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.

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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

part, from heterogeneity in PCOS diagnostic criteria used and technical challenges in the reliable assessment of this clinical population. We evaluated whether cardio-metabolic (abdominal adiposity, hypertension, impaired glucoregulatory status) and reproductive (hyperandrogenism, polycystic ovarian morphology [PCOM], menstrual irregularity) outcomes were different in PCOS (n = 120, 18-36 yrs.) across 4 groups: (1) Non-Hispanic White (n = 76); (2) Non-Hispanic Black (n = 14); (3) Non-Hispanic Asian (n = 15); and, (4) Hispanic White (n = 15). Women were prospectively recruited across 3 academic medical centers in New York State and were matched for age and body mass index. PCOS was defined by the Rotterdam criteria using the recommended thresholds of the 2018 International Evidence-based Guideline for the Assessment and Management of PCOS. Concerning abdominal adiposity, the Asian group (mean ± standard deviation; 0.78 ± 0.06) had a lower waist to hip ratio (WHR) compared to the White group (0.85 ± 0.09; P = 0.01). Also, the Asian group had a higher sex hormone binding globulin (SHBG, 65.9 ± 23.4 nmol/L) compared to all other groups (White [40.5 ± 22.3]; Black [43.8 ± 21.9]; Hispanic [36.8 ± 18.8] nmol/L; All: P < 0.04). In contrast, the White group were most hyperandrogenic, evidenced by their higher modified Ferriman-Gallwey (mFG) scores (10 ± 4) compared to other groups (Black [4 ± 0]; Asian [2 ± 0]; Hispanic [4 ± 1]; All: P ≤ 0.001). Consistently, the White group (1.0 ± 0.5 ng/dL) exhibited increased free testosterone (FT) compared to other groups (Black [0.5 ± 0]; Asian [0.4 ± 0]; Hispanic [0.6 ± 0.1] ng/dL; All: P ≤ 0.001), unlike total testosterone (P = 0.12). Regarding PCOM, the White group exhibited higher follicle numbers per ovary (FNPO 2-9 mm, 48 ± 22) compared to other groups (Black [30 ± 16]; Asian [26 ± 5]; Hispanic [22 ± 17]; All: P ≤ 0.05). Unlike Black (12.4 ± 1.3 mm; P = 0.05) and Hispanic (13.5 ± 1.1 mm; P = 0.89) groups, the White group (13.9 ± 2.1 mm) also exhibited larger ovarian volume (OV) compared to Asian group (12.4 ± 1.5 mm; P = 0.03). Women had comparable blood pressure (systolic, diastolic), fasting glucose, homeostatic model assessment of insulin resistance, or intermenstrual interval length (All: P ≥ 0.09). Overall, Asian women in the US likely exhibit the mildest PCOS metabolic (decreased WHR, increased SHBG) phenotype, whereas White women show the most severe reproductive (increased mFG, FT, FNPO, OV) phenotype. If confirmed by larger studies, our observations warrant additional population-specific diagnostic considerations to prevent and manage PCOS cardio-metabolic (e.g., metabolic syndrome risk) and reproductive (e.g., hirsutism, PCOM) complications across ethnicities.

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Evaluation of Thyroid Function and Its Relationship With Metabolic Parameters in Indian Adolescents With PCOS

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Background: Women with PCOS have high insulin resistance and a higher prevalence of raised TSH levels. Thyroid dysfunction can lead to the alterations in lipid and metabolic parameters. There is a very little data regarding the relationship between TSH and indices of insulin resistance in Indian adolescents with PCOS. **Aim of Study:** To assess the status of thyroid function and its impact on biochemical parameters and cardiovascular (CV) risk factors in Indian Adolescents with PCOS. **Methods:** Study group was 130 adolescents aged between 13 to 19 years, recently diagnosed with PCOS as per Revised Rotterdam criteria and a control group of 75 age matched, healthy, non PCOS females. Participants were subjected to an elaborate clinical, anthropometric and biochemical assessment. Hormonal analysis included serum FT3, FT4, TSH, anti-TPO antibody, LH, FSH, prolactin, free testosterone, 17 OH progesterone, Lipid profile. Fasting plasma glucose and Insulin were used to calculate HOMA-IR. Statistical analysis was done by SPSS. P value of <0.005 was significant. **Results:** Mean age of the subjects was 15.9 ± 3.1 years. Mean level of TSH was higher in PCOS group than in controls (4.1 ± 3.1 vs 2.8 ± 1.9; p-<0.001). There was significantly higher prevalence of subclinical hypothyroidism (SCH) (19.2%vs 6.7%;p-0.01), Anti TPO antibody titre (18.6 vs 4.7%; p,0.01) and goitre (14.1%vs 3.2%; p - 0.02) in PCOS subjects compared to controls. BMI and Systolic BP were higher in PCOS with SCH. Free testosterone (p-0.002), HOMA-IR (p- 0.03) and dyslipidaemia (p < 0.01) were significantly higher in PCOS subjects with SCH as compared to both euthyroid PCOS and euthyroid controls. **Discussion:** 50-70% women with PCOS, have been reported to have insulin resistance and hyperinsulinemia and are at a higher risk for developing metabolic and CV diseases. Literature supports the high prevalence of SCH/thyroid autoimmunity in PCOS. In this study we have found that Indian adolescents with PCOS have a high prevalence of SCH. Also we have observed significant changes in insulin resistance indices in PCOS subjects with SCH as compared to those with normal thyroid functions. The association between TSH level and insulin resistance indices is complex and one probable mechanism is that the hypothyroidism leads to increase in adiposity and pro inflammatory markers. This unique interplay of PCOS, adiposity, thyroid dysfunction and autoimmunity forms a complex pathophysiological pathway which leads to the potentiation of insulin resistance thereby resulting in a further increase in metabolic and CV risk in women with PCOS. **Conclusion:** There is a high prevalence of SCH in Indian Adolescents girls with PCOS and it is associated with significant changes in insulin resistance indices, which may increase the risk of metabolic and CV disorders in these already vulnerable young subjects.

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HYPERANDROGENIC DISORDERS THROUGHOUT THE LIFESPAN AND INTO THE NEXT GENERATION

Lifestyle and Weight Change in Women With Polycystic Ovary Syndrome During COVID19 Pandemic

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