

# From adolescent PCOS to adult MAFLD: opposing effects of randomised interventions

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Asfari *et al* reported that non-alcoholic fatty liver disease (NAFLD) is fourfold more prevalent in women with than without PCOS, and concluded that 'further studies are needed to assess if specific PCOS treatments can affect NAFLD progression'.<sup>1</sup>

In the meantime, an international consensus has replaced NAFLD by metabolic dysfunction-associated fatty liver disease (MAFLD).<sup>2</sup> In the absence of overweight and obesity, the definition of MAFLD requires not only that steatosis be present, but also that at least two markers point to metabolic dysfunction, for example, a circulating concentration of C reactive protein (CRP) >2.0 mg/L, and an Homeostasis Model Assessment-Insulin Resistance (HOMA-IR) value ≥2.5.

Adolescent polycystic ovary syndrome (PCOS) is a prevalent condition (~10% of girls and women between 2 and 8 years postmenarche) that is characterised by androgen excess and menstrual irregularity (as a proxy of oligoanovulation)<sup>3</sup> but seems to be driven by ectopic lipid accumulation in the liver, essentially resulting from a mismatch between (reduced) prenatal weight gain and (augmented) postnatal weight gain.<sup>4,5</sup> Adolescent PCOS is increasingly viewed as a state of metabolic dysfunction, often with low-grade

inflammation (by CRP) and/or insulin resistance (by HOMA-IR); a polycystic appearance of the ovaries is no longer a diagnostic criterion of PCOS in adolescence.<sup>3,4,6</sup>

The new definitions of MAFLD and adolescent PCOS have led to the insight that there may be an overlap between both entities, and that interventions for PCOS in late adolescence could indeed influence the prevalence of MAFLD in early adulthood. We investigated the latter possibility by taking advantage of recent data from randomised pilot studies in non-obese adolescents with PCOS.<sup>6</sup> These studies compared the effects of a widely recommended treatment (targeting the ovaries) to those of a new treatment (targeting ectopic fat), each on top of lifestyle measures.<sup>6</sup> The recommended treatment was an oestrogen-progestin contraceptive (OC; 20 µg ethinylestradiol plus 100 mg levonorgestrel for 21/28 days, and placebo for 7/28 days) that silences the gonadotropic axis, thereby reducing the androgen excess and ensuring anovulation.<sup>7,8</sup> The new treatment was a low-dose combination of three generics (SPIOMET),<sup>6</sup> namely spironolactone 50 mg/day (to activate brown adipose tissue),<sup>9</sup> pioglitazone 7.5 mg/day (to double high-molecular-weight adiponectinaemia,<sup>10</sup> and to prioritise subcutaneous adipogenesis)<sup>11</sup> and metformin 850 mg/day (to triple

the circulating concentrations of appetite-attenuating GDF15).<sup>12</sup> SPIOMET does not elicit a loss of body weight, but redistributes body fat from ectopic to subcutaneous depots, thereby conferring more broadly normalising benefits than OC, in particular on liver fat (by MRI) and on post-treatment androgen excess and ovulation rate<sup>6,13</sup> (online supplemental table 1).

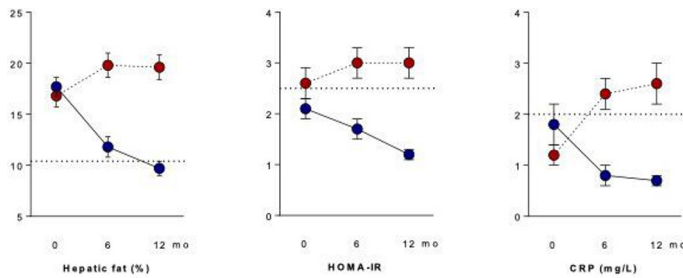
Here, we highlight the effects of OC versus SPIOMET intervention on a key MAFLD ensemble in non-obese young women with PCOS, namely the triad of hepatic fat, HOMA-IR and circulating CRP.<sup>6</sup> Figure 1 shows that the randomised interventions were accompanied by opposing influences on these MAFLD components, so that the prevalence of the MAFLD triad increased from 13% to 35% during OC treatment, and decreased from 13% to 0% during SPIOMET treatment (p<0.001 for between-group difference at 6 and 12 months, by  $\chi^2$  test). Mean body mass index increased over 12 months on OC (from 24.2 to 24.9 kg/m<sup>2</sup>; p≤0.01) but did not change detectably on SPIOMET (from 24.2 to 23.9 kg/m<sup>2</sup>).<sup>6</sup>

In conclusion, the new MAFLD concept unmask that the widely recommended OC therapy for PCOS does not attenuate the underpinning problem of metabolic dysfunction, and that approximately one-third of OC-treated non-obese adolescents with PCOS become young women with MAFLD. SPIOMET treatment represents a more pathophysiological approach: it is a weight-loss-mimicking intervention that normalises liver fat, HOMA-IR and circulating CRP, and that may be particularly preferable in adolescent settings of sexual abstinence, where contraception is not at stake. PCOS in adolescent girls and young women is, in essence, a postmenarcheal or pregestational central obesity syndrome (PCOS) that should not only be treated from

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**Figure 1** Opposing effects of randomised interventions on the MAFLD triad of hepatic fat, HOMA-IR and circulating CRP in adolescent girls with polycystic ovary syndrome (PCOS). Adolescents with PCOS (mean age 16 years) were randomised to receive an oestro-progestagen contraceptive (OC; red) or a low-dose combination of spironolactone-pioglitazone-metformin (SPIOMET; blue). On-treatment (0–12 months) results are shown as mean and SEM; n=31 in each treatment group. The dotted line in the hepatic-fat panel refers to the average fraction in healthy controls.<sup>6</sup> The dotted lines in the HOMA-IR and CRP panels refer to the cut-off levels for these MAFLD criteria.<sup>2</sup> Original data are from reference 6. CRP, C reactive protein; MAFLD, metabolic dysfunction-associated fatty liver disease.

a gynaecological but also from a hepatological perspective. OCs should be prescribed with more caution, and metabolic corrections should receive more attention. It is a shared responsibility to prevent that millions of non-obese adolescents with PCOS continue to become young women with both PCOS and MAFLD.

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