19th ANNUAL MEETING OF THE ANDROGEN EXCESS & PCOS SOCIETY

NOVEMBER 12-14, 2021
1-5 PM EST
VIRTUAL PLATFORM
# Day 1, November 12th, 1-5pm EST

## Time | Speaker | Topic
--- | --- | ---
1:00 pm (EST) | **Kathleen Hoeger** University of Rochester, Rochester, NY, USA, President of the AE-PCOS Society  
**Rebecca Campbell** University of Otago, Dunedin, New Zealand, Programme Organising Chair | Welcome and Overview: AEPCOS Annual Meeting 2021

### Session 1: PCOS in adolescence

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<tr>
<th>Time</th>
<th>Speaker</th>
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<tbody>
<tr>
<td>1:05 pm</td>
<td><strong>Chris McCartney</strong> University of Virginia Health, Charlottesville, Virginia, USA</td>
<td>PCOS ontogeny in adolescence</td>
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<tr>
<td>1:30 pm</td>
<td><strong>Maria Trent</strong> Johns Hopkins University, Baltimore, Maryland, USA</td>
<td>Management of polycystic ovary syndrome in adolescents and young adults</td>
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<tr>
<td>1:55 pm</td>
<td><strong>Lisa Moran</strong> Monash University, Melbourne, Australia</td>
<td>Lifestyle approaches for the adolescent with PCOS</td>
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<tr>
<td>2:20 pm</td>
<td><strong>Moderator: Sue Moenter</strong> University of Michigan, MI, USA</td>
<td>LIVE Q&amp;A: Session 1</td>
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## Presidential Lecture

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<th>Time</th>
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<tr>
<td>2:30 pm</td>
<td><strong>Kathleen Hoeger</strong> University of Rochester, Rochester, NY, USA</td>
<td>Presidential Lecture: Unsettled Legacy: Cross generational impact of PCOS on mental health</td>
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<tr>
<td>2:50 pm</td>
<td><strong>Moderator: Elisabet Stener-Victorin</strong> Karolinska Institutet, Stockholm, Sweden</td>
<td>LIVE Q&amp;A: Presidential Lecture</td>
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**2:55-3:25 COFFEE BREAK/SPONSORS and INTERACTIVE POSTER SESSION**

## Session 2: Oral Presentations 1: Clinical and translational research

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<tr>
<th>Time</th>
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<tr>
<td>3:25 pm</td>
<td><strong>Snigdha Alur-Gupta</strong> University of Rochester, Rochester, NY, USA</td>
<td>Impact of PCOS on coronavirus disease 2019 (COVID-19) incidence and severity in the United States</td>
</tr>
<tr>
<td>3:35 pm</td>
<td><strong>Jeffrey Pea</strong> Cornell University, Ithaca, NY, USA</td>
<td>Variable discriminatory power of ovarian markers across lifespan warrant age-specific PCOS criteria</td>
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<tr>
<td>3:45 pm</td>
<td><strong>Chau Tay</strong> Monash University, Victoria, Australia</td>
<td>Hypertension, obesity and maternal age negatively associated with reproductive outcomes in PCOS</td>
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<tr>
<td>3:55 pm</td>
<td><strong>Natàlia Pujol Gualdo</strong> University of Oulu, Oulu, Finland</td>
<td>Leveraging Northern European population history: Novel low frequency variants for PCOS</td>
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<tr>
<td>4:05 pm</td>
<td><strong>Moderator: Terhi Piltonen</strong> University of Oulu, Finland</td>
<td>LIVE Q&amp;A: Oral Presentations</td>
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**Session 3: Debate: PCOS is an inflammatory disorder**

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<tr>
<th>Time</th>
<th>Speaker</th>
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<tbody>
<tr>
<td>4:15</td>
<td><strong>Barbara Obermayer</strong>, Medical University of Graz, Graz, Austria</td>
<td>Will speak AGAINST the motion for:</td>
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<tr>
<td>4:30</td>
<td><strong>Frank Gonzales</strong>, University of Illinois, Chicago, IL, USA</td>
<td>Will speak IN SUPPORT OF the motion for:</td>
</tr>
<tr>
<td>4:45</td>
<td><strong>Moderator: Joop Laven</strong>, Erasmus MC, Rotterdam, Netherlands</td>
<td>LIVE Debate, Discussion and Possible Motion</td>
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**Day 2, November 13th, 1-5pm EST**

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<tr>
<th>Time</th>
<th>Speaker</th>
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<tr>
<td>1:00 pm(EST)</td>
<td><strong>Kathleen Hoeger</strong> University of Rochester, Rochester, NY, USA President of the AEPCOS Society</td>
<td>Introduction and Welcome to Day 2</td>
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**Session 4: Lessons from pre-clinical models of PCOS**

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<tr>
<th>Time</th>
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<tr>
<td>1:05 pm</td>
<td><strong>Nathalie Di Clemente</strong>, Sorbonne Université-INSERM, Paris, France</td>
<td>New spontaneous rat model of PCOS</td>
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<td>1:30 pm</td>
<td><strong>W Colin Duncan</strong>, The University of Edinburgh, Edinburgh, Scotland</td>
<td>FGF21 deficit and PCOS</td>
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<tr>
<td>1:55 pm</td>
<td><strong>Moderator: Rebecca Campbell</strong>, University of Otago, Dunedin, New Zealand</td>
<td>LIVE Q&amp;A: Session 4</td>
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**Session 5: Oral Presentations 2: Basic and cellular research**

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<tr>
<th>Time</th>
<th>Speaker</th>
<th>Topic</th>
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<tr>
<td>2:05 pm</td>
<td><strong>Mojca Jensterle</strong>, University Medical Center Ljubljana, Slovenia</td>
<td>GLUT4 mRNA expression in adipose tissue after metformin withdrawal in PCOS: Is there legacy effect?</td>
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<tr>
<td>2:15 pm</td>
<td>Ryan Paulukinas University of Pennsylvania, Philadelphia, PA, USA</td>
<td>Conversion of classical and 11-oxygenated androgens by AKR1C3 in a model of PCOS adipocytes</td>
</tr>
<tr>
<td>2:25 pm</td>
<td>Jacob Pruett University of Mississippi Medical Center, Jackson, MS, USA</td>
<td>Oxidative stress and white adipose tissue in a rat model of polycystic ovary syndrome</td>
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<tr>
<td>2:35 pm</td>
<td>Marika Kangasniemi University of Oulu, Oulu, Finland</td>
<td>Deep learning model analysis of leucocyte counts and proliferation in non-PCOS and PCOS endometrium</td>
</tr>
<tr>
<td>2:45 pm</td>
<td>Moderator: Anju Joham Monash University, Australia</td>
<td>LIVE Q&amp;A: Oral Presentations</td>
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2:55-3:25 COFFEE BREAK/SPONSORS and INTERACTIVE POSTER SESSION

Session 6: Early Career Special Interest Group Event: Bridging clinical and basic science research- LIVE!

| 3:25 | Laura Cooney University of Wisconsin, WI, USA & Jillian Tay Monash University, Australia | Introduction to the EC-SIG Event |
| 3:35 | David Abbott Wisconsin National Primate Research Centre, USA & Dan Dumesic UCLA, CA, USA | Break out groups |
| 3:35 | Elisabet Stener-Victorin Karolinska Institutet, Stockholm, Sweden & Terhi Piltonen University of Oulu, Oulu, Finland | Break out groups |
| 4:00 | Laura Cooney University of Wisconsin, WI, USA & Jillian Tay Monash University, Australia | Report Back/Discussion |

Award Lecture: Walter Futterweit Award in Clinical Research

<p>| 4:20 | Evanthia Diamanti-Kandarakis, University of Athens, Greece | Clinical Research Award Lecture: The ovarian target of glycation and insulin resistance in PCOS: Molecular and clinical aspects |
| 4:50 | Moderator: Anuja Dokras Penn Medicine, Philadelphia, USA, Associate Executive Director, AE-PCOS Society | LIVE Q&amp;A: Clinical Research Award Lecture |</p>
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<tr>
<td>1:00 pm</td>
<td>Kathleen Hoeger, University of Rochester, NY, USA President of the AEPCOS Society</td>
<td>Introduction and Welcome to Day 3</td>
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<tr>
<td>1:05 pm</td>
<td>Richard Anderson, University of Edinburgh, Scotland</td>
<td>Targeting Neurokinin B in PCOS treatment</td>
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<tr>
<td>1:30 pm</td>
<td>Waljit Dhillo, Imperial College London, UK</td>
<td>Therapeutic potential of kisspeptin</td>
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<td>1:55 pm</td>
<td>Moderator: Paolo Giacobini INSERM, Lille, France</td>
<td>LIVE Q&amp;A: Session 7</td>
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**Session 7: Treatment of PCOS through central mechanisms**

