P-231 6:45 AM Tuesday, October 25, 2022

THE EFFECTIVENESS OF INTRAUTERINE INSEMINATION (IUI) WITH OR WITHOUT OVARIAN STIMULATION (OS) IN WOMEN WITH "OVERT" OR "AT RISK" FOR TUBAL-FACTOR INFERTILITY (TFI).

Yao Lu, MD,[1] Panagiotis Cherouveim, MD,[2] Victoria S. Jiang, MD,[1] Karissa C. Hammer, MD,[3] Irene Dimitriadis, MD,[1] Charles L. Bormann, PhD,[1] Kaitlyn E. James, PhD,[4] Irene Souter, MD[1]
[1]Massachusetts General Hospital Fertility Center, Massachusetts General Hospital and Harvard Medical School, Boston, MA; [2]Massachusetts General Hospital Fertility Center, Boston, MA; [3]Institute for Human Reproduction, Chicago, IL; [4]Deborah Kelly Center for Outcomes Research, Massachusetts General Hospital and Harvard Medical School, Boston, MA.

OBJECTIVE: To investigate the effectiveness of IUI±OS for women with "overt" or "subtle" TFI (such as those with endometriosis) in comparison to those with unexplained infertility (UI)

MATERIALS AND METHODS: *Design*: Retrospective cohort.

Setting: Academic Center.

Patients: 4613 IUI±OS cycles from 1625 women with one of the following diagnoses: TFI (269 cycles, 105 women), endometriosis (ENDO: 242 cycles, 87 women), or UI (4102 cycles, 1433 women).

Interventions: IUI±OS.

Outcomes:

Primary: Ongoing pregnancy rate (OPR).

Secondary: Clinical (CPR) and ectopic pregnancy rate (EcPR), as well as spontaneous abortion rate (SABR).

Statistics: Chi-square, Fisher's exact, analysis of variance, and Kruskal-Wallis tests were used as appropriate. Risk ratios (RR) and 95% confidence intervals (CI) for the incidence of ectopic pregnancy were calculated. Odds ratios (OR) and 95% CI were calculated with generalized estimating equations (GEE) logistic regression models and adjusted for maternal age, BMI, day-3 FSH, prior parity, OS regimen, and total progressive motile sperm count.

RESULTS: CPRs and SABRs did not differ significantly between groups (CPR: 10.0% vs. 10.3% vs. 12.6%, p=0.304; SABR: 25.9% vs. 8.0% vs. 17.9%, p=0.221; for TFI vs. ENDO vs. UI, respectively). Yet EcPR in TFI was 8.17 times that of UI group (11.1% vs. 1.4%, p=0.010; RR: 8.17, 95%CI: 2.24-29.87, UI: *ref.*). No ectopic pregnancies were observed in ENDO group.

OPRs per identified clinical pregnancy were lowest among patients with TFI (63.0% vs. 92.0% vs. 80.8%, for TFI vs. ENDO vs. UI, respectively, p=0.025). Following adjustments for confounders, TFI cycles had 47% lower odds to result in an ongoing pregnancy compared to those with UI (adjOR: 0.53, 95% CI: 0.31-0.91, p=0.021, UI: *ref.*), while no such association was observed for ENDO (adjOR: 0.81, 95% CI: 0.46-1.42, p=0.457, UI: *ref.*).

Interestingly, although cumulative OPRs after 3 or 4 IUI cycles were lowest in TFI group, the differences among groups did not reach statistical significance (3 cycles: 16.2% vs. 17.2% vs. 22.5%, p=0.178; 4 cycles: 16.2% vs. 18.8% vs. 24.7%, p=0.080; for TFI vs. ENDO vs. UI, respectively).

CONCLUSIONS: Overt TFI seemed to be associated with impaired IUI outcomes with regard to increased EcPR and decreased OPR as compared to UI, whereas our results do not suggest such associations for women "at-risk" for TFI such as those with endometriosis.

IMPACT STATEMENT: Because of the potential higher risk of ectopic and lower chances of ongoing pregnancy, women with overt tubal factor infertility may benefit from earlier transition to IVF.

SUPPORT: None.

P-232 6:45 AM Tuesday, October 25, 2022

SENSITIVITY, SPECIFICITY, AND PREDICTIVE VALUE OF URINARY ANDROGEN METABOLITES FOR THE DIAGNOSIS OF POLYCYSTIC OVARY SYNDROME.

Mark Newman, MS,[1] Doreen Saltiel, MD, JD,[1] Bryan P. Mayfield, PharmD,[1] Frank Z. Stanczyk, PhD[2] [1]Precision Analytical, Inc, McMinnville, OR; [2]University of Southern California, Los Angeles, CA.

