post-treatment phase; in contrast, spiomet treatment elicited no detectable changes in ALT and GGT concentrations. In relation to organokines after 6 mo on treatment, (1) FGF21 levels were significantly higher in PCOS adolescents than in control girls; (2) DBI levels were lower in OC-treated girls as compared to controls and spiomet-treated girls; (3) no differences were observed in METRNL concentrations between PCOS girls and controls. Serum ALT and GGT levels directly correlated with circulating METRNL levels only in OC-treated girls (R=0.449; P=0.036 and R=0.552; P=0.004, respectively).

Conclusion: The on-treatment increase in ALT and GGT levels occurring only in OC-treated girls associates with circulating METRNL levels suggesting an enhanced METRNL synthesis as a reaction to the hepatic changes elicited by OC treatment.

P1-90

Decreased serum DHEAS to cortisol ratio in adolescents evaluated for gender dysphoria

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Background: DHEAS is the most abundant adrenal steroid and it is also a neurosteroid, produced at the cerebral level from pregnenolone and 17OH-pregnenolone. It antagonizes the effects of cortisol at the level of glucocorticoid receptors, modulating biological energy output, inflammatory status, action of other steroidal hormones, and different brain functions, hypothalamus being rich in corticosteroid receptors. DHEAS secretion is usually synchronized with cortisol and a normal DHEAS to cortisol ratio is considered a marker of the biological activity of cortisol at the level of glucocorticoid receptor. This hypothesis is proven by the decrease of DHEAS to cortisol ratio in many pathological conditions, such as depression and anorexia nervosa.

Methods: We recruited consecutively 41 children and adolescents evaluated for gender dysphoria (GD) (cases) and 235 controls among individuals who underwent a standard dose Synacthen test. All participants underwent a medical visit and fasting blood sampling.

Results: Among the 235 controls, serum DHEAS to cortisol ratio resulted as correlated with age (Spearman's rank correlation, ρ=0.524, p<0.001), BMI SDS (ρ=0.245, p<0.001), but not with assigned sex at birth, height SDS, ACTH, peak cortisol, basal 17-hydroxyprogesterone, peak 17-hydroxyprogesterone, total testosterone (all p-values >0.05). Since the median age in GD was significantly higher than controls (Kruskal Wallis test, 16.0 vs. 9.5 years, p<0.001), we compared the 41 individuals with GD with 82 age-matched control subjects (ratio 1:2): those with GD showed a significantly lower DHEAS to cortisol ratio compared to controls (0.182 vs. 0.271, p=0.016), with no significant differences for BMI SDS (p=0.396). The association between GD and DHEAS to cortisol ratio was confirmed at multivariate analysis in the entire cohort (n=276) after correction for assigned sex at birth, age, and BMI SDS (β of linear regression for GD=-0.08, p=0.009).

Conclusions: To our knowledge, this is the first study that evaluated DHEAS to cortisol ratio in adolescents with suspected GD. This ratio was correlated with age and BMI SDS, but not with assigned sex at birth. Our results suggest that the dysphoria due to the incongruence between gender identity and sex assigned at birth might be reflected by lower DHEAS/cortisol ratios, indicating dysregulation of the stress response system. While it was already known that GD leads to distress and adaptation difficulties, this is the first biological proof.

P1-91

Serum steroid metabolite profiling by LC-MS/MS in two phenotypic male patients with HSD17B3 deficiency: implications for hormonal diagnosis

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Background: HSD17B3 deficiency is diagnosed when a testosterone/androstenedione (T/A-dione) ratio after hCG stimulation is below 0.8, and this cut-off value is primarily based on hormonal data measured by conventional immunoassay (IA) in patients with feminized or ambiguous genitalia suggesting severely compromised T production. Liquid chromatography-tandem mass spectrometry (LC-MS/MS) has been regarded as the gold standard for steroid measurement, and it is necessary to examine whether the cut-off value can be utilized for hormonal diagnosis with LC-MS/MS in a wide range of patients including phenotypic male patients.

Case presentation: We examined two 46,XY Japanese patients with undermasculinized genitalia including hypospadias (patient 1 and patient 2). Endocrine studies by IA demonstrated a well increased serum T value following hCG stimulation (2.91 ng/mL) and a high T/A-dione ratio (4.04) in patient 1 at 2 weeks of age and sufficiently elevated basal serum T value (2.60 ng/mL) in patient 2 at 1.5 months of age. Despite partial androgen insensitivity syndrome (PAIS)-like findings, whole exome sequencing identified biallelic pathogenic or likely pathogenic variants in *HSD17B* (c.188C>T:p.(Ala63Val) and c.194C>T:p.(Ser65Leu) in patient 1, and c.139A>G:p.(Met47Val) and c.672+1g>a in patient 2) (NM_000197.2). Functional analysis revealed that the missense variants resulted in reduced HSD17B3 activities (~ 43% for p.Met47Val, ~ 14% for p.Ala63Val, and ~ 0% for p.Ser65Leu). Thus, we investigated hCG-stimulated serum steroid metabolite profiles by LC-MS/MS in patient 1 at 7 months of age and in patient 2 at 11 months of age as well as those of five control males