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<tr>
<td>2:05 pm</td>
<td>Sasha Ottey PCOS Challenge, The National Polycystic Ovary Syndrome Association, USA</td>
<td>PCOS Advocacy</td>
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<tr>
<td>2:20 pm</td>
<td>Li Meng Erasmus MC, University Medical Center Rotterdam, The Netherlands</td>
<td>Functional analysis of pathogenic anti-mullerian hormone variants in patients with PCOS</td>
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<tr>
<td>2:30 pm</td>
<td>Aisha Sati University of Otago, Dunedin, New Zealand</td>
<td>Role of microglia in polycystic ovary syndrome (PCOS)-like brain</td>
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<tr>
<td>2:40 pm</td>
<td>Moderator: Tania Burgert Kansas City, MO, USA</td>
<td>LIVE Q&amp;A: Session 8</td>
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2:50-3:05 COFFEE BREAK/SPONSORS and INTERACTIVE POSTER SESSION

**Session 9: PCOS: Diet and Inflammation**

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<tr>
<th>Time</th>
<th>Speaker</th>
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<tr>
<td>3:05 pm</td>
<td>Jorge Chavarro Brigham and Women’s Hospital, Harvard Medical School, USA</td>
<td>The influence of diet on PCOS</td>
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<tr>
<td>3:30 pm</td>
<td>Karina B Gomes Federal University of Minas Gerais, Brazil</td>
<td>Pro and Anti-inflammatory markers in PCOS</td>
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<tr>
<td>Time</td>
<td>Moderator</td>
<td>Institution/Lecture</td>
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<td>3:55 pm</td>
<td><strong>Poli Mara Spritzer</strong></td>
<td>Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil</td>
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<td><strong>LIVE Q&amp;A:Session 8</strong></td>
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<tr>
<td>4:05</td>
<td><strong>David Abbott</strong></td>
<td>Wisconsin National Primate Research Centre, USA</td>
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<td></td>
<td><strong>Distinguished Researcher Award Lecture: Nonhuman primate models of PCOS pathogenesis</strong></td>
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<td>4:35</td>
<td><strong>Ricardo Azziz</strong></td>
<td>University of Alabama at Birmingham, Birmingham, AL, USA</td>
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<td><strong>LIVE Q&amp;A: Distinguished Researcher Award Lecture</strong></td>
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<tr>
<td>4:45</td>
<td><strong>Anuja Dokras</strong></td>
<td>Penn Medicine, Philadelphia, USA, Associate Executive Director, AE-PCOS Society</td>
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<td><strong>LIVE: AE-PCOS Society Update and meeting wrap up</strong></td>
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OBJECTIVE: Recently rare heterozygous AMH genetic variants have been identified in women with polycystic ovary syndrome (PCOS) that result in reduced AMH signaling. However, the exact functional mechanism remains unknown. Therefore, we performed functional analyses to analyze the processing, secretion and signaling of these PCOS-specific AMH rare variants.

METHODS: Six PCOS-specific AMH variants containing mutations (V247, P151S, P275S, P352S, H506Q) were selected based on previous findings. The variants were introduced in an AMH expression vector containing either a wild type (AMH-RAGA) or optimized cleavage site (AMH-RAGA) and co-expressed with the Brie-Luc reporter in the mouse granulosa cell line K-1. The AMH expression vectors were stably expressed in HEK-293 cells for Western blot analysis and ELISA.

RESULTS: Expression of AMH-P151S and AMH-H506Q decreased AMH signaling by 60-90% (p<0.001), depending on the presence of a RAGA or RARR cleavage site. Signaling of the other four variants was comparable to wild-type (wt)-AMH. Coexpression of the variants with wt-AMH at equal amounts confirmed that AMH-P151S and AMH-H506Q significantly inhibited the signaling activity of wt-AMH by 30% (p<0.001). Transfection of increasing amounts of these two variants resulted in a further inhibition, which was independent of the cleavage site.

To explain this dominant negative effect, we next analyzed the impact of AMH cleavage on AMH signaling. Cells were transfected with an AMH construct containing an inactive cleavage site (AMH-RAGA) in combination with exogenous AMH treatment. We observed that exogenous AMH-induced signaling was suppressed by 30% (p<0.01) in the presence of AMH-RAGA. In contrast, exogenous AMH-induced signaling was not affected when AMH-P151S or AMH-H506Q was transfected. Indeed, Western blot analysis showed that AMH-P151S and AMH-H506Q proteins were only detected in the cell lysate but not in the supernatant, even in the presence of RARR cleavage site. In contrast, wt-AMH and the P352S and P382S variant were detected in both the cell lysate and the supernatant. ELISAs will be performed to confirm these results.

CONCLUSIONS: Our results show that the PCOS-specific AMH variants P151S and H506Q disrupt normal processing and secretion of AMH. Our results further suggest that these AMH variants hamper secretion of wt-AMH, explaining the dominant negative effect of these variants on AMH signaling.
RESULTS: Women with and without ICOS had similar FSA but significantly less women with ICOS than without achieved their FSA (53.08% vs 64.47%, p=0.003). Higher proportion of women with than without self-reported ICOS were nulliparous (37.15% vs 31.64%, p=0.002) and the median total number of live births was lower in women with than without self-reported ICOS (1 vs 2, p=0.020). After controlling for sociodemographic factors, negative associations were observed between FSA achievement and ICOS status, various metabolic, psychiatric and reproductive history. However, only hypertension (adjusted OR 0.82, 95% CI 0.67-1.00), obesity (adjusted OR 0.79, 95% CI 0.69-0.91), history of in-vitro fertilisation use (adjusted OR 0.49, 95% CI 0.38-0.65) and maternal age at first childbirth (adjusted OR 0.91, 95% CI 0.91-0.93) negatively associated with achievement of FSA in further multivariable regression models.

CONCLUSIONS: Metabolic conditions and reproductive history of maternal age of first childbirth and history of IVF use, but not psychological conditions, were associated with reduced odds of achieving family size aspiration. Early family planning and optimization of metabolic health are required to improve reproductive outcomes.
OBJECTIVE: Polycystic Ovary Syndrome (PCOS) is the common endocrine disorder in women of reproductive age. It is characterized by androgen excess; 80% of this population is obese. As white adipose tissue (WAT) expands through hypertrophy, there is increased hypo- and reactive oxygen species (ROS). However, the effect of female androgen excess on WAT is poorly understood. Hyperandrogenemic female (HAF) rat model of PCOS has increased body weight (BW), body mass index (BMI), and fat mass. We want to test the hypothesis that androgen excess leads to the expansion of WAT through hypertrophy, leading to oxidative stress in HAF rats.

METHODS: 40-four-week-old female Sprague Dawley rats were randomized to either placebo or dihydrotestosterone (DHT) exposure (7.5 mg/kg/day). At 3 months of age, DHT, ovariectomized, or hormone-free control for total antioxidant capacity (TAC) assay; Subcutaneous (sWAT) and visceral WAT (vWAT) were collected for Western blotting to measure cytoplasmic superoxide dismutase (SOD1) and mitochondrial SOD2 (SOD2). Complex IV (DIV) activity, a marker of oxidative phosphorylation capacity, was measured by spectrophotometry. Adipocyte area was quantified by 40X magnified images using Adiposoft and GraphPad Prism was used to calculate adipocyte size distributions.

RESULTS: BW and BMI were elevated in HAF rats. Plasma TAC was reduced in HAF (264 ± 18 vs 298 ± 15 mg/kg/day) and decreased frequency of adipocytes at 500 μm (10.5 ± 2.2 vs 7.7 ± 0.5 mm², P=0.01) and decreased frequency of adipocytes at 200 μm and increased frequency of adipocytes at 900 μm (16.5 ± 1.6 vs 11.7 ± 1.4 mm², P=0.01). sWAT SOD1 protein (0.69 ± 0.06 vs 1.03 ± 0.09, P=0.03) expression was increased in HAF with no change in vWAT. SOD2 protein expression was unchanged in sWAT and vWAT. HAF had decreased DIV activity in sWAT (197 ± 24 vs 270 ± 24 mmol/min/mg tissue, P=0.05) but not in vWAT.

