normalization of ovulation rate [Figure 1]. The same Figure shows also that the lowering of the androgen excess with an estro-progestagen contraceptive failed to reduce liver fat: NAFLD is thus a cause rather than a consequence of androgen excess. Our pilot evidence remains to be corroborated in double-blind multicenter studies of larger and more diverse populations. In the meantime, the future armamentarium to tackle NAFLD is anticipated to include not only measures and medications that aim at weight loss – as explained by Wegermann *et al* – but also weight-loss-mimicking strategies that reduce ectopic adiposity without lowering body weight.

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Figure 1. Reduction of liver fat – without changing body weight – is followed by more ovulations in adolescent girls with Polycystic Ovary Syndrome (PCOS).

Longitudinal changes in the hepatic fat fraction (by magnetic resonance imaging) are shown in adolescents with PCOS, first on treatment (0-12 months), and then post treatment (12-24 months). The dotted line indicates the average percentage of hepatic fat in healthy control girls. The adolescents with PCOS (mean age 16 years) were randomized to receive an oral estro-progestagen contraceptive (OC; red circles/bar) or a low-dose combo of spironolactone-pioglitazone-metformin (SPIOMET; blue circles/bar). Both treatments reduced the androgen excess within 12 months towards normal, without changing body weight or lean mass.

Treatment with OC failed to reduce the hepatic fat excess, and was followed by a rebound of the androgen excess. In contrast, treatment with SPIOMET was accompanied by a normalization of hepatic adiposity and insulin resistance that extended beyond the time window of active treatment. The annualized post-treatment number of ovulations was nearly 3-fold higher after SPIOMET than after OC treatment (results are shown as mean and SEM; N=31 in each treatment group).

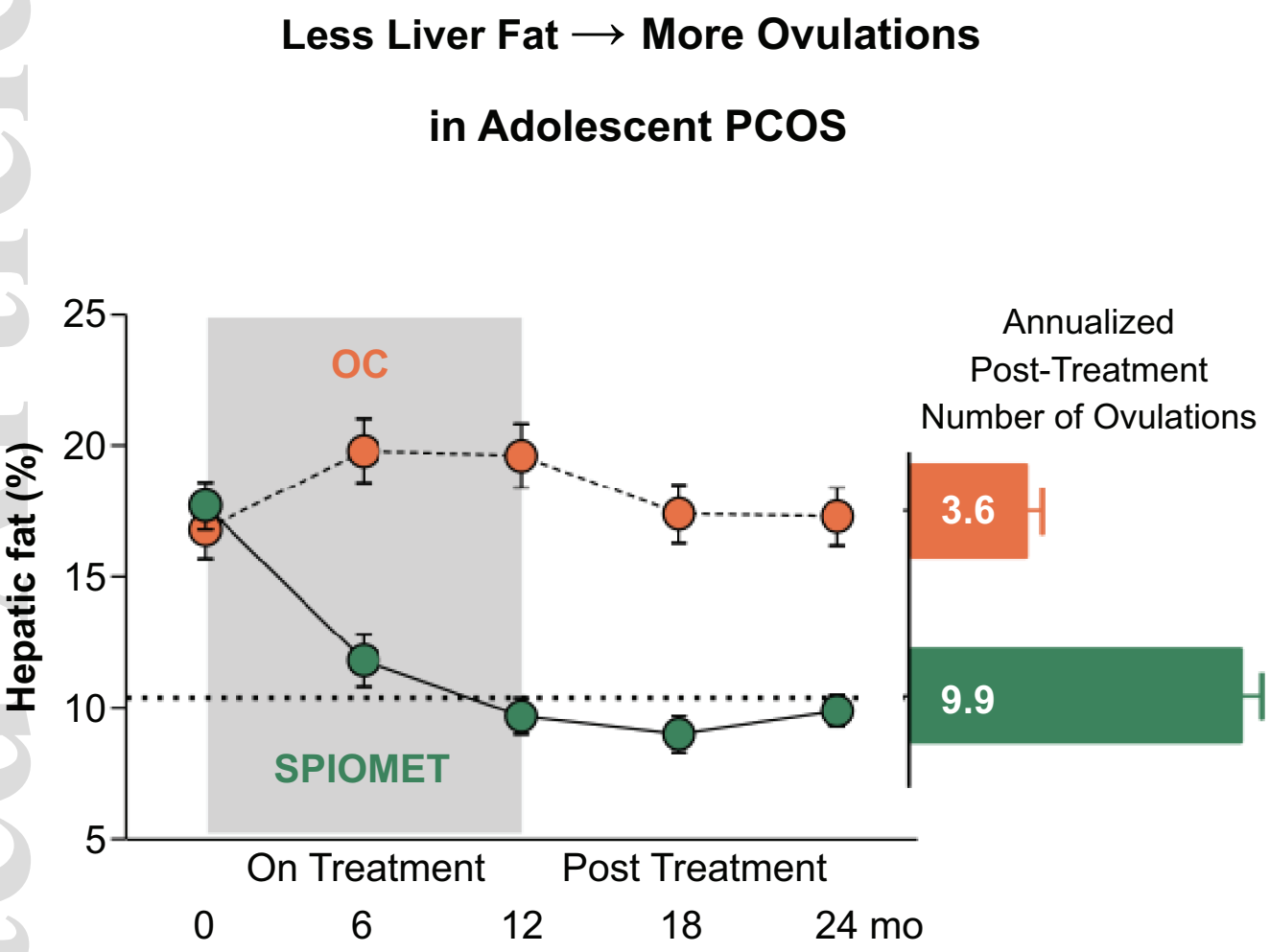
$P<0.001$ for between-group differences in on-treatment changes of hepatic fat, in post-treatment hepatic fat fractions, and in post-treatment ovulation rates. Original data are from reference [5].

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Figure 1.



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