OBJECTIVE: The objective of this study was to determine if urinary androgen metabolite concentrations measured using an at-home dried urine sampling method and an accompanying gas chromatography-tandem mass spectrometry (GC-MS/MS) assay could be used to confirm or rule out polycystic ovary syndrome (PCOS).

MATERIALS AND METHODS: This was a retrospective observational cohort study conducted using a database containing 144,561 laboratory accessions that were submitted between January 1, 2016 and December 9, 2019 by 129,883 patients. These patients collected urine samples on filter paper at home and sent the collections to the laboratory to be processed. Urinary concentrations of androsterone, dehydroepiandrosterone sulfate (DHEA-S), epitestosterone, etiocholanolone, testosterone, 5α-androstanediol, 5β-androstanediol, and 5α-dihydrotestosterone (DHT) were measured. The database included a total of 2050 patients with a reported diagnosis of PCOS and 27488 patients who did not report a PCOS diagnosis. A "urinary androgen index" was created comprising all measured androgen metabolites. Mixed models were then created to determine sensitivity, specificity, and predictive values of the components of this urinary androgen index.

RESULTS: Mixed models determined that for patients with a measured urinary androgen index greater than or equal to 4 (4 or more androgen metabolites above the reference range) the sensitivity was 0.44, the specificity was 0.78, the positive predictive value was 0.13, and the negative predictive value was 0.95. For patients with a measured epitestosterone, etiocholanolone, or testosterone above the reference range the sensitivity was 0.70, the specificity was 0.53, the positive predictive value was 0.10, and the negative predictive value was 0.96. For patients with a measured urinary testosterone higher than the 75th percentile of the reference range, the sensitivity was 0.47, the specificity was 0.76, the positive predictive value was 0.13, and the negative predictive value was 0.95.

CONCLUSIONS: Urinary androgen metabolites measured using a dried urine sample and a validated GC-MS/MS assay demonstrated low positive predictive values, but high negative predictive values for PCOS suggesting that these measures may be of use in ruling out PCOS.

IMPACT STATEMENT: In this large general population study, a dried urine sampling method measuring androgen metabolites demonstrated the potential to be effective at ruling out PCOS. This method may represent a new, convenient, at-home, non-invasive tool for clinicians and researchers to use in settings where barriers exist to in-person patient evaluation or ultrasonography. When combined with additional information available from urine sampling, this tool may provide a comprehensive panel of results to inform both clinical investigation and decision making.

P-233 6:45 AM Tuesday, October 25, 2022

PREDICTING THE DIAGNOSIS OF POLYCYSTIC OVARIAN SYNDROME (PCOS) AMONG AT RISK WOMEN WITHIN AN ELECTRONIC HEALTH RECORD.

Victoria S. Jiang, MD,[1] Zahra Zad, BS,[2] Taiyao WANG, PhD,[2] Ioannis Paschalidis, PhD,[2] Shruthi Mahalingaiah, MD, MS[3] [1]Massachusetts General Hospital Fertility Center, Boston, MA 02114, MA; [2]Boston University, Boston, MA; [3]Harvard T.H. Chan School of Public Health, Boston, MA.

OBJECTIVE: To determine informative predictor variables associated with the diagnosed and undiagnosed polycystic ovarian syndrome (PCOS) through an electronic health record (EHR)

MATERIALS AND METHODS: *Design*: Retrospective cohort

Setting: Academic Medical Center between October 2003 to December 2016.

Patients: 30,874 female patients aged 18-45 years without concurrent endocrinopathy.

Intervention: Patients were classified into three models: patients with ICD-9 code for PCOS (Model I), patients diagnosed with PCOS by Rotterdam criteria by ICD-9 without the ICD-9 PCOS code (Model II), and all patients with PCOS diagnosis within Model I and Model II (Model III).

Outcomes: Clinical, biochemical, socioeconomic, and demographic predictive variables.

Statistics: Machine learning predictive models including logistic regression with statistical features selection (LR-SFS) were generated to determine the predictive variables for each model. Area under the receiver operating curve (AUC) determined the accuracy of each model. The importance of each predictive variable was determined by its predictive coefficient (PC). To accommodate their nonlinear relationship, FSH, LH, Estradiol, and SHBG were combined using a neural network to create a MLP score for each model. All reported predictive coefficients had a p-value<0.001.

RESULTS: Within Model I, the predictive model achieved an AUC(SD) of 80.9% (1.2). MLP score (PC = 0.62) and obesity (PC = 0.43) were positively correlated with PCOS diagnosis. Pregnancy (gravidity PC = -0.55; positive pregnancy test PC = -0.49), normal BMI (PC = -0.22), and smoking (PC = -0.18) were inversely correlated with PCOS diagnosis.