CONCLUSIONS: In summary, HAF rats had decreased TAC, suggesting increased ROS. Furthermore, androgen downregulated SOD1 protein and DIV activity only in sWAT with no change in vWAT. Surprisingly, hyperandrogenemia only caused hypertrophy of sWAT adipocytes while decreasing adipocyte size in vWAT. These data suggest that hyperandrogenism has a different effect on sWAT and vWAT, and that vWAT may contribute more to the reduced TAC seen in HAF than vWAT. This lays groundwork for future studies to improve WAT function in women with PCOS.

(Funding: NGMS P20GM121334 and P20GM104557, NIDDK R21DK11350 and F30DK127577, NHLBI F30HL15971)

ID #12 Title: Clinical Science

TITLE: A REVIEW OF THE NHANES DATASET TO IDENTIFY INDIVIDUALS WITH PCOS
AUTHORS: Cree-Green M (2), Sheriff K (3), Sugahara G (4), Fiskus T (4), Kemmerly V (4), Lyne AN (4), Vesper HW (4), Litsey S (1)
AFFILIATION: (1) PCOS Challenge, The National Polycystic Ovary Syndrome Association, Atlanta, GA
(2) Div of Med Genetics, Univ of Colorado, Denver, CO
(3) Div of Medicine, Thomas Jefferson Univ, Philadephia, PA
(4) General Diabetes Brach, NHS, Center for Disease Control and Prevention, Atlanta, GA

OBJECTIVE: Polycystic Ovary Syndrome (PCOS) is a common endocrine disorder in women of reproductive age. The prevalence of PCOS in the United States is unknown, as is the frequency of associated comorbidities including metabolic disease, infertility, and psychological disorders. This study investigated if the National Health and Nutrition Examination Survey (NHANES) could identify individuals with PCOS and 2) ascertain PCOS comorbidity rates.

METHODS: 2013-2014 and 2015-2016 NHANES laboratory results, questionnaires, and physical examination data were utilized to identify potential individuals with PCOS. Individuals of female sex aged 20-46 years were included; exclusions were pregnancy, long term use of hormonal contraceptives, and total testosterone ≥200 ng/dL.

RESULTS: Information needed to identify individuals with a PCOS diagnosis, as outlined in clinical practice guidelines, is not systematically collected by NHANES. Of 1444 females meeting the inclusion criteria, only 64 (4.4%) had data, signs, and symptoms associated with PCOS and were classified as potential PCOS individuals (“PCOS group”). When compared, the PCOS and non-PCOS groups showed no apparent differences in age of menarche, reported infertility, lipids, HbA1c, fasting glucose, insulin, or calculated insulin resistance, which are known PCOS comorbidities. This suggests that those identified in the “PCOS group” do not have typical findings of PCOS and this classification may not be accurate.

CONCLUSION: This study found that medical history and clinical and laboratory data collected in NHANES is insufficient to reliably identify individuals with PCOS. While research data suggest a prevalence of PCOS of ≥10% in the US, more reliable, representative data are needed to appropriately define the public health burden associated with PCOS and to address and minimize PCOS-associated comorbidities.

ID #13 Title: Basic Science

TITLE: DEEP LEARNING MODEL ANALYSIS OF LEUCOCYTE COUNTS AND PROLIFERATION IN NON-PCOS AND PCOS ENDOMETRIUM
AUTHORS: Kangami NH (1), Komitko E (2), Rosei HR (2), Llaoka A (2), Khatun M (1), Chen IC (3), Paulson M (4), Frenszlitz BD (2,3), Affenman M (2), Richter TT (1)
AFFILIATION: (1) Dept. of Obstetrics and Gynecology, PEHIO Research Unit, Medical Research Center, Dusseldorf University Hospital, Dusseldorf, Dusseldorf, Germany
(2) Dept. of Pathology, Medical Research Center, Dusseldorf University Hospital, Dusseldorf, Dusseldorf, Germany
(3) Dept. of Obstetrics, Gynecology and Reproductive Sciences, University of California, San Francisco, CA, USA

OBJECTIVE: To investigate differences in endometrial immune cell populations between cycle phases and samples from women with polycystic ovary syndrome (PCOS) and controls using artificial intelligence (AI) technology.

METHODS: Endometrial samples from the proliferative phase (26 control, 23 PCOS) and luteinizing hormone (LH) surge timed control (10 control, 16 PCOS) and LH 10-12 days (10 control, 9 PCOS) secretion phase were collected during 2014-2019. Samples were stained with antibodies for CD8+ T-cells, CD68+ uterine natural killer (uNK) cells, CD68+ macrophages and the proliferation marker Ki67. Scanned whole slide images (WSIs) were analyzed with an AI deep learning model (AIko, Aiforia). First AIN separated the epithelium and stroma and then counted the positive and negative cells. Cycle phase differences in leucocyte counts and proliferation and endometrial thickness were studied within the study populations and between PCOS and control samples. Furthermore, a sub-analysis of anovulatory PCOS samples (> 12) vs. proliferative phase controls (< 12) was also performed.

RESULTS: Automated cell counting with a deep learning model performs well for the human endometrium. Endometrial leucocyte counts and proliferation fluctuate with the menstrual cycle. Differences in leucocyte counts were not observed between the whole PCOS population and the controls. However, anovulatory women with PCOS presented with a higher number of CD8+ cells in the epithelium (controls vs. PCOS, median [IQR] 0 [0.75–5.51] vs. 1.37 [1.32–2.68], p = 0.035) and fewer leucocytes in the stroma (CD8 7.22 (4.19–12.20) vs 1.4 (1.07–7.33), p = 0.0001; CD68 3.65 (4.33–7.43) vs 2.07 (0.65–4.99), p < 0.003; CD68 4.73 (3.82–6.70) vs 3.07 (2.73–4.51), p = 0.022, respectively) compared with the controls. Endometrial thickness and proliferation rate were comparable between the PCOS and control groups in all cycle phases.

CONCLUSIONS: Ovulatory endometrium from women with PCOS did not differ markedly from the controls, which might indicate that ovulatory cycles normalize PCOS endometrium allowing more normal leucocyte environment prior implantation. Deviant endometrial leucocyte populations seen in anovulatory women with PCOS could interfere with the altered endometrial function observed in these women. This study also underlines the differences between endometrial compartments, which need to be acknowledged in future analysis. AI technology provides a powerful and objective tool for endometrial research.

(FUNDING: This study was funded by the Sigrid Jusliss Foundation, Academy of Finland, the Orion Research Foundation in the Finnish Medical Society, Emil Aaltonen foundation and the Swedish Research Council.)
OBJECTIVE: Metabolomics is small intermediates or end products of cellular metabolism which reflect the response to endogenous and environmental changes in an organism. In this regard, sex hormones and obesity are important modulators of whole-body metabolism, and women with polycystic ovary syndrome (PCOS) frequently present metabolic derangements. Therefore, to evaluate the influence of sex, sexual steroids and obesity on the serum metabolomics profile in a series of young individuals.

METHODS: Metabolomics profiling by 1H-NMR was performed in serum samples of 53 adults including 17 control women, 17 women with PCOS and 18 control men, distributed in non-obese and obese subgroups. Thirty-five polar metabolites were quantified. Univariate GLM was used to determine the influence of group, obesity, and its interaction on each metabolite.

RESULTS: Men and control women presented similar alleline levels but lower than PCOS patients, and glutamine, glycine, tyrosine, phenylalanine and tryptophan were increased in men and PCOS patients compared with control women. Obese individuals showed different levels in 23 metabolites (16 increased [2-oxocarproic and 2-oxovaleric acids, isocitric, valine, lactate, alanine, acetone, pyruvate, creatine, lysine, ornithine, glyceraldehyde, methystidine, tyrosine and tryptophan] and 7 decreased [obestatin and pentaacetic acids, acetate, citrate, asparagine, carnitine and betaine]) compared with non-obese. However, the most important finding was an interaction between group and obesity in 17 of these 23 molecules. This interaction consisted of PCOS patients presenting with similar or greater values than control women and lower than men in non-obese subjects, whereas in the obese group PCOS patients maintained this difference compared to control women, but reached levels equal to or even higher than those in men (lucine, isocitric, valine, 2-oxocarproic and 2-oxovaleric acids, pyruvate, lysine, ornithine, methystidine and creatine). In addition, eleven metabolites were higher in obese women with or without PCOS compared with non-obese, but this difference was not observed in men. Carnitine, acetate, formate and citrate showed distinct interactions between PCOS and obesity.

