AE-PCOS

ANDROGEN EXCESS & PCOS SOCIETY

19th ANNUAL MEETING OF THE ANDROGEN EXCESS & PCOS SOCIETY

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		
1:05 pm	**Chris McCartney** University of Virginia Health, Charlottesville, Virginia, USA	PCOS ontogeny in adolescence
1:30 pm	**Maria Trent** Johns Hopkins University, Baltimore, Maryland, USA	Management of polycystic ovary syndrome in adolescents and young adults
1:55 pm	**Lisa Moran** Monash University, Melbourne, Australia	Lifestyle approaches for the adolescent with PCOS
2:20 pm	**Moderator: Sue Moenter** University of Michigan, MI, USA	LIVE Q&A: Session 1
Presidential Lecture		
2:30 pm	**Kathleen Hoeger** University of Rochester, Rochester, NY, USA	Presidential Lecture: Unsettled Legacy: Cross generational impact of PCOS on mental health
2:50 pm	**Moderator: Elisabet Stener-Victorin** Karolinska Institutet, Stockholm, Sweden	LIVE Q&A: Presidential Lecture
2:55-3:25 COFFEE BREAK/SPONSORS and INTERACTIVE POSTER SESSION		
Session 2: Oral Presentations 1: Clinical and translational research		
3:25 pm	**Snigdha Alur-Gupta** University of Rochester, Rochester, NY, USA	Impact of PCOS on cornovirus disease 2019 (COVID-19) incidence and severity in the United States
3:35 pm	**Jeffrey Pea** Cornell University, Ithaca, NY, USA	Variable discriminatory power of ovarian markers across lifespan warrant age-specific PCOS criteria

3:45 pm	**Chau Tay** Monash University, Victoria, Australia	Hypertension, obesity and maternal age negatively associated with reproductive outcomes in PCOS
3:55 pm	**Natàlia Pujol Gualdo** University of Oulu, Oulu, Finland	Leveraging Northern European population history: Novel low frequency variants for PCOS
4:05 pm	**Moderator: Terhi Piltonen** University of Oulu, Finland	LIVE Q&A:Oral Presentations
Session 3: Debate: PCOS is an inflammatory disorder		
4:15	**Barbara Obermayer,** Medical University of Graz, Graz, Austria	Will speak AGAINST the motion for:
4:30	**Frank Gonzales,** University of Illinois, Chicago, IL, USA	Will speak IN SUPPORT OF the motion for:
4:45	**Moderator: Joop Laven** Erasmus MC, Rotterdam, Netherlands	LIVE Debate, Discussion and Possible Motion

Day 2, November 13th, 1-5pm EST		
Time	**Speaker**	**Topic**
1:00 pm (EST)	**Kathleen Hoeger** University of Rochester, Rochester, NY, USA President of the AEPCOS Society	Introduction and Welcome to Day 2
Session 4: Lessons from pre-clinical models of PCOS		
1:05 pm	**Nathalie Di Clemente,** Sorbonne Université-INSERM, Paris, France	New spontaneous rat model of PCOS
1:30 pm	**W Colin Duncan,** The University of Edinburgh, Edinburgh, Scotland	FGF21 deficit and PCOS
1:55 pm	**Moderator: Rebecca Campbell,** University of Otago, Dunedin, New Zealand	LIVE Q&A: Session 4
Session 5: Oral Presentations 2: Basic and cellular research		
2:05 pm	**Mojca Jensterle,** University Medical Center Ljubljana, Slovenia	GLUT4 mRNA expression in adipose tissue after metformin withdrawal in PCOS: Is there legacy effect?

2:15 pm	**Ryan Paulukinas** University of Pennsylvania, Philadelphia, PA, USA	Conversion of classical and 11-oxygenated androgens by AKR1C3 in a model of PCOS adipocytes
2:25 pm	**Jacob Pruett** University of Mississippi Medical Center, Jackson, MS, USA	Oxidative stress and white adipose tissue in a rat model of polycystic ovary syndrome
2:35 pm	**Marika Kangasniemi** University of Oulu, Oulu, Finland	Deep learning model analysis of leucocyte counts and proliferation in non-PCOS and PCOS endometrium
2:45 pm	**Moderator: Anju Joham** Monash University, Australia	LIVE Q&A:Oral Presentations
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		
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&A: Clinical Research Award Lecture

Day 3, November 14th, 1-5pm EST		
Time	**Speaker**	**Topic**
1:00 pm (EST)	**Kathleen Hoeger,** University of Rochester, Rochester, NY, USA President of the AEPCOS Society	Introduction and Welcome to Day 3
Session 7: Treatment of PCOS through central mechanisms		
1:05 pm	**Richard Anderson,** University of Edinburgh, Scotland	Targeting Neurokinin B in PCOS treatment
1:30 pm	**Waljit Dhillo,** Imperial College London, UK	Therapeutic potential of kisspeptin
1:55 pm	**Moderator: Paolo Giacobini** INSERM, Lille, France	LIVE Q&A: Session 7
Session 8: Advocacy and the Azziz-Baumgartner Family Early Career Investigators Awards		
2:05	**Sasha Ottey** PCOS Challenge, The National Polycystic Ovary Syndrome Association, USA	PCOS Advocacy
2:20	**Li Meng** Erasmus MC, University Medical Center Rotterdam, The Netherlands	Functional analysis of pathogenic anti-mullerian hormone variants in patients with PCOS
2:30	**Aisha Sati** University of Otago, Dunedin, New Zealand	Role of microglia in polycystic ovary syndrome (PCOS)-like brain
2:40	**Moderator: Tania Burgert** Kansas City, MO, USA	LIVE Q&A: Session 8
2:50-3:05 COFFEE BREAK/SPONSORS and INTERACTIVE POSTER SESSION		
Session 9: PCOS: Diet and Inflammation		
3:05 pm	**Jorge Chavarro** Brigham and Women's Hospital, Harvard Medical School, USA	The influence of diet on PCOS
3:30 pm	**Karina B Gomes** Federal University of Minas Gerais, Brazil	Pro and Anti-inflammatory markers in PCOS