Within Model II, the predictive model achieved an AUC(SD) of 75.0% (1.8). MLP score (PC = 0.56), obesity (PC = 0.18), normal BMI (PC = 0.15), negative pregnancy test (PC = 0.11), and normal HDL (PC 0.09) were positively correlated with undiagnosed PCOS. Age (PC = -0.27), pregnancy (gravidity PC = -0.24; positive pregnancy test PC = -0.2), and Hispanic race (PC = -0.18) were inversely correlated with undiagnosed PCOS.

Within Model III, the predictive model achieved an AUC(SD) of 79.1% (1.1). MLP score (PC = 0.7), obesity (PC = 0.31), normal BMI (PC = 0.15), and hypertension (PC = 0.07) were positively correlated with PCOS diagnosis. Age (PC = -0.21), pregnancy (gravidity PC = -0.37; positive pregnancy test PC = -0.34; negative pregnancy test PC = -0.05), Hispanic race (PC = -0.12), smoking (PC = -0.08), and were inversely correlated with PCOS diagnosis.

CONCLUSIONS: These predictive models are a novel approach to identifying barriers to PCOS diagnosis. While some factors like age, pregnancy status, obesity, and hypertension were predictive of PCOS diagnosis, other factors like normal BMI and normal blood pressure were predictive of undiagnosed PCOS may suggest leaner phenotypes can potentially lead to missed PCOS diagnosis or that disease severity may be a factor in diagnosis.

IMPACT STATEMENT: As the use of machine learning expands, these algorithms may serve as an important tool in conjunction with the EHR to assist in predicting diagnoses that may be otherwise missed.

P-234 6:45 AM Tuesday, October 25, 2022

PRENATAL ANDROGEN EXPOSURE IN MICE LEADS TO A METABOLICALLY DISTINCT PCOS WITHOUT OBESITY. Alexandra Gannon, M.D.,[1] Janet Bruno-Gaston, M.D.,[2] Vipin A. Vidyadharan, PhD,[3] Marta L. Fiorotto, PhD,[2] Shaji Chacko, PhD,[2] Juan Marini, PhD,[2] Amy K. Schutt, MD, MSCI,[2] William Gibbons, MD,[1] Chellakkan Selvanesan Blesson, B.SC., M.PHIL., M.SC., PH.D.[1] [1]Baylor College of Medicine, Dept of Obstetrics & Gynecology, Houston, TX; [2]Baylor College of Medicine, Houston, TX; [3]Houston, TX.

OBJECTIVE: Our objective was to elucidate the mechanisms of glucose metabolism in a lean polycystic ovary syndrome (PCOS) mouse model.

MATERIALS AND METHODS: Lean PCOS mice were created by administering dihydrotestosterone prenatally on days 16.5, 17.5 and 18.5 of gestation. Control group mice received vehicle only. We evaluated their weight gain, body mass index (BMI) body composition and estrous cycles at 3 months of age. To ascertain how these PCOS mouse remain lean, we evaluated their feeding and activity patterns, energy expenditure, respiratory exchange ratio (RER) and sleep pattern using a Comprehensive Laboratory Animal Monitoring System. To identify the regulation of total hepatic glucose production, we measured the rate of glucose production (GPR) during fasting and glucose-rich states by infusing deuterated tracer glucose and measuring the penta-acetate derivative of deuterium-enriched glucose using isotope ratio mass spectrometry. Further, we compared the expression of key enzymes involved in glycogenolysis and gluconeogenesis in liver using qPCR. We also compared the expression of signaling molecules involved in insulin signaling by qPCR and Western blot in the lean PCOS and control group liver and ovary.

RESULTS: Prenatally androgenized PCOS mice remained lean with no differences in weight, BMI, body composition or mean cycle length, but they had irregular estrus cycles and higher frequency of irregular cycles (34% in lean PCOS vs 11% in controls; $p<0.001$). PCOS mice showed no differences in feed intake, total energy expenditure, RER, activity patterns or sleep patterns when compared to controls. Interestingly, the percentage suppression of GPR during simulated fed state was greater in lean PCOS mice (40±3 in lean PCOS vs. controls 27±5; $p<0.05$) when normalized to lean body mass. Hepatic glycogen content was lower in lean PCOS mice (55±9 μg/g tissue in lean PCOS vs 106±20 μ/g tissue in controls). Multiple metabolic pathways, including gluconeogenesis, glycogenolysis, insulin-signaling, and glycolysis were affected in the lean PCOS ovary and liver. Further, insulin signaling pathways in the ovary and glycolysis in the liver were also affected.