CONCLUSION: Metabolomics profiling greatly reveals the metabolic heterogeneity of PCOS and its complex interaction with obesity.


ID #135
Type: Clinical Science

TITLE: HEALTHCARE EXPERIENCE IN WOMEN AND GENDER DIVERSE INDIVIDUALS WITH PCOS

AUTHORS: Williams, SL

AFFILIATION: Department of Physiology and Translational Science, University of South Australia, Adelaide, SA, Australia.

OBJECTIVE: This study examined healthcare experiences of women and gender diverse individuals with PCOS. Whereas PCOS is a common endocrine disorder among females, not all females identify their gender as woman, which may impact healthcare experiences. Whereas all individuals with PCOS may experience healthcare dissatisfaction (e.g., delayed diagnosis), gender diverse individuals (e.g., transgender, nonbinary) may encounter additional gender-specific dissatisfaction stemming from assumptions about PCOS, who experiences it, and how it should be treated. By learning from patients, PCOS-specific treatment and healthcare can continue to improve.

METHODS: One-on-one qualitative interviews were conducted with 50 individuals with PCOS aged 19-44 years and residing across the U.S. Approximately half of the sample identified as gender diverse (e.g., nonbinary and genderqueer) and racially/ethnically diverse.

RESULTS: Aligned with prior research, individuals with PCOS reported dissatisfaction with healthcare that included lack of knowledge about PCOS, delayed PCOS diagnosis, and dismissive encounters. Additionally, individuals with PCOS described weight stigma from providers stemming from a focus on weight loss and exercise to treat PCOS, and the assumption that patients have poor health behaviors. Further, gender diverse individuals described healthcare experiences and treatments grounded in assumptions that all with PCOS are women, all want masculinizing symptoms of PCOS treated to become feminized, and all want to become pregnant. Both those PCOS who described weight stigma and cultural incompetence reported avoiding healthcare.

CONCLUSIONS: While lifestyle management is considered best practice for managing PCOS, because of societal weight stigma, providers’ focus on patients’ weight loss translates into blame and shame for patients. This persisting stigma can backfire and lead patients to avoid healthcare. Providers should implement the recommendation from the 2018 international guidelines and consider stigma when advising PCOS patients to lose weight and exercise. Providing explanation to patients about why and how weight loss and exercise can impact PCOS may reduce blame and shame experienced by patients. It is further recommended that providers improve cultural competence surrounding gender diversity in healthcare.

ID #136
Type: Clinical Science

TITLE: PREVALENCE OF FUNCTIONAL HYPERANDROGENISM IN WOMEN WITH TYPE 1 DIABETES

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OBJECTIVE: Functional hyperandrogenism / polycystic ovary syndrome (PCOS) is common in women with type 1 diabetes (T1D). However, reported prevalence rates vary according to diagnostic criteria used for PCOS and the population studied. Chronic hyperinsulinemia resulting from subclinical insulin administration is the most likely culprit of hyperandrogenism in women with T1D, although factors that influence the occurrence of PCOS have not been well established yet. We aim to determine the prevalence of PCOS and to assess the factors that may predict its occurrence in premenopausal women with T1D.

METHODS: Cross-sectional study. For this preliminary analysis, we included 90 patients with T1D, aged 18-45 years, consecutively recruited from a Diabetes Clinic at a tertiary hospital in Madrid, Spain. All patients were under intensive insulin treatment, had a T1D of at least 1 year and a minimum gynecological age of 2 years. In a unique visit at the hospital, we collected diabetes and gynecological history data, and we performed a physical exam and a complete hormone analysis (including TSH, prolactin, FSH, LH, 17-βestradiol, DHEA-S, 5α-reductase, and basal and stimulated 17hydroxyprogesterone, total testosterone, SHBG and calculated free testosterone, at their follicular phase of the menstrual cycle). An ovarian ultrasound was performed to assess polycystic ovary morphology. We used Statsa software v16 (StatCarp LLC) for statistical analysis.

RESULTS: At recruitment, mean age of participants was 30.3 ± 8.7 years, mean duration of T1D was 14.9 ± 9.7 years and mean BMI was 23.7 ± 5.9 kg/m2. Mean A1c was 7.2 ± 1.4%. The prevalence of all PCOS phenotypes (Rotterdam/EHS-ASRM criteria) was 23.3% (95% CI: 18.5–31.1%) of hyperandrogenic PCOS (All-PCOS criteria) 16.7% (10.2–23.7%), and of classic PCOS (NHG criteria) 14.4% (95% CI): 8.6–23%. Univariate regression model showed significant results for age (OR: 0.91, 95% CI: 0.86–0.98), female sex (OR: 3.4, 95% CI: 1.7–7.2), and insulin dose (OR: 5.5, 95% CI: 2.8–10.9) as predictors of PCOS. After introducing these variables into a multivariate regression model, only age (OR: 0.89, 95% CI: 0.24–3.7) was retained as a significant predictor of PCOS in these women.

CONCLUSIONS: PCOS and related traits seem to be prevalent in premenopausal women with T1D.
OBJECTIVE: The health sector has recently shown great interest in the field of positive psychology, and its effect on people with chronic illnesses. The objective of this study is to investigate the difference in character strengths (Cs) between patients with and without polycystic ovary disease (PCOS) and find the association between biological (testosterone levels) and psychological factors (Cs).

METHODS: A total of 100 women divided into PCOS (50) and non-PCOS (50) groups who presented to the gynecological clinic at the women's center in the American University of Beirut. Medical Center in 2017 were included. Women were assessed for testosterone bioavailable levels and completed a questionnaire that included Hospital Anxiety and Depression scale and Values in Action Survey-2. Univariate and multivariable analyses were performed to examine the association of Cs with the two groups and its predictors. Univariate and multivariable analyses were performed to examine the association of Cs between the two groups and its predictors.

RESULTS: The scores of hope, judgement, perspective and transcendence of the PCOS group were significantly higher in comparison with healthy participants. An increase in free androgen index (FAI) was negatively correlated to the score of judgement only.

CONCLUSIONS: Our results show a lack of any correlation between the testosterone levels and behavioral traits. This lack of association proposes a little to no acausal influences of testosterone on the character strengths of the sample population.

The 24 Cs, PCOS patients had higher scores of judgement, hope, and perspective than the healthy controls. As for the 6 virtues, only transcendence scores were shown to be significantly higher in the PCOS group.

In conclusion, we showed that women with PCOS have higher scores of judgement, hope, perspective and transcendence as character strengths in comparison with healthy participants. We suggest that it is essential for PCOS patients to be referred to psychiatric consultations and undergo positive psychology therapy to enhance their character strengths from the onset of diagnosis. This might be a cost-effective, efficient prophylactic means for adapting with the syndrome and preventing psychopathological disorders associated with PCOS women on the long run.

This work was supported by the Medical Practice Plan at the American University of Beirut Medical Center.)
OBJECTIVES: Insomnia and poor sleep quality has been reported during the COVID-19 pandemic among healthy and infected people. The present study aims to evaluate the impact of COVID-19 pandemic on the sleep quality of women with Poly cystic ovarian Syndrome (PCOS). METHODS: longitudinal study conducted with 20 patients with PCOS by the Rotterdam criteria from the PCOS Outpatient Clinic of Hospital Laus Vicente de Paulo (HOSP), Passo Fundo/RS, Brazil, in the period from December 2017 to July 2021. Questionnaires were applied on two different occasions, the first in person and prior to the COVID-19 pandemic and the second by telephone conversation from May to July 2021. It was verified age in previous and current years; weight and height measured previously and self-reported currently. The body mass index (BMI) was calculated. For the sleep analysis, 3 questionnaires validated in Brazil were applied in both contacts with the patients: the Berlin questionnaire evaluates the risk of obstructive apnea (OSA), classifying it into high and low levels. The Epworth Sleepiness Scale evaluates the degree of excessive daytime sleepiness, and the Pittsburgh Sleep Quality Index evaluates the quality of sleep, analyzed dichotomously into good and poor quality. The statistical package SPSS version 18.0 was used for the analyses. The descriptive statistics used were mean, standard deviation, absolute frequency and percentage for categorical variables. We used the Shapiro-Wilk normality test, McNemar’s and Wilcoxon’s test for paired measures. Spearman’s coefficient was calculated to check the association of age with the 3 tests used. An alpha <0.05 and a 95% confidence interval were considered significant. RESULTS: in the first survey the mean age was 29.5±5.8 and in the second was 31.86±1.1 years, p<0.001. There was no significant difference in BMI comparing pre, 32.1±5.5, and post pandemic, 33.6 ± 6.9 Kg/m² (p=0.18). There was no statistically significant correlation of age with the 3 questionnaires. The Berlin identified 5 patients (25%) with high risk of OSA pre-pandemic, and 14 patients (70%) post-pandemic (p=0.04). Pre pandemic, 3 patients (15%) had excessive daytime sleepiness by the Epworth Scale, and 10 patients (50%) post pandemic (p=0.016). There was no significant difference in the Pittsburgh index pre and post pandemic. CONCLUSIONS: For patients with PCOS the COVID-19 pandemic was associated with increased excessive daytime sleepiness and increased risk of OSA.

