

gene. It is responsible for decreased activity of several P450 enzymes including CYP21A2, CYP17A1 and CYP19A1 that are involved in adrenal and/or gonadal steroidogenesis. PORD is typically diagnosed in neonates and children with ambiguous genitalia and/or skeletal abnormalities. Adult-onset PORD has been very seldom reported and little is known about the optimal way to investigate and treat such patients. In this series, we report five women aged 19-38 years, who were referred for unexplained oligo-/amenorrhea and/or infertility. Genetic testing excluded 21-hydroxylase deficiency (21OH-D), initially suspected due to increased 17-hydroxyprogesterone (17-OHP) levels. Extensive phenotyping, steroid profile by mass spectrometry, pelvic imaging and next-generation sequencing of 84 genes involved in gonadal and adrenal disorders were performed in all patients. *In Vitro* Fertilization (IVF) followed by frozen embryo transfer under glucocorticoid suppression therapy was performed in two patients. All patients had oligomenorrhea or amenorrhea. None had hyperandrogenism. Low-normal serum estradiol (E2) and testosterone levels contrasted with chronically increased serum progesterone (P) and 17-OHP levels, which further increased after ACTH administration. Despite excessive P, 17OH-P and 21-deoxycortisol rises after ACTH stimulation suggesting non-classic 21-hydroxylase deficiency, *CYP21A2* sequencing did not support this hypothesis. Basal serum cortisol levels were low to normal, with inadequate response to ACTH in some women, suggesting partial adrenal insufficiency. Pelvic imaging revealed bilateral ovarian macrocysts in all women. All patients were found to harbor rare bi-allelic *POR* mutations classified as pathogenic according to American College of Medical Genetics standards. IVF was performed in two women after retrieval of a normal oocyte number despite very low E2 levels during controlled ovarian hyperstimulation. Frozen embryo transfer under glucocorticoid suppression therapy led to successful pregnancies. These observations suggest that diagnosis of PORD must be considered in infertile women with chronically elevated P and 17OH-P levels and ovarian macrocysts. Differentiation of this entity from non-classic 21-hydroxylase deficiency is important, as the multiple enzyme deficiency requires a specific management. Successful fertility induction is possible by IVF, providing that P levels be sufficiently suppressed by glucocorticoid therapy prior to implantation.

Adrenal

ADRENAL MEDICINE — CLINICAL APPLICATIONS AND NEW THERAPIES

Durable CYP21A2 Gene Therapy in Non-Human Primates for Treatment of Congenital Adrenal Hyperplasia

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Severe Congenital Adrenal Hyperplasia (CAH) is most commonly caused by genetic defects in the *CYP21A2* gene,

which leads to a deficiency of 21-hydroxylase enzyme and disruption in the biosynthesis of Adrenal corticosteroids. Despite treatment with corticosteroids, patients remain at significant risk for adrenal crisis, experiencing a 3-fold higher mortality rate than age matched controls. They also suffer from significant infertility, bone, metabolic, and cardiovascular disease, and hyperandrogenism in women leading to genital abnormalities, hirsutism, and other complications. We are developing an AAV5- based gene therapy (BBP-631) that will provide a functional copy of the *CYP21A2* gene to the adrenal glands of CAH patients. To determine the durability of this therapy we treated cynomolgus monkeys with increasing doses of BBP-631 via intravenous injection. At 4-, 12- and 24-weeks post treatment, expression of hCYP21A2 mRNA and vector genome copies (VGC) in the adrenals and other peripheral tissues was measured. VGC was present in the liver and adrenals at 4 weeks, with durable detection through 24 weeks and total vg levels were dose dependent. hCYP21A2 RNA expression in adrenal and liver tissues was also dose dependent and continued to increase from 4 weeks through 12 weeks. There were no adverse safety signals in any of the treated animals. This data combined with efficacy data of BBP-631 in a *Cyp21*^{-/-} mouse model supports our continued clinical development of BBP-631 as a treatment for congenital adrenal hyperplasia.

Neuroendocrinology and Pituitary

PITUITARY TUMORS II

Glucose Metabolism in Acromegaly Patients Resistant to First Generation Somatostatin Receptor Ligands Treated with Pegvisomant And/Or Pasireotide Lar

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Introduction: Acromegaly (Acro) is a systemic disease characterized by high growth hormone (GH) and insulin like growth factor-I (IGF-I), insulin resistance, glucose intolerance (IGT) and higher diabetes mellitus (DM) risk in 15% - 38% of patients (pts). Moreover, different medical therapies of Acro are reported to have variable effects on glucose metabolism. An association between blood glucose (BG) and serum IGF-I levels in patients with DM and Acro has been suggested, while IGF-I levels and hemoglobin A1c (HbA1c) correlation is still controversial because of the multifactorial influence. Study aim: to investigate glucose metabolism in pts with Acro resistant to 1st gen somatostatin receptor ligands (SRLs) treated with Pegvisomant (Peg) or Pasireotide LAR (Pasi). **Patients and Methods:** Retrospective, international, multicenter study; consecutive pts enrolled according to following inclusion criteria for at least 6 consecutive months: (1) resistant to 1st gen