CONCLUSIONS: Prenatal androgen exposure causes PCOS with a lean phenotype. The lean phenotype is due to metabolic and not behavioral changes. Lean PCOS mice displayed increased suppression of GPR suggesting a stressed glucose production suppression system. Further, these animals also showed dysregulated expression genes involved in multiple metabolic pathways in liver and ovary.

IMPACT STATEMENT: Lean PCOS is metabolically distinct than the obese population. We show for the first time that the hepatic glucose production suppression mechanism is overworked to maintain homeostasis in these mice. The metabolic differences could be due to the timing of the androgen exposure.

P-235 6:45 AM Tuesday, October 25, 2022

LOW-DOSE FLUTAMIDE ALTERS ABDOMINAL ADIPOGENIC FUNCTION IN NORMAL-WEIGHT POLYCYSTIC OVARY SYNDROME WOMEN (PCOS); A DOUBLE-BLIND, PLACEBO-CONTROLLED, RANDOMIZED CLINICAL TRIAL. Chloe Winnett, B.S.,[1] Gwyneth Lu, B.S.,[1] Tristan R. Grogan, M.S.,[1] Rajanigandha Naik, M.D.,[1] David H. Abbott, Ph.D,[2] Gregorio D. Chazenbalk, Ph.D.,[1] Daniel A. Dumesic, M.D.[1] [1]UCLA, Los Angeles, CA; [2]University of Wisconsin, Madison, WI.

OBJECTIVE: In normal-weight women with polycystic ovary syndrome (PCOS), hyperandrogenism accompanies increased abdominal fat mass and accelerated subcutaneous (SC) abdominal stem cell differentiation into adipocytes *in vitro* (1-4). This study examined whether androgen receptor blockade by low-dose flutamide administration to normal-weight PCOS women lowers abdominal fat mass and/or reduces accelerated SC abdominal stem cell lipid accumulation during adipocyte development *in vitro* and if so whether such changes alter metabolism.

MATERIALS AND METHODS: Twelve normal-weight, NIH-defined PCOS women and 12 age- and body mass index (BMI)-matched normoandrogenic ovulatory (control) women underwent circulating hormone/metabolic determinations, intravenous glucose tolerance testing, total-body dual-energy x-ray absorptiometry and SC abdominal fat biopsy. Interventions were repeated in PCOS women after randomization to flutamide (125 mg orally daily) or placebo treatment for 6-months. Clinical characteristics and SC abdominal stem cell lipid accumulation *in vitro* were compared between PCOS and control subjects. Changes in abdominal fat mass and SC abdominal stem cell lipid accumulation *in vitro* were compared between flutamide- and placebo-treated PCOS women and correlated with endocrine-metabolic outcomes. An unpaired Student's *t*-test, two-way ANOVA with repeated measures and Pearson correlation coefficients, adjusting for serum free testosterone (T) levels, were used.

RESULTS: Serum luteinizing hormone and androgen levels, and SC abdominal stem cell lipid accumulation *in vitro*, were greater in PCOS than control women (all values, $P<0.01$). During flutamide versus placebo treatment, treatment-time interactions existed for percent (%) android fat ($P=0.040$), SC abdominal stem cell lipid accumulation *in vitro* ($P=0.004$) and serum log nonHDL ($P=0.026$) and log LDL ($P=0.034$) values. After adjusting for serum free T levels, only % android fat ($P=0.013$) and SC abdominal stem cell lipid accumulation *in vitro* ($P=0.008$) remained significant. Flutamide versus placebo treatment in PCOS women reduced % android fat ($P=0.040$), serum log nonHDL ($P=0.056$) and log LDL ($P=0.034$) values, and partially lowered SC abdominal stem cell lipid accumulation *in vitro* relative to control cells ($P=0.004$). In all PCOS subjects, changes in % android fat positively correlated with those of serum log nonHDL values (R=0.69, $P=0.019$) and also were affected by hyperandrogenemia (adjusting for serum free T: nonHDL, R=0.56, P=0.096; log LDL, R=0.31, $P=0.385$). Changes in SC abdominal stem cell lipid accumulation *in vitro and* serum lipid levels were unrelated.

CONCLUSIONS: Low-dose flutamide administration to normal-weight PCOS women lowers abdominal fat mass and serum atherogenic lipoprotein levels, and partially reduces accelerated SC abdominal stem cell lipid accumulation during adipocyte development *in vitro*.

IMPACT STATEMENT: Androgen receptor blockade in normal-weight PCOS women alters metabolism by reducing abdominal fat mass relative to accelerated SC abdominal stem cell differentiation into adipocytes *in vitro*.

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