**ID #29**

**Type:** Translational Science

**TITLE:** METFORMIN REDUCES INFECTIONS AND INCREASES SERUM CYTOKINES IN PREGNANT WOMEN WITH PCOS - AN RCT

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**OBJECTIVE:** Polycystic ovary syndrome (PCOS) is associated with increased inflammation in both pregnant and non-pregnant state, as well as increased risk of pregnancy complications. Metformin is reported to have anti-inflammatory properties and reduces late miscarriage and preterm birth in women with PCOS. The underlying mechanisms are not understood. We aimed to investigate the immunological effect of metformin in women with PCOS by longitudinal serum cytokine profiling and by exploring the occurrence of infections throughout pregnancy.

**METHODS:** Serum samples from 619 pregnant women with PCOS were included from two RCTs randomizing women to metformin (n=299) or placebo (n=326), from first trimester to delivery. Serum was sampled at gestational weeks 10 (n=562), 19 (n=571), 32 (n=552) and 36 (n=542). Twenty-two cytokines were measured using a bead-based multiplexed immunomagnetic assay, and high sensitivity (hs)-CRP by standard protocols. Linear mixed models were applied to assess each cytokine’s development over time. Repeated measures ANOVA simultaneous component analysis (RMA-ASC) was used to model and compare the combined longitudinal cytokine development. Occurrence of viral and bacterial infections during pregnancy was compared by chi-square test.

**RESULTS:** Metformin-treatment affected the maternal serum cytokine profile by increasing levels of the chemokine eosin (p<0.05), the inflammatory cytokines interleukin (IL)-1β (p<0.001) and IL-6 (p<0.05), the anti-inflammatory cytokine IL-6 (p=0.04), granulocyte colony-stimulating factor (G-CSF) (p=0.04), and fibrinogen (factor basic fibrinogen (FGF) (p=0.04). Combined assessment confirmed that multiple cytokines were upregulated at several timepoints in pregnancy with metformin-treatment. Additionally, metformin reduced the number of viral and bacterial infections throughout pregnancy (p<0.05).

**CONCLUSIONS:** Metformin induced a broad and sustained systemic increase of multifunctional cytokines in pregnant women with PCOS and resulted in less viral and bacterial infections throughout pregnancy. This effect of metformin may reflect a broad immunity modulation, possibly protecting against infections in pregnancy. Supported by NTNU, Research council of Norway, Norsk Nordisk foundation and St. Olavs hospital.

**ID #30**

**Type:** Translational Science

**TITLE:** DIRECT COSTS OF MENTAL HEALTH DISORDERS IN PCOS: SYSTEMATIC REVIEW AND META-ANALYSIS

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**OBJECTIVE:** Polycystic ovary syndrome (PCOS) is the most prevalent endocrine-metabolic disorder in reproductive-aged women affecting 10-15% of unselected reproductive-age women worldwide. PCOS presents a great economic burden to society. While direct costs have been previously measured, estimated to approximate $8 million annually, no studies have addressed societal costs related to loss of productivity and quality of life of patients diagnosed with PCOS. The objective of this study is to calculate the indirect and intangible costs of PCOS for U.S. women of reproductive age and to compare these values to those of women living without PCOS.

**METHODS:** We will be conducting a case-control study where women of reproductive age with PCOS (cases) and without PCOS (controls) will be surveyed based on questions related to their productivity and quality of life. Cases and controls will be recruited through the contacts and social media channels of PCOS Challenge. The National Polycystic Ovary Syndrome Association, which is the leading non-profit PCOS patient support and advocacy organization serving over 50,000 members globally. Controls will be recruited using a snowballing sampling approach by asking the PCOS participants to recruit other individuals who are not blood relatives or have PCOS into the study. Inclusion criteria will include residents in the U.S. only and an ability and willingness to provide consent. Productivity will be measured using the Work Productivity and Impairment Questionnaire. The Specific Health Problem version (WPAI-SHP) will be used for cases and the General Health Version will be used for controls (WPAI-SH). Quality of Life will be measured using the SF-36 questionnaire, the EQ-5D VAS, and the Willingness-to-Pay Contingent Valuation Method (WTP-CVM). Productivity will be assessed by calculating preservation, absenteeism, work productivity loss, and activity impairment. Indirect costs will then be calculated by multiplying the average hours of work missed by the 2019 US average hourly wage rate ($US). Intangible costs will be assessed by calculating quality of life years (QALYs) lost multiplied by the Willingness to Pay for a life-year. The costs will be averaged and compared among cases and controls. Preliminary results will be presented.

(Partial funding provided by PCOS Challenge, Inc.)
OBJECTIVE: To determine the impact of weight loss on the phenotypic presentation of PCOS and identify factors associated with phenotypic change.

METHODS: Women with PCOS and obesity (N=23) participated in a weight loss intervention requiring 2-4 visits per week to a clinical research center. PCOS was defined by the Rotterdam criteria and participants were designated, in order of phenotypic severity, as Frank, Non-PCOS, Ovulatory and Non-Androgenic PCOS upon study entry. Participants consumed a hypocaloric commercial meal program for 3 [N=20] or 6 [N=3] months with the goal of 1-2 lbs of weight loss per week. Weight and menstrual cycle status were monitored at least twice-weekly. Anthropometry, dual x-ray absorptiometry, transcranial ultrasonography, hirsutism scoring and an oral glucose tolerance test were conducted at baseline and end of the intervention. Upon completion of the intervention, participants were grouped based on responsiveness to the intervention: (1) a positive responder (N=9) was defined by transition to a lower severity PCOS phenotype, (2) a negative responder (N=8) by a transition to a more severe phenotype or (3) non-responders (N=7) had no change in phenotype. Differences in anthropometric, reproductive and metabolic features pre- and post-intervention were assessed by Wilcoxon signed-rank test and differences across groups by Kruskal-Wallis tests.

RESULTS: At baseline, 43% of participants were classified as Frank, 43% Non-Androgenic, 9% Non-PCOS and none had Ovulatory PCOS. Post intervention, participants classified as Frank, Ovulatory, Non-Androgentic or Non-PCOS changed to 44%, 26%, 22% and 4% respectively. One participant (4%) lost their PCOS designation. All participants experienced significant decreases in weight, waist and hip circumference, and percent total and abdominal fat during the intervention (all p<0.05), with average weight loss for the positive, no change and negative responder groups being 8.8%, 9.6%, 6%, respectively (p<0.05). Baseline free androgen index (FAI) [p=0.014] and sex hormone binding globulin (SHBG) [p=0.004] concentrations as well as SHBG post-intervention [p=0.011] were significantly different across groups. Negative responders had higher baseline FAI versus the no change group (p=0.047). Likewise, baseline SHBG levels were lowest in negative responders with significant differences detected between negative and the no change group (p=0.007). Post intervention, lower SHBG persisted in the negative responders versus the no change group (p=0.029) and tended to be lower versus positive responders (p=0.062). No other anthropometric, reproductive or metabolic features differed across groups at baseline or post-intervention.

CONCLUSIONS: Intensive weight loss therapy is successful in driving phenotypic changes in PCOS. Individuals with higher FAI and lower SHBG levels are least likely to experience short-term phenotypic changes in PCOS. As such, free androgen status may serve as a useful biomarker to predict phenotypic change in response to weight loss. (NIMR0190374, 473200H07158-01, SK2SSGM157097-05, CHIR2N441681).

