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## SAT-028

### Abstract

### Context

Leptin is an adipokine involved in many pleiotropic and key physiological actions and circulates free and active, or inactive bound to the leptin binding protein and sOB-r. Thus, the ratio Leptin/sOB-r or free leptin index (FLI) is commonly used as a marker of leptin sensitivity in different pathologies.

### Objective

Evaluate serum concentrations of leptin and sOB-r and determine FLI in healthy pregnant and mild pre – eclamptic women in the three trimesters of gestation.

### Design

A nested case-control study within a prospective cohort study of pregnant women, enrolled in the Department of Obstetrics and Gynecology of the School of Medicine at Universidad Nacional.

### Main Outcome Measure and Methods

From the initial cohort, 46 healthy pregnant women and 19 mild pre – eclamptic pregnant women were randomly selected. Anthropometric, biochemical and clinical parameters were determined during three stages of pregnancy [1<sup>st</sup> (11.3±2.3 weeks), 2<sup>nd</sup> (24.4±3.10 weeks) and 3<sup>rd</sup> (34.84±4.41 weeks) periods of gestation]. Data were presented as mean ± SD. A p value <0.05 was considered to be statistically significant.

### Results

Serum leptin levels and sOB-r levels rose significantly throughout pregnancy in both healthy women [Leptin (1<sup>st</sup> 23.28±9.87 ng/mL; 2<sup>nd</sup> 34.58±18.45 ng/mL; 3<sup>rd</sup> 38.27±19.64 ng/mL trimester) (p=0.0001); sOB-r (1<sup>st</sup> 32.12±7.29 ng/mL; 2<sup>nd</sup> 43.26±9.25 ng/mL; 3<sup>rd</sup> 45.16±10.70 ng/mL trimester) (p<0.0000)] and preeclamptic women [Leptin (1<sup>st</sup> 29.91±9.91 ng/mL; 2<sup>nd</sup> 47.10±25.70 ng/mL; 3<sup>rd</sup> 63.00±30.12 ng/mL trimester) (p<0.0000); sOB-r (1<sup>st</sup> 32.09±6.97 ng/mL; 2<sup>nd</sup> 37.54±6.33 ng/mL; 3<sup>rd</sup> 36.96±7.66 ng/mL trimester) (p=0.0380)].

Serum leptin levels were significantly higher in preeclamptic pregnant women compared to healthy pregnant women at 2<sup>nd</sup> (p=0.029) and 3<sup>rd</sup> trimesters of pregnancy (p<0.000). Additionally, serum sOB-r levels were also significantly lower in pre - eclamptic pregnant women during the 2<sup>nd</sup> (p=0.017) and 3<sup>rd</sup> trimester (p=0.0036) of pregnancy compared to healthy pregnant women. As a result, the FLI index did not vary significantly during any of the three periods of pregnancy studied in healthy pregnant women [(1<sup>st</sup> 7.99±4.85; 2<sup>nd</sup> 8.72±6.5; 3<sup>rd</sup> 9.15±5.84 trimester) (p >0.05)], whereas, in contrast, this index markedly increased throughout pregnancy in pre - eclamptic women [(1<sup>st</sup> 8.69±4.96; 2<sup>nd</sup> 13.54±8.78; 3<sup>rd</sup> 18.06±10.35 trimester) (p=0.0044)]. Indeed, the FLI index was significantly higher at 2<sup>nd</sup> (p=0.0186) and 3<sup>rd</sup> (p<0.000) trimesters of pregnancy in pre - eclamptic women compared to healthy pregnant.

### Conclusions

The present results demonstrate for the first time in a longitudinal study that FLI increases significantly in pre - eclamptic pregnant women towards the end of pregnancy. Hence, high FLI index values should be further explored as a potentially valuable indicator for the clinical manifestations of this pathology.

## Cardiovascular Endocrinology

### ENDOCRINE HYPERTENSION AND ALDOSTERONE EXCESS

#### *Genetic Profile of Early-Onset Aldosterone-Producing Adenomas*

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#### SAT-554

Genetic profile of early-onset aldosterone-producing adenomas

**Background:** Aldosterone-producing adenoma (APA) is a major subtype of primary aldosteronism (PA) which is the most common cause of endocrine-related hypertension. The Endocrine Society clinical practice guideline suggests that young patients (< 35 years old) with a CT-detected adrenocortical adenoma and typical phenotype of PA may not need adrenal venous sampling prior to adrenalectomy. In recent years, aldosterone-driver somatic mutations have been identified in APA, and prevalence studies suggest potential effects of patient age and sex. However, the rare

nature of early-onset PA has prevented a detailed study of the histologic characteristics and aldosterone-driver somatic mutations in adrenal tumors from these patients.

**Objective:** To determine histologic and somatic mutation profile in early-onset APA.

**Methods:** Fifty-five formalin-fixed paraffin-embedded (FFPE) adrenals from patients at the age of 35 years old or younger who underwent adrenalectomy at the participating centers were studied (45 women, 9 men, and 1 unknown sex). CYP11B2 immunohistochemistry (IHC)-guided tumor capturing was used to selectively obtain DNA from APA. Mutation status was determined either by Sanger sequencing or targeted next-generation sequencing.

