Objective: To describe the clinical, histopathological and molecular features of a novel inherited *SRY* allele (pMet64Val; consensus box position 9) observed within an extensive pedigree: two 46, XY sisters with primary amenorrhea (16 and 14 years of age; probands P1 and P2), their normal father and brother, and an affected paternal XY grandaunt.
Design, Setting, Participants and Outcome Measurements: Following DNA sequencing to identify the SRY mutation, hormonal studies of the probands and histopathological examination of their gonads were performed. Functional consequences of p.Met64Val (and other mutations at this site) were also investigated.
Results: Breast development in P1 and P2was Tanner II and IV, respectively. Müllerian structures and gonads resembling ovaries were found in each sister. Histopathology revealed gonadal dysgenesis, gonadoblastoma and dysgerminoma. AMH/MIS, P450 SCC, and P450 aromatase were expressed in gonadoblastoma tissues. Variant p.Met64Val impaired *Sox9* transcriptional activation associated with attenuated occupancy of the testis-specific enhancersEnh13 and TESCO.
Conclusion: The partial biological activity of p.Met64Val SRY, maintained at the threshold of SRY function, rationalizes opposing paternal and proband phenotypes (the "the father-daughter paradox").Sex steroids biosynthesis by gonadoblastoma may delay genetic diagnosis and recognition of gonadal tumors. Quantitative assessment of inherited SRY alleles highlights the tenuous transcriptional threshold of developmental decision-making in the bipotential gonadal ridge.

Reproductive Endocrinology

CLINICAL STUDIES IN FEMALE REPRODUCTION I

Prolactin Is Expressed in Uterine Leiomyomas and May Promote Their Growth

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SAT-003

Prolactin is Expressed in Uterine Leiomyomas and May Promote Their Growth

(DiMauro A., Dahal A., Okeke I., Lerman I., Amitrano A., Seger C., Kumar D., Bhagavath B., Taya M., Hammes S. R.)

Uterine leiomyomas, commonly referred to as fibroids, are benign, estrogen sensitive smooth muscle tumors that occur in the myometrium of the uterine wall. Leiomyomas are common, as it is estimated that 60% of reproductive-aged women are affected, and 80% of women develop leiomyomas during their lifetime. In fact, uterine leiomyomas are the leading cause of abnormal menstrual bleeding or menstrual pain, as well as the number one reason for hysterectomy. Novel treatment options are necessary as current treatments are limited to anti-estrogen therapy or hysterectomy. Estrogen is known to have an effect on the etiology of leiomyomas, but little is known about the proliferative roles of other hormones in leiomyomas. One hormone of interest is prolactin (PRL) which is primarily secreted from the pituitary to regulate lactation, but has been linked to proliferation in breast cancer, perhaps via local prolactin production in breast tissue. With this background, we examined local PRL production and its effects on leiomyomas. RNA isolation and quantitative PCR of human leiomyoma samples (n=20) relative to adjacent myometrium in the same patients confirmed significant expression of both PRL ($p= 0.0028$) and dopamine receptor D2, a known regulator of PRL production in the pituitary ($p<0.0001$), with no difference in prolactin receptor expression. Using both immunohistochemistry and immunofluorescence of human leiomyomas samples, we find increased prolactin expression in leiomyomas when compared to adjacent myometrium or control uteri. These results suggest that leiomyomas contain cells producing PRL, which in turn may promote signaling in smooth muscle leiomyoma cells to regulate proliferation. Accordingly, we find that PRL robustly activates STAT5 and MAPK signaling in the rat leiomyoma cell line ELT3. Functional assays were also conducted to evaluate the ability of PRL to induce migration, invasion and proliferation of ELT3 cells. Together, our findings suggest that local prolactin production in leiomyomas may promote their growth, migration, invasion and proliferation. It is possible that this local production is mediated by the dopamine receptor D2. Thus, anti-PRL therapy or dopamine receptor D2 modulation may prove useful in treating this prevalent and often debilitating disease.

Bone and Mineral Metabolism

BONE DISEASE FROM BENCH TO BEDSIDE

Sex Is a Strong Variable in the Mineral Metabolism Defects and Endocrine Dysfunction Associated with the Murine Adenine Diet Model of Chronic Kidney Disease (CKD).