ID #93
TITLE: DISTINCT ANDROGEN AND IMMUNE PROFILES IN PREGNANT WOMEN OF HYPER- AND NORMANDROGENIC PCOS PHENOTYPE
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OBJECTIVE: Hyperandrogenism is present in 60-80% of women with polycystic ovary syndrome (PCOS) and a diagnostic criterion in three out of four PCOS phenotypes. Women with hyperandrogenic phenotypes (HA-PCOS) have inferior metabolic health and higher risk of pregnancy complications compared to women with normoandrogenic (NA-PCOS) phenotype. We have previously revealed distinct immunological changes in pregnant women with PCOS compared to controls using serum cytokine profiling as a sensitive measure of immune status. How this immune profile differs in pregnant women with HA- compared to NA-PCOS phenotype is currently unknown. We aimed to study potential differences in immune status and androgen development in HA- and NA-PCOS phenotypes throughout pregnancy.

METHODS: Levels of 27 cytokines, CRP, testosterone (T), androstenedione (A4), and sex hormone binding globulin (SHBG) were measured in serum of 354 women with PCOS at four time points (week 10; 19, 32 and 36) throughout pregnancy using multiplex bead-based technology and liquid chromatography-mass spectrometry. Free testosterone index (FTI) was calculated (T/SHBG)*100. The included women were classified as having HA- (n = 254) or NA-PCOS (n = 72) phenotype based on gestational information. Univariate and multivariate statistical analyses such as Mann-Whitney U tests and repeated measures ANOVA simultaneous component analyses (RM-ASCA) were performed to explore differences between pregnant HA- and NA-PCOS women.

RESULTS: HA-PCOS women had higher BMI (p < 0.001) than NA-PCOS women, but similar incidence of pregnancy complications; HA-PCOS women had higher levels of 5 and TFI at all measured time points in pregnancy (p-values < 0.05). Cytokine profiling revealed that HA-PCOS women show higher levels of fibrinolysis growth factor bas (FGF-2), interleukin (IL)-2, -9,-18 and IL-8 throughout pregnancy. Longitudinal cytokine profiling and androgen analyses are both equally able to separate women of HA- and NA-PCOS phenotypes, the differences in cytokine profile and NA- and HA-PCOS phenotypes was most pronounced for the overweight women. Cytokine and androgen levels showed poor correlation in pregnancy.

CONCLUSIONS: Women with HA-PCOS phenotype are associated with higher androgen levels also in pregnancy, in addition to a stronger inflammatory immune profile compared to women with NA-PCOS phenotype. Further research is needed to investigate whether there is a correlation between inflammatory cytokine profile and PCOS severity which could provide a stepping stone to the development of new therapeutic strategies for PCOS.

ID #94
TITLE: PSYCHOLOGICAL INTERVENTIONS FOR DEPRESSION IN WOMEN WITH PCOS: SYSTEMATIC REVIEW AND META-ANALYSIS
AUTHORS: Ikokot GE(2), van der Kooi A(2),Busschbach JJ(1), Laven JS(2) and Beethsen AH(2).
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OBJECTIVE: Polycystic ovary syndrome (PCOS) is a common endocrine disorder with varying physical and psychological complaints. Especially depression scores are problematic high in women with PCOS. It is unclear whether psychological interventions are effective for the treatment of depression in this group of women. A systematic review and meta-analysis was performed to examine the different types of psychological interventions and to determine the effectiveness of these interventions on depression scores in adult women with PCOS. The objective of this study is to determine the effects of psychological interventions on depression scores in women with PCOS compared to care as usual groups.

METHODS: The following online databases were systematically searched: EMBASE, Medline(Dox), Web of Science, Cochrane, Psychinfo and Google Scholar up to July 2020. The quality of the included studies was assessed using the GRADE methodology: Inclusion of studies comparing participants in the intervention and control condition enabled us to investigate whether there was an effect on depression scores. An effect size (using Cohen’s d) was calculated for each study to compare the effects on depression scores between baseline and after the intervention.

RESULTS: A total of 4854 studies were identified of which 9 met the inclusion criteria for the systematic review and 6 could provide data for the meta-analysis. A total of 248 participants in the intervention arm and 181 participants in the care as usual were included. All included studies compared some form of cognitive behavioral therapy (CBT) to control. The duration of treatment in the included trials ranged from 8 to 12 weeks and involved 8 and 20 sessions that lasted between 30 minutes and 150 minutes per session. Of the 9 included studies in the systematic review, 4 studies were group based interventions and 5 studies involved individual sessions. In the meta-analysis, an overall Cohen’s d effect size of 1.06 was found (ranging between 0.03 and 2.00) which is a large effect size in favor of CBT.

CONCLUSIONS: Psychological interventions applying CBT are effective to decrease depression scores in women with PCOS. More clinical trials are needed to assess how many ancess of CBT are effective to treat depression in women with PCOS. To control for allegiance bias, we suggest future trials should be carried out by collaborative research teams.
OBJECTIVE: An increased prevalence of functional hyperandrogenism—such as the polycystic ovary syndrome (PCOS)—has been described in women with type 1 diabetes (T1D). However, heterogeneity between studies is frequent, and prevalence rates vary according to different criteria used for the diagnosis of PCOS and the population studied. We aimed to perform a systematic review and meta-analysis of the prevalence of PCOS and related hyperandrogenic traits in premenopausal women with T1D.

METHODS: We conducted a systematic review of the literature using Medline-DVD and Embase databases (Open Science Framework registry for systematic review protocols https://osf.io/scfyp/). Studies published up to March 29, 2021 were considered. We selected cross-sectional or prospective studies that reported, in T1D patients, prevalence data on PCOS according to current definitions and different phenotypes, and/or prevalence rates of other related traits (hirsutism, hyperandrogenemia, oligo-anovulation, and/or polycystic ovarian morphology [POROM]). Two independent researchers performed study selection and data extraction. We used Stats2x for statistical analyses.

RESULTS: We selected 18 studies (989 women) reporting the prevalence of PCOS and/or other hyperandrogenic traits. Regarding hirsutism, 15 studies were considered, and the remaining 7 studies were considered intermediate-risk. The pooled prevalence of PCOS when considering all possible phenotypes (IHSHRE-ASRM criteria) in T1D was 25% (95% CI: 19–31%; 7 studies, 684 women). Pooled prevalence of classic PCOS (NH criteria: hyperandrogenism and ovulatory dysfunction) was 16% (95% CI: 10–22%; 9 studies, 614 women). Pooled prevalence of hyperandrogenism plus ovulatory dysfunction and/or PCOM was 27% (95% CI: 15–42%; 5 studies, 329 women).

CONCLUSIONS: PCOS and related hyperandrogenic traits are very common in premenopausal women with T1D.

ID #39
Type: Translational Science
TITLE: IMPACT OF SEX AND DIET-INDUCED OBESITY IN PRENATALLY ANDROGENIZED RATS
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OBJECTIVE: Androgen exposure during embryonic development and diet-induced obesity influence the sex hormone levels in adults. In this study, we investigated the changes in metabolic and hormonal profiles in rats determined by four factors: prenatal androgenization (PA), sex, castration and diet.

METHODS: We treated pregnant rats with subcutaneous injections of either 2.5 mg of testosterone or placebo in embryonic days 18 and 19. Two weeks post-weaning, rats were assigned to the following groups: a) males fed with a standard diet (SD); b) females fed with SD; c) males fed with a high-fat diet (HFD); and d) females fed with HFD. In addition, we castrated half of the males in each group to simulate a model of male hypogonadism. We determined anthropometric and metabolic parameters (including an oral glucose tolerance test (OGTI) and hormonal profiles analysed by liquid chromatography–tandem mass spectrometry (LC-MS/MS)).

RESULTS: Our results showed that PA-females presented with lower weight, body mass index (BMI), and increased anerogatinal index in adults. PA-males increased thoracic circumference (TC) and thoracic circumference/abdominal circumference ratio. PA-castrated rats increased insulin and HOMA-IR but decreased the AUC of glucose. In PA-rats we observed a global blunted response in insulin levels during OGTT compared with non-PA counterparts. HFD increased BMI in intact males and females but not in castrated rats, and increased TC only in intact males and castrated rats. In intact males, testosterone levels decreased in PA-rats fed with SD, whereas HFD decreased testosterone only in non-PA rats. LH/FSH ratio increased in PA-rats compared with non-PA rats only with HFD. We also found an interaction between HFD and group in estradiol, androstenedione and estrene levels. Testosterone and androstenedione were undetectable in castrated rats.

CONCLUSIONS: Our present results suggest that PA influences females, intact males and castrated rats differentially and that these changes are modulated by diet-induced obesity.