SRLs, (2) treated with Pasi or Peg for active Acro. Patients with concomitant treatments with known action on glucose metabolism were excluded, with the exception of glucocorticoid replacement for central hypoadrenalism. **Results:** 72 pts with active Acro, mean age at study entry 37 ±15 yrs, 47 females (65.3%). 28 (38.9%) pts were treated with Pasi and 44 pts with Peg (61.1%). Peg was monotherapy in 18 pts (40.9%) and in combo with first generation SRLs for 26 pts (59.1%). The number of pts with IGT and DM2 was superimposable between the 2 groups (Pasi and Peg). In Pasi group, 19 pts had Acro control (67.9%); glucose metabolism worsened in 16 pts (57.1%). Worsening of glucose metabolism occurred most frequently in pts with persistently active Acro (62.5%) and in pts with higher BG and HbA1c values at study start. Similarly, HbA1c was higher in pts with active Acro, although HbA1c worsened during Pasi treatment both in euglycemic and IGT at study entry, regardless of Acro control. In Peg group, 31 pts reached Acro control (73%); glucose metabolism worsened in 12 (27.3%) but improved in 5 pts (11.4%). All pts who experienced glucose metabolism improvement had controlled Acro, regardless of the use of a combo with first generation SRL. Among the 13 pts with active Acro Peg, BG worsened in 5 cases (38.4%). Moreover, we found that pts with worsening BG control had higher HbA1c ($p=0.03$) and required higher Peg doses (mean ±SD 25 ±10 mg/day; $p=0.04$). Patients with higher HbA1c had higher IGF-I, both at study entry and at study end and were treated with higher Peg dose (mean 25 mg/day). **Conclusion:** Impaired glucose metabolism was more frequent after Pasireotide treatment and in patients of both Pasireotide and Pegvisomant groups with altered pre-treatment glucose and persistently active disease. Therefore, in such acromegaly patients close monitoring of glucose status is recommended during treatment.

Reproductive Endocrinology

CLINICAL STUDIES IN FEMALE REPRODUCTION I

Association of Inflammatory Markers with Depressive Symptoms Across the Perinatal Period

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Perinatal depression (PND) is a mood disorder affecting 10-15% of women during pregnancy and postpartum. Its aetiology is complex with contribution from both genetic background and psychosocial as well as environmental stressors that determine individual responses shaped

by chronic and acute disease burden (1). It is thought that the molecular basis of PND involves dysregulation of the HPA axis associated with neurotransmitter and neuroactive steroids imbalance. Inflammation appears to be a contributing mechanism, with increased levels of cytokines exerting adverse effects on serotonin metabolism, neuroplasticity and HPA hyperactivity (2). With only 50% of women detected through current screening strategies, there is an urgent unmet need for the development of biomarker-based strategies to identify women at risk of PND. In this study we used data and blood samples from the prospective Coventry and Warwickshire PND study; we investigated for inflammatory markers associated with depressive symptoms, assessed using the Edinburgh Postnatal Depression Score (EPDS) questionnaire between 24-29 weeks of gestation and again 6-10 weeks postpartum. A cut-off score of 10 categorize 'high' or 'low' risk for depression. Blood samples collected at 28 weeks of gestation were profiled for either IL-6 and IL-10 levels or a panel of 92 inflammatory markers. Individual inflammatory markers were compared across groups using Welch's ANOVA. Results suggest that IL-10 levels were significantly correlated with EPDS score, exerting a protective effect ($r= -.10$), with reduced levels in the highest severity category (EPDS ≥ 15). The IL-6/IL-10 ratio was also associated with a raised EPDS score ($r=.10$, $p=.01$), as well as delivery complications ($r=.09$). The highest IL-6/IL-10 ratio is observed in women who had emergency caesarean section. Bayes' theorem analysis suggested that IL-6/IL-10 ratio could be used as a negative screen to rule out low risk pregnancies. From the 92 inflammatory markers, 14 analytes were below the limit of detection for more than 50% of samples and so were excluded from further analysis. Upon comparison of groups determined by antenatal and postnatal EPDS scores, 29 markers displayed a significance value of $P<0.05$. Upon the application of post hoc tests, 8 markers including: STAM-BP, SIRT2, CD40, CASP8 and ADA, all associated with apoptotic processes, remained statistically significant in pregnant women with raised antenatal EPDS scores. This data support an association between inflammatory markers and perinatal depression and adverse pregnancy outcomes. Detailed quantitative analysis of such biomarker signatures at different stages of pregnancy, might lead to early detection of disease and application of targeted treatment. (1) Pariante, C. M. & Lightman, S. L. (2008) Trends Neurosci, 31 (9): 464-468. (2) Raison et al., (2006) Trends Immunol, 27 (1): 24-31.

Bone and Mineral Metabolism

BONE AND MINERAL CASE REPORTS II

The Mystery of Recurrent PTH-Independent Hypercalcemia with Severe Hypophosphatemia

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Background

The differential diagnoses for PTH independent hypercalcemia with hypophosphatemia are broad. Careful