**Results:** CYP11B2 IHC identified APAs in all adrenal specimens. Solitary APAs were found in 53 adrenals. One adrenal had multiple APAs and one had a dominant CYP11B2-negative tumor and a smaller APA. In total, DNA from 57 APAs were sequenced. Two APAs were excluded from the analysis due to low sample quality. In 52 of the 55 APAs, somatic mutations were identified in one of the aldosterone-driver genes or *CTNNB1* gene, encoding  $\beta$ -catenin. The most common genetic alteration was seen in *KCNJ5* (37/55, 67%), followed by *CACNA1D* (7/55, 13%), *ATP1A1* (3/55, 5%), *CTNNB1* (3/55, 5%), and *ATP2B3* (2/55, 4%). No sex difference in the prevalence of *KCNJ5* mutation was observed in this age group.

**Conclusion:** The majority of adrenals from early-onset PA patients had a solitary APA. Regardless of sex, the most common genetic cause of early-onset APA was somatic mutations in *KCNJ5*.

## Neuroendocrinology and Pituitary

### PITUITARY TUMORS II

#### *Prevalence of Silent Corticotroph Adenomas in a Large Cohort of Nonfunctioning Pituitary Adenomas: Plasma Proopiomelanocortin (POMC) Levels and Response to Pasireotide LAR*

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#### MON-309

Silent corticotroph adenomas (SCAs) are tumors of the TPIT anterior pituitary cell lineage that do not lead to biochemical or clinical Cushing's syndrome. Thus, they present as clinically nonfunctioning pituitary adenomas (CNFPAs) and are only diagnosed pathologically. Since they are often aggressive tumors, identification of a peripheral blood marker of SCA activity would be useful for diagnosis and monitoring. Some data suggest that aberrant processing of POMC, the precursor of ACTH, underlies the lack of elevated biologically active ACTH and thus cortisol excess in SCAs. We hypothesized that these tumors could secrete POMC, resulting in elevated plasma levels of POMC in patients with SCAs. Therefore, we investigated plasma

POMC levels as a potential marker of this tumor type and correlated with tumor ACTH immunoreactivity (IR), which may be detecting unprocessed POMC. We studied 267 patients (134M, 133F, age 56.3±13.6yr) with CNFPAs (Cushing's excluded) prior to surgery and at enrollment in a prospective, observational study. We also studied 9 patients with known SCAs with residual macroadenomas after surgery. Peripheral blood was sampled for POMC, ACTH and cortisol levels. POMC was measured by in-house two-site ELISA (detects POMC and 22kD pro-ACTH) and ACTH and cortisol by Immulite (Siemens). POMC levels were compared to the 95%CI of the mean of 70 healthy subjects and considered elevated if  $\geq$  the 97.5 percentile of 39 fmol/mL. Of the CNFPA cohort, 12/267 had elevated POMC levels (range 39-166 fmol/mL) and 4 of the 12 had elevated ACTH levels ( $> 50$  pg/ml)(range 53.6-76 pg/ml). Of the 12 with elevated POMC, 9 underwent surgery and 6 of them had positive ACTH IR in their tumors. An additional 13 patients in the CNFPA cohort had weak ACTH IR tumors, but POMC  $< 39$  fmol/mL and normal ACTH. POMC levels were elevated in all 9 known SCA patients (range 40-996 fmol/mL), being highest in those with the most aggressive tumors. ACTH levels were elevated in 6 of them (range 50.6-397 pg/ml). POMC levels were lowered with surgery in 4 of 4 SCA patients followed longitudinally. Two SCAs were treated with monthly pasireotide LAR (40 mg escalated to 60 mg) for 8 months. Plasma POMC levels fell from 104 to 21 fmol/mL in 1 patient, but did not change in the 2<sup>nd</sup>, 124 to 112 fmol/mL. Both patients had no change in the size of their macroadenomas during treatment. In summary, patients with elevated plasma POMC levels were correctly identified as SCAs in most surgically treated patients and POMC levels were lowered by tumor removal in all who were tested longitudinally. Although POMC levels were not elevated in some other patients with weakly positive ACTH IR tumors, further characterization of these tumors by lineage specific transcription factors is underway to confirm them to be of corticotroph cell origin. These data suggest that plasma POMC measurements may have clinical utility in the evaluation of SCAs and this warrants further study.

## Steroid Hormones and Receptors

### STEROID BIOLOGY AND ACTION

#### *Sources of Error in Estimation of Cortisol Half-Life Using Conventional, Single-Compartment Model: Bias Due to Variation in CBG Concentration*

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#### SAT-738

Most reports of cortisol half-life in the literature report a range of 90-130 min, which results are based on *descriptive* model that assumes mono-exponential decay of a single, total cortisol compartment. Free cortisol half-life has been similarly assessed using a *descriptive* single compartment model (1). However, the descriptive model is not physiologic