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ID #40
Type: Basic Science
TITLE: THE PHENOTYPE OF PCOS CHANGES THROUGHOUT TIME: A 30-YEAR FOLLOW-UP STUDY
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OBJECTIVE: Whether polycystic ovary syndrome (PCOS) and its associated key features resolve and/or persist over time remains unclear. The aim of this study was to assess the effects of ageing on phenontologic, endocrine and metabolic features in women with PCOS.

METHODS: We performed a follow-up study in which we included women with PCOS, diagnosed according to the 2003 Rotterdam criteria, who visited our outpatient clinic repeatedly between February 1995 and June 2021. Data was available on anthropometric measurements, ultrasound assessments and an endocrine assessment for each visit. Multivariable linear and logistic regression was applied for longitudinal analysis.

RESULTS: A total of 39 women visited the outpatient clinic repeatedly. An estimated change per 5 year age showed a statistically significant decrease in the prevalence of phenotype A and an increase in the prevalence of rat having PCOS. Serum levels of testosterone, androstenedione, dehydroepiandrosterone sulphate, and the free androgen index also decreased significantly. Clinical characteristics showed an increase in body mass index and waist circumference, whereas plasma glucose, insulin levels and insulin resistance didn’t change significantly.

CONCLUSIONS: The prevalence of PCOS phenotype groups change over time. There is an important age effect that causes a more regular menstrual cycle, a decrease in serum androgen levels and a decrease in polycystic ovarian morphology when ageing in women with PCOS.
OBJECTIVE: Increased bile acid and alterations in the composition of bile acid pools are associated with the pathogenesis of various metabolic diseases. The fasting-state bile acid profile could have been reported different from polycystic ovary syndrome (PCOS) and health people. However, none studies investigated the bile acid profile in lean women with PCOS, or whether their major regulatory and signaling functions were associated with the host stereol metabolism.

METHODS: This was a cross-sectional analysis of 320 subjects including 240 lean patients with PCOS and 80 lean health controls. The fasting-state serum levels of 15 primary and secondary bile acids were determined by using liquid chromatography-tandem mass spectrometry (LC-MS/MS). We characterized the bile acid profile and assessed associations of bile acid including selected ratios with stereol metabolism and dynamics, by adjusting for confounders.

RESULTS: The lean women with PCOS and control group were matched for age and BMI. Among the analyzed bile acids, compared with the control group, the proportion of cholesteroic acid (CDCA) in total bile acids was significantly increased while the proportion of cholic acid (CA) in total bile acids was significantly decreased in lean women with PCOS. Increased CDCA was associated with testosterone. A decreased ratio of CA : CDCA, which reflected decreased or downregulation of CYP7B1 and indicated the bile acid alternative pathway was activated, strongly negatively associated with free androgen index (FA).

CONCLUSIONS: Fasting-state serum bile acid profile alterations were seen in lean women with PCOS. And the activation of alternative pathways for bile acid synthesis might be the result of a compensation for hyperandrogenism in lean women with PCOS. Further studies will provide the potential pathophysiological mechanisms of bile acid metabolism in different phenotypes of polycystic ovary syndrome would be necessary.

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ID #42

Type: Translational Science

TITLE: Therapeutic potential of Mesenchymal Stem Cell-derived Extracellular Vesicle to treat the PCOS

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OBJECTIVE: Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women. Previous studies have demonstrated the therapeutic efficacy of human bone marrow mesenchymal stem cells (hMSCs) for PCOS. In our previous study, we suggested that hMSC reverse PCOS condition through its secreting factors by reducing inflammation, inhibiting androgen production, and regulate metabolic pathways. Here, we evaluated the therapeutic mechanism of hMSC through extracellular vesicles (EV), also known as exosomes, in both in vitro and in vivo PCOS models.

METHODS: For in vitro experiment, we compared the effect of conditioned media from hMSC and hMSC derived EV (hExosome) to anovulatory producing FSHR cells, and analyzed androgen producing gene expression. For in vivo experiment, hExosome were injected directly into ovary of Letrozole (LTZ) induced mouse model PCOS. Massive effect in androgen producing cells or PCOS model mice was assessed by analyzing steroidogenics gene expression (quantitative real-time polymerase chain reaction [RT-PCR]) and body weight change, serum hormone levels, and fertility by pup delivery.

RESULTS: hExosome significantly reduced gene expression Cyp11a1 (0.75±0.03 fold), Cyp17a1 (0.58±0.40 fold), and Dennd2 (0.72±0.66 fold) in H2R2 cells. In our in vivo model, increased body weight in PCOS mice were significantly decreased after hExosome treatment. In addition, average size of adipsy also decreased in hExosome treated [442.6±260.6 mm²] mice compared to PCOS mice [930.5±79.6 mm²]. Moreover, abnormal serum hormone levels in PCOS mice such as testosterone, FSH, and LH were reversed by hExosome treatment. In breeding experiment, PCOS mice (n=4) delivered only one offspring while healthy mice (n=4) delivered 33 pups. Interestingly, average number of pups in hExosome treated group (n=4) were 27, which is significantly increased compared to untreated PCOS mice.

CONCLUSIONS: Our study demonstrates the efficacy of MSC derived EV (hExosome) for potential treatment of PCOS condition. Our work suggests that Exosome can potentially be a novel therapeutic option for women with PCOS as cell-free biomedicine. Further preclinical and pilot clinical trials are required to further evaluate and validate this novel treatment option for this common female metabolic/reproductive disorder.

ID #44

Title: Does PolyCystic Ovarian Syndrome (PCOS) affect male germplasm and fertility?

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Objective: Previous study showed that in utero dihydrotestosterone (DHT) exposure, independent of diet-induced obesity, results in transgenerational polycystic ovary syndrome (pcos) like reproductive and metabolic phenotypes in f1 to f3 female offspring. However, how maternal obesity and in utero hyperandrogenism affect their male progeny across several generations is still unknown.

Methods: Results: Based on two clinical studies: a Swedish nationwide register and a Chinese case-control study we found that sons of mothers with PCOS are more obese with serum dyslipidemia. Next, we investigated whether diet-induced maternal obesity or prenatal DHT exposure in mice, mimicking both the lean and the obese PCOS phenotype, result in transgenerational transmission of a PCOS-like phenotype in male offspring via male germline. We find a transmission of reproductive and metabolic dysfunction in F1 and F3 male offspring in both androgenized and control lines, respectively, but with stronger phenotype in the obese lineage. Small non-coding RNAs (ncRNAs) sequencing of sperm from F1 and F3 male offspring revealed common differential expressed ncRNAs (DiDiRNAs) across generations in androgenized, obese, and obese and androgenized lines, with distinct regulatory patterns among lines. Three of the predicted targets of pRNAs and mRNAs were also differentially expressed in serum from the sons of PCOS mothers.

Conclusion: Our results reveal a previously unknown risk of reproductive and metabolic dysfunction in male progeny of PCOS mothers, which is likely caused by epigenetic changes by ncRNAs.
CONCLUSIONS: The effects of insulin observed in Polyovity Ovary Syndrome (PCDS) is directly related to the increased production of androgen hormones. Thus, the use of metabolites to control hyperinsulinemia could lead to a reduction in hyperandrosterone in these patients. This aim of the study was to evaluate the effects of metformin treatment on markers of hyperandrosterone in patients diagnosed with PCOS through a systematic review and meta-analysis.

METHODS: We conducted a systematic review, with meta-analysis, of randomized placebo-controlled clinical trials evaluating the effects of metformin treatment in adult patients with PCOS on the outcomes dehydroepiandrosterone (DHEAS) and total testosterone in accordance with the Cochrane Handbook for Systematic Reviews of Interventions recommendations. Searches were performed in the main electronic databases: MEDLINE via PubMed, CENTRAL, Embase, CINAHL, Web of Science and Scopus, including studies published until June 2021. The meta-analysis was conducted based on the mean differences and standard deviations between the values of the evaluated outcomes, at the baseline (before the use of metformin) and at the end (after the use of metformin) of the study, using the random effect and the effect measure both presented as the standardized mean difference (SMD). Significant values were considered as p<0.05 and 95% CI. The substantial heterogeneity for the outcomes assessed by the meta-analysis was explored from the sensitivity analysis, in order to examine changes in the size of the combined effect, excluding each study successively.

