OR17-3: A Genetically Defined Male Counterpart of Polycystic Ovary Syndrome: Evidence for Ovarian-Independent Pathogenesis

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Background: Polycystic ovary syndrome (PCOS) is a heterogeneous condition that affects 6-10% of women of reproductive age. PCOS is often characterized by a triad of ovulatory dysfunction, hyperandrogenism, and cardiometabolic dysfunction. Both ovarian-related and ovarian-independent factors have been implicated in the pathogenesis of PCOS, but it remains to be determined which are the inciting events and which are the secondary consequences. Studies of male relatives of women with PCOS have proposed a male counterpart of PCOS, which suggests that PCOS is not always a primary disorder of female reproduction, but rather can be, at least in part, a condition of cardiometabolic dysregulation and hyperandrogenism, with ovarian dysfunction as a secondary consequence.

Methods: To investigate a genetically defined male counterpart of PCOS, we optimized a polygenic risk score (PRS) algorithm for predicting PCOS based on 206,851 unrelated women of European ancestry in the UK Biobank, then used this algorithm to calculate PCOS PRS for 176,360 men in the UK Biobank. We used logistic regression to calculate odds ratios for dichotomous outcomes by comparing men with high and low PRS (testing a variety of percentile cutoffs) and ANCOVA to compare continuous outcomes across deciles of PRS. All analyses were adjusted for age, age2, assessment center, genotyping array, and the first 10 principal genetic components to account for ancestry.

Results: Men who carried a high PCOS PRS (top 20%) had a 17% increased risk of obesity defined as BMI ≥30 kg/m2 (OR 1.17, 95% confidence interval [CI] 1.14-1.20, p=1.3x10-30), 15% increased risk of type 2 diabetes mellitus (OR 1.15, 95% CI 1.09-1.20, p=5.3x10-8), 5% increased risk of coronary artery disease (OR 1.05, 95% CI 1.01-1.09, p=0.03), and 5% increased risk for androgenic alopecia (OR 1.05, 95% CI 1.01-1.08, p=0.01). BMI, hemoglobin A1c, triglycerides, and the free androgen index all increased across deciles of the PRS, while HDL and SHBG decreased across PRS deciles (p all <0.001). The relationship between the PCOS PRS and coronary artery disease, HDL, and triglycerides appeared to be mediated by BMI. In contrast, the associations between the PCOS PRS and type 2 diabetes mellitus and hemoglobin A1c remained significant after adjusting for BMI, suggesting independent mechanisms of pathogenesis.

Conclusions: By demonstrating associations between PCOS genetic risk factors and cardiometabolic dysfunction and androgenic conditions in men, we have shown that these genetic risk factors can act independently of ovarian function. Thus, at least in some cases, the reproductive dysfunction of PCOS in women may arise secondarily from disruption of biological pathways common to both men and women. Future dissection of these biological pathways will further inform efforts to identify pathological mechanisms underlying PCOS.

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