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SUN-351

The adenine diet is widely used in animal models to produce a tubulointerstitial fibrosis and inflammation that mimics human CKD in many aspects. These include the biochemical manifestations hyperphosphatemia and anemia, as well as endocrine dysfunction with elevated FGF23 and hyperparathyroidism. Male rodents are known to be less tolerant of adenine diet regimen than females, however the underlying mechanisms driving the sex differences remain unclear. Additionally, much of the data for adenine studies arises from rats, whereas mice are more commonly used in laboratory settings and are far easier to manipulate genetically. To this end, as part of a larger study to test the effects of iron-handling in CKD, we assessed the biochemical,

molecular, and physical differences between male and female mice receiving an adenine diet to induce CKD. Flox-Fgf23 mice (8 weeks of age, n=4-6/group; mice were Cre negative, thus phenotypically wild type) were placed on a 0.2% adenine-containing diet (CKD); a matching casein-based diet served as control. After 6 weeks, mice were euthanized, and blood and tissues were collected for analysis. As expected, body weight at baseline was initially higher in males than in females, however males lost significantly more weight. Serum BUN was also elevated in both sexes receiving adenine, although males were higher (1.2 fold; $p<0.01$). Males also had elevated creatinine and lower total serum iron from baseline whereas females had no significant changes. FGF23 was elevated in all mice, with no significant differences between sexes. Kidney fibrosis and inflammation markers were elevated in the CKD mice, with males having higher expression of Col1a1 and -3a1 versus females (3.5/1.5 fold; $p<0.001$) and TNFα mRNA (2 fold; $p<0.001$). Renal expression of the anabolic vitamin D metabolizing enzyme Cyp27b1 (1α-hydroyxlase) and early growth response 1 (Egr1) were increased in CKD mice, with males having higher expression over females. Conversely, CKD males had lower kidney Klotho mRNA expression, and both sexes fed adenine expressed significantly lower NPT2a (sodium- phosphate co-transporter2a) mRNA. Liver expression of ferritin (Fth1) was elevated in male CKD mice compared to diet controls, whereas female mice had no differences. Elevated FGF23 has been linked to ventricular hypertrophy, and CKD males had significantly higher heart weight to femur ratio at completion of the study. Our results support that male mice succumb more rapidly than females to adenine diet mediated CKD phenotypes, potentially enhanced by fibrosis and inflammation. It remains to be determined whether the more rapid onset of defects in iron handling parameters accelerate the severe male CKD phenotype.

Reproductive Endocrinology

MALE REPRODUCTIVE HEALTH - FROM HORMONES TO GAMETES

Utility of Ultrasensitive Inhibin B Measurement for the Management of Men with Non-Obstructive Azoospermia

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SAT-043

Inhibin B measurement by conventional assay(s) may be useful in the assessment of spermatogenesis in infertile male patients, especially in cases of azoospermia. Indeed, numerous previous studies have shown that Inhibin B could be helpful to predict a positive testicular sperm extraction (TESE). However, an undetectable Inhibin B concentration (<10pg/mL) does not predict a TESE failure in all cases. These findings explained that most medical centers have precluded the use of Inhibin B assay in the pre-operative hormonal assessment of azoospermic men. Recently, an ultrasensitive Inhibin B assay has been developed allowing the measurement of concentrations below 10pg/mL. The current study aims to assess the clinical relevance of this new assay in men with azoospermia with undetectable Inhibin B levels by conventional assay(s).

Methods: This retrospective study included 71 non-obstructive azoospermic men who had undetectable Inhibin B levels (i.e. <10pg/mL by Gen II ELISA from Beckman Coulter, USA) and who underwent a TESE procedure between 2013 and 2019 in the Lille University Hospital. Serum LH, FSH and testosterone levels were systematically measured by routine immunoassays. Cryopreserved serum samples were used to perform ultrasensitive Inhibin B assay (Ultrasensitive Inhibin B, AL-195, Ansh Labs, USA). Additional hormonal assays including Inhibin A, Activin B and Activin A were performed on available subset of samples.

Results: The TESE was successful, allowing sperm cryopreservation in 32.5 % (25/71) of the cases. No significant statistical difference was found in FSH, LH, or testosterone levels between patients with positive or negative TESE. By contrast, men with positive TESE had more than twice higher serum ultrasensitive Inhibin B levels (median 5.03pg/mL [1.93-8.5] vs. 2.19pg/mL [0.2-4.72], $p=0.006$). An ultrasensitive Inhibin B serum level >3.67pg/mL (determined by ROC analysis) was associated with increased odds ratio (OR= 4.82; 95% CI: 1.647-12.93) for positive TESE. Inhibin A, Activin B and Activin A serum concentrations did not differ significantly between the two groups.

Conclusion: FSH measurement which is routinely performed in men with azoospermia was not predictive of successful TESE whereas, Inhibin B was found to be a valuable marker in predicting TESE success in this population using ultrasensitive Inhibin B assay.

Neuroendocrinology and Pituitary

NEUROENDOCRINOLOGY AND PITUITARY

FGFR-4 Expression in Pituitary Adenomas Is Associated with Aggressive Tumor Features

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MON-269

Biomarkers predicting tumor aggressiveness in pituitary adenomas have been largely investigated, albeit, with inconsistent results. We investigated the relationship of Fibroblast Growth Factor Receptor-4 (FGFR-4) expression and determined its relationship with radiological, pathological, and clinical parameters.