292 individuals with *AMH* PAVs were identified, resulting in a combined 0.95% prevalence of *AMH* PAVs in an unselected population (1.07% in Europeans, 0.28% in African Americans, 0.54% in Hispanics, and 0.07% in Asians). After adjusting for age, BMI, and race/ethnicity, there was a statistically significant increased prevalence of hypertriglyceridemia in both women (OR 7.29, 95% CI 3.77-14.00) and men (OR 10.15, 95% CI 4.68-22.00) with *AMH* PAVs compared to sex-, age- and BMI-matched controls. There was also a statistically significant increased prevalence of elevated cholesterol in men with *AMH* PAVs compared to controls (OR 2.48, 95% CI 1.15-5.34). There were no significant differences between individuals with *AMH* PAVs and matched controls with respect to the other outcomes. These findings suggest that decreased bioactivity of AMH is causally related to dyslipidemia in the general population. TG levels are elevated in both sexes, whereas increases in cholesterol are only seen in men. The mechanisms by which decreases in AMH bioactivity alter circulating lipid levels are of considerable interest since AMH has no known metabolic actions. It is possible that the putative metabolic effects of AMH are mediated by increases in circulating testosterone (T) levels that in turn alter lipid metabolism. Since T levels are not commonly available in EHR, future studies will be needed to investigate this hypothesis as well as to explore metabolic actions of AMH.

Reproductive Endocrinology

HYPERANDROGENIC DISORDERS THROUGHOUT THE LIFESPAN AND INTO THE NEXT GENERATION

Assessment of Depression Among Adolescent Indian Girls With PCOS

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Background: Prevalence of PCOS is increasing among Indian women due to growing changes in environment and lifestyle and also due to awareness of symptoms and willingness to seek medical help. Six out of ten females diagnosed with PCOS are teenage girls. Studies have shown that the women with PCOS often suffer from psychiatric comorbidities including depression but the data regarding the prevalence of depression in adolescent Indian girls with PCOS are scarce. **Aim:** To find out the prevalence of depression and its associations among adolescent Indian girls with PCOS. **Methods:** This was a cross sectional, case-control study conducted in the Endocrinology department of a speciality hospital of North India. We evaluated 160 newly diagnosed adolescent PCOS girls aged between 13-19 years, diagnosed by Revised Rotterdam criteria. Control group included 80 healthy, age matched, non-PCOS girls. Detailed history, Anthropometric measurements and standard hormonal evaluation were done. Depression was assessed by administering Patient Health Questionnaire-Adolescents (PHQ-A), a self-administered questionnaire based on DSM IV criteria. PHQ-A score of >10 was considered as the threshold for significant depression. Statistical evaluation was done with SPSS and P value of <0.05 was significant**. Results:** Mean age of the patients was 16.3 +/- 3.2yrs. The frequencies of significant depression in PCOS and control groups were 36.5% and 11.9% respectively. PCOS adolescents having higher HOMA-IR value (p-0.03), higher hirsutism score (P-0.01) and higher BMI (p-<0.01) had a higher risk of significant depression. Menstrual irregularity, acne, dyslipidaemia, serum testosterone, 17-OHP, prolactin and serum TSH levels had no significant correlation with depression. **Discussion:** PCOS commonly prevails during adolescence, a phase when girls are more concerned about their physiology and physical health. Negative body image and chronic stress can lead to disturbed mental health. Our study by using a simple and patient friendly clinical tool the PHQ-A has found higher prevalence of depression (almost 3 times) in Indian adolescent PCOS girls as compared to controls and it significantly corelates with insulin resistance, hirsutism and obesity. PCOS puts tremendous burden, on both physical as well as mental health, especially in adolescents, due to its effects on physical appearance, self-esteem, fertility and also due to other long term metabolic complications associated with it. PCOS is an urgent health problem that needs careful assessment and appropriate treatment of its all aspects. Timely recognition of mental health issues in these girls can help with early interventions including referral to mental health specialists (if needful) and add to the wellbeing of these young girls. **Conclusion:** The initial evaluation of PCOS in adolescent girls should also include the assessment of mental health disorders.

Reproductive Endocrinology

HYPERANDROGENIC DISORDERS THROUGHOUT THE LIFESPAN AND INTO THE NEXT GENERATION

Circulating HMGB1 Levels Are Associated With Glucose Clamp-Derived Measures of Insulin Resistance in Women With PCOS

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Context: High mobility group box 1 (HMGB1) is a nuclear constitutive and highly conserved mammalian protein which shows several important physiologic functions, playing a crucial role in local and systemic inflammation. It also seems to be implicated in the development of metabolic syndrome, whereas some in vitro and animal models and recent preliminary human studies suggested its potential role in polycystic ovary syndrome (PCOS) pathophysiology. In particular, some data suggested a potential role of HMGB1 in follicular maturation block. Moreover, increased blood and follicular fluid HMGB1 concentrations have been reported in PCOS women, showing a direct correlation with surrogate indexes of insulin-resistance (IR) (i.e. HOMA-IR).
Objective: The purpose of the present study was to investigate the relationships between serum HMGB1 levels and clinical, endocrine and metabolic parameters of PCOS patients.