RESULTS: 3,944 primary studies were selected and, after removing duplicates and analyzing titles, abstracts, and full text, considering the pre-established inclusion and exclusion criteria, eleven studies were included in the quantitative evaluation. A significant increase in DHEAS levels (SMD: 0.50 (95% CI: 0.05 to 0.94) points; I² = 74%; p-value for heterogeneity: <0.00001) and significant reduction in total testosterone levels (SMD: -0.53 (95% CI: -1.18 to -0.00) points; I² = 88%; p-value for heterogeneity: <0.00001) were observed in both outcomes, in the metformin treatment group, when compared to the placebo group, after combining the results.

CONCLUSIONS: The results indicate that the use of metformin can lead to changes in androgen levels in patients with PCOS. (Support: CNPq and CAPES).

RHEUMS MACAQUE: MODELS FOR POLYCYSTIC OVARY SYNDROME & ENDOMETRIOSIS

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Objective: Nonhuman rhesus macaques (Macaca mulatta) have been proposed as relevant models for studying endometriosis. Both endometriosis and PCOS are highly prevalent in humans, and their pathogenesis may share certain similarities. In particular, both conditions are characterized by an increased risk of polycystic ovary syndrome, hyperandrogenism, and endometriosis.

Materials and Methods: In this study, we aimed to evaluate the incidence of PCOS and endometriosis in nonhuman rhesus macaques (M. m. mulatta) and to compare their prevalence with that observed in humans. We also aimed to assess the potential role of genetic and environmental factors in the development of these disorders.

Results: The incidence of PCOS and endometriosis in nonhuman rhesus macaques was found to be significantly higher than that observed in humans. This suggests that these disorders may share common genetic and environmental factors.

Conclusions: The results of this study support the use of nonhuman rhesus macaques as models for studying the pathogenesis of PCOS and endometriosis. Further research is needed to better understand the underlying mechanisms and to develop effective therapeutic strategies.
**ID #53** Type: Clinical Science

**TITLE:** CHARACTERIZING PCOS BY ANDROGEN EXCESS AND Oligo-ANovulation IN AN ELECTRONIC HEALTH RECORD DATASET

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**Objectives:** To characterize PCOS by using International Classification of Disease (ICD) codes for PCOS, androgen excess (AE) and oligo-anovulation (OA).

**METHODS:** The Research Patient Data Registry (RPDR) was used to identify women aged 18-34, between January 1st, 2005 and December 31st, 2005, from 9 Mass General Brigham institutions with 1) a PCOS ICD-9-CM code (256.4 or E28.2) or 2) undiagnosed PCOS with AE and OA. Women with any other endocrinopathies were excluded, such as thyroid, prolactin, or adrenal disease. Patients with a PCOS ICD code were further characterized by the presence of one or more conditions attributed to both AE (Hirsutism, alopecia, acne) and OA (amenorrhea or irregular menses ICD codes). Age of diagnosis for those meeting the Rotterdam criteria but lacking a PCOS ICD code was recorded as time when the patient first received an ICD code for any condition under AE or OA. We compared characteristics including race/ethnicity, BMI, age at diagnosis, and AE features between those with a PCOS ICD code and those meeting Rotterdam criteria by AE and OA ICD code.

**Results:** We identified 12,669 patients aged 18-34 who met the Rotterdam criteria for PCOS, which included 8,023 (63.3%) with a PCOS ICD code and 4,646 (36.7%) who lacked a PCOS code despite meeting the Rotterdam criteria for AE and OA. Among the total cohort 63.7% were Non-Hispanic whites, 25.5% were obese (BMI 30 or greater), and 52.2% were diagnosed between the ages of 25-34 years. Those with a PCOS ICD code had a higher prevalence of obesity (34.5%) at time of diagnosis compared to 10.1% of those that meet Rotterdam criteria for OA and DD without but a PCOS ICD code. The majority (61.9%) of those with a PCOS ICD code were diagnosed with the syndrome between ages 18-24, while most patients without a PCOS diagnosis (76.6%) first received an ICD code for a condition under OA or DD between ages 25-34. Among the patients with a PCOS ICD code, there were 1865 who had additional codes for DD and OA. Among these 2065, the leading feature of DA was hirsutism (46.2%), followed by acne (38.7), and alopecia (15.9%). Among the 4658 lacking the PCOS code who met Rotterdam, the leading feature of AE was acne (88.4%), followed by alopecia (26.3%), and hirsutism (11.9%).

**Conclusions:** This study highlights the need for an inclusive coding approach to PCOS when using EHR sourced datasets to include PCOS cases meeting Rotterdam criteria in addition to PCOS ICD code.

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**ID #6** Type: Translational Science

**TITLE:** CANADIAN WOMEN’S PERSONAL NARRATIVE ACCOUNTS OF PCOS DIAGNOSIS AND TREATMENT

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**Objective:** Polycystic ovary syndrome (PCOS) is a chronic health condition affecting 8-13% of reproductive-aged women worldwide. It is associated with metabolic, reproductive, and psychological impacts potentially leading to a risk of life-long comorbidities (e.g., diabetes, infertility). In Canada, it is estimated that 1.4 million women are living with and managing PCOS their experiences are under-represented in the literature. While early diagnosis is crucial in mitigating comorbidities, a robust literature points to lengthy diagnosis times, misdiagnoses, frustrating diagnosis encounters, and substantial unmet healthcare needs. OBJECTIVE: We argue that women’s negative experiences of PCOS diagnosis can be situated within the context of invisibility, a form of interpernal maltreatment that lies at the intersection of interpersonal deviance in healthcare. We sought to understand how women with PCOS negotiate power, resist sexism and institutional oppression, and advocate for just care. Two overarching research questions directed our analysis: 1. How do institutional power dynamics manifest, impact, and then shape the diagnosis narratives of women with PCOS, who are seeking care over an extended period of time in their lives? 2. How do women resist authoritative power, and leverage context to meet their health care needs and to pursue more equitable health care practices? METHOD: Women diagnosed with PCOS in Canada (N = 72) charted their diagnosis timeline, and then constructed their diagnosis narrative. They were also interviewed about their diagnosis experiences, and we focus our interview on patient-provider communications throughout this process. We analyzed the interview transcripts using Braun and Clarke’s codebook thematic analysis. RESULTS: Our analysis generated three main themes related to power and resistance while seeking a diagnosis and continued treatment plan, which, for many participants spanned years of medical consultations. 1. physicians as gatekeepers; 2. oppression as intersectional, and 3. antagonistic provider communications. Emotional and mental health impacts, as well as self-doubt, distrust in medical systems, and health-care avoidance were also a large part of participants’ narratives. However, participants engaged in numerous forms of resistance by mobilizing information and resources through some form of collective action CONCLUSION: Implications for these findings are discussed in relation to women’s health equity.

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**ID #8** Type: Clinical Science

**TITLE:** LIFESTYLE INTERVENTIONS IN WOMEN WITH POLYCYSTIC OVARY SYNDROME: A SCOPING SYSTEMATIC REVIEW

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**OBJECTIVE:** Lifestyle interventions (LSI) are recommended as first-line treatment for polycystic ovary syndrome (PCOS), yet the strength of evidence underpinning LSIs effectiveness remains unclear. We systematically reviewed the literature on LSIs in PCOS, evaluated evidence quality and summarised recommendations for clinical practice.

**METHODS:** We searched MEDLINE, EMBASE and CENTRAL for all randomised trials evaluating any LSI in PCOS until April 2021. We extracted data on the LSIs’ characteristics, dietary composition, duration, implementation, compliance assessment, and reported outcomes. We evaluated the evidence gap using a network-map of evaluated interventions.

**RESULTS:** We screened 550 citations and included 79 trials (n=4659 women). Most trials were from high-income countries (97/99, 72%) over a decade ago (48/79, 61%) and enrolled obese/overweight (97/77, 74%). BMI was the commonest reported outcome (58/79, 73%), followed by weight (49/79, 62%), and testosterone (45/79, 57%). More than half of the trials had high risk of randomisation (51/79, 66%) and allocation bias (49/79, 62%). Only 27 were registered prospectively (27/79, 34%). Two-thirds evaluated a dietary intervention (50/79, 88%); most commonly a hypocaloric diet (32/79, 48%); nineteen evaluated a combined dietary with pharmacological intervention (19/79, 24%), six combined diet with physical or behavioural intervention (6/79, 8%), and only one trial included all four elements.

**CONCLUSIONS:** Evidence on LSIs in PCOS is of poor quality with high variations in trial design, comparisons, and outcome reporting. Hypocaloric diet is the most commonly recommended LSI intervention for primary care. Future trials are needed to evaluate pragmatic and simple LSIs in robust multi-centre studies.