Design and patients: Sixty women with PCOS, 30 with IR and 30 with normal insulin sensitivity (IS), and 30 healthy controls were included in the study. In these subjects, body fat was quantified by bioelectrical impedance; plasma HMGB1 levels were measured using a specific ELISA method (Tecan, Mannedorf, Switzerland); and serum androgens were measured by liquid chromatography/mass spectrometry and equilibrium dialysis. In PCOS women, IR was measured using the gold standard hyperinsulinemic-euglycemic clamp technique, combined with indirect calorimetry.
Results: HMGB1 levels did not differ between PCOS women and healthy controls (4.11 ± 3.22 vs 3.77 ± 2.50 ng/mL, respectively; p=0.61). Moreover, HMGB1 levels did not differ between PCOS phenotype subgroups. However, PCOS IR women showed higher levels of this protein as compared with PCOS IS (5.00 ± 3.53 vs 3.16 ± 2.59 ng/mL, respectively; p=0.017). In women with PCOS, HMGB1 levels were associated with several metabolic parameters, including IR measured by glucose utilization during the clamp (rho -0.37, p=0.005). This correlation was preserved after adjusting for potential confounding parameters, such as age, fat mass and serum free testosterone. HMGB1 levels did not change during glucose-clamp induced acute hyperinsulinemia, either in the whole cohort of patients or in IR and IS subgroups analyzed separately. Both in the whole population under study and in PCOS women, HMGB1 levels did not correlate with anthropometric parameters, hormonal features and ovarian morphology.
Conclusions: In women with PCOS, HMGB1 blood levels show an independent association with insulin resistance. However, no associations with other typical features of the syndrome were found. Further research is needed in order to establish whether this protein may play a role in the pathogenesis of PCOS.

Reproductive Endocrinology

HYPERANDROGENIC DISORDERS THROUGHOUT THE LIFESPAN AND INTO THE NEXT GENERATION

Early Phenotypes in Girls at Risk for PCOS Replicate Metabolic and Reproductive Subtypes: An Unsupervised Clustering Analysis

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Both daughters of women with PCOS (PCOS-d) and overweight girls (OW-g) are proposed to be at increased risk of PCOS because they have peripubertal increases in testosterone (T) levels, a cardinal feature of PCOS. We are testing this hypothesis by performing longitudinal studies in these girls after menarche. In adult women with PCOS, we have recently identified reproductive and metabolic subtypes using unsupervised cluster analyses. These subtypes were associated with novel PCOS susceptibility genetic loci suggesting that the subtypes reflect biologically discrete entities. We performed similar analyses in our cohort of early postmenarchal PCOS-d and OW-g to test the hypothesis that these subtypes are present in girls at risk for PCOS.
Fifteen PCOS-d and 10 OW-g aged 11-16 years and with postmenarchal age less than 2 years were studied. Mothers of PCOS-d fulfilled NIH criteria for PCOS, mothers of OW-g were reproductively normal with no history of irregular menses or clinical hyperandrogenism. OW-g had a BMI above the 85th percentile for age. There was no BMI inclusion criterion for PCOS-d; four PCOS-d had a BMI above the 85th percentile. The girls were of comparable age, postmenarchal age and BMI z score. A fasting morning blood sample was drawn for T, SHBG, DHEAS, glucose and insulin. Leuprolide 10 mcg/kg SC was administered. LH and FSH levels were measured at baseline, 30 min, and 60 min following leuprolide.
Unsupervised hierarchical cluster analysis adjusted for age was performed on quantitative traits including BMI, T, fasting insulin, fasting glucose, DHEAS, SHBG, and LH and FSH. These are the same quantitative traits used for clustering in adult PCOS. The clustering revealed 2 distinct PCOS subtypes: a reproductive group (41%), characterized by higher SHBG levels, LH and FSH with relatively low BMI and insulin levels, and a metabolic group (41%), characterized by higher BMI and insulin levels and lower SHBG, LH, and FSH. Jaccard coefficients indicated cluster stability (0.70 reproductive, 0.69 metabolic). There was a significant difference in the distribution of the two subgroups in PCOS-d and OW-g: PCOS-d 60% reproductive, 13% metabolic, 27% indeterminate; OW-g 25% reproductive, 50% metabolic, 25% indeterminate (Chi Sq P=0.05).
We found that early postmenarchal PCOS-d and OW-g demonstrate reproductive and metabolic subtypes similar to those identified in adult women with PCOS. The majority of PCOS-d had the reproductive subtype. These findings suggest that this subtype, which is characterized by disordered gonadotropin secretion, is an early harbinger of PCOS. Longitudinal studies are ongoing to test this hypothesis.

Reproductive Endocrinology

HYPERANDROGENIC DISORDERS THROUGHOUT THE LIFESPAN AND INTO THE NEXT GENERATION

Ethnic Disparities in Cardio-Metabolic and Reproductive Profiles in Women With Polycystic Ovary Syndrome per the New International Guideline: A United-States Based Multi-Center Study

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The magnitude and direction to which cardio-metabolic and reproductive aberrations may disproportionately impact diverse populations of women with PCOS are relevant yet unclear. The uncertainty stems, in