3:55 pm	**Moderator: Poli Mara Spritzer** Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil	LIVE Q&A:Session 8
Award Lecture: Ricardo Azziz Distinguished Researcher Award		
4:05	**David Abbott** Wisconsin National Primate Research Centre, USA	Distinguished Researcher Award Lecture: Nonhuman primate models of PCOS pathogenesis
4:35	**Moderator: Ricardo Azziz** University of Alabama at Birmingham, Birmingham, AL, USA	LIVE Q&A: Distinguished Researcher Award Lecture
4:45	**Anuja Dokras** Penn Medicine, Philadelphia, USA, Associate Executive Director, AE-PCOS Society	LIVE: AE-PCOS Society Update and meeting wrap up

ID #21 Type: Clinical Science

TITLE: Functional analysis of pathogenic anti-mullerian hormone variants in patients with PCOS

AUTHORS: Meng L, McLuskey A , Visser JA

Affiliation: Dept. of Internal Medicine, Erasmus MC, University Medical Center Rotterdam, The Netherlands

OBJECTIVE: Recently rare heterozogous 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 have 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 (V12G, P151S, P270S, P352S, P362S, H506Q) were selected based on previous findings. The variants were introduced in an AMH expression vector containing either a wild type (AMH-RAQR) or optimized cleavage site (AMH-RARR) and co-expressed with the BRE-Luc reporter in the mouse granulosa cell line KK-1. The AMH expression vectors were stably expressed in HEK293 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 RAQR 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 P362S 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.

ID #37 Type: Clinical Science

TITLE: Role of microglia in polycystic ovary syndrome (PCOS)-like brain

AUTHORS: Sati A (1), Prescott M (1), Jasoni CL (2), Desroziers E (1), Campbell RE (1).

Affiliation: (1) Department of Physiology and Centre for Neuroendocrinology, School of Biomedical Sciences, University of Otago, Dunedin, New Zealand;

(2) Department of Anatomy and Centre for Neuroendocrinology, School of Biomedical Sciences, University of Otago, Dunedin, New Zealand.

OBJECTIVE: Prenatally androgenized (PNA) models of PCOS exhibit excessive GABAergic wiring associated with PCOS-like reproductive deficits in adulthood. Although the mechanisms driving this aberrant brain wiring are poorly defined, we recently identified that microglia, the immune cells of the brain, are likely to shape the atypical brain wiring associated with PCOS development. Microglia number and morphology are altered by prenatal androgen excess and microglia engulfment of GABAergic terminals is reduced, suggesting that microglia are key mediators of androgen excess-induced changes in the brain. However, whether prenatal androgen excess acts directly on microglia is unknown. Here, we aimed to determine whether microglia express the androgen receptor (AR) and whether microglia sensitivity to androgen signaling is altered in PCOS-like PNA mice.

METHODS: Specific immunolabelling was used in the CX3CR1-GFP transgenic mice that express GFP in microglia to assess androgen receptor expression in microglia in adult PNA and control mice (N = 8-10 per group) in the rostral preoptic area (rPOA), where the PCOS-associated wiring abnormalities are detected, and the arcuate nucleus (ARN), where the aberrant wiring originates. Normal distribution and homogeneity of variance were determined with the Shapiro-Wilk test and Fisher's F test, respectively. Control and PNA groups were compared with unpaired Students t tests when data met the assumptions of normality and variance homogeneity. A Mann-Whitney test was used to compare the groups otherwise.

RESULTS: Microglia and AR were evident throughout the hypothalamus, however, there was no evidence for colocalization of the AR with microglia in any hypothalamic region assessed in PNA or control mice.

CONCLUSIONS: The absence of AR expression in microglia indicates that androgen excess-mediated changes in microglia morphology and behaviour in the PCOS-like brain must be indirect. The specific androgen targets in the female brain that are upstream of observed changes in microglia function remain to be determined

ID #28 Type: Clinical Science

TITLE: IMPACT OF PCOS ON CORNOVIRUS DISEASE 2019 (COVID-19) INCIDENCE AND SEVERITY IN THE UNITED STATES

AUTHORS: Alur-Gupta, S (1), Boland, MR (2), Dokras, A (3)

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(2) Department of Biostatistics, Epidemiology & Informatics, University of Pennsylvania, Philadelphia, PA, USA;

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OBJECTIVE: PCOS is the most common endocrine disorder in the reproductive years, with 5 million affected women in the United States (US). Several of the cardiometabolic risk factors associated with PCOS are also known risk factors for severe COVID-19 disease. There is limited data on the risk of COVID-19 in PCOS with a United Kingdom study suggesting higher incidence of suspected or confirmed COVID-19 in women with PCOS. We seek to determine the incidence of laboratory-confirmed COVID-19 and its severity in a large US dataset.

METHODS: The National COVID Cohort Collaborative (N3C) de-identified dataset is a centralized electronic health record derived data resource containing over 6.3 million unique individuals residing in the US, including 2.1 million who are COVID-19 positive. We used the N3C dataset to conduct a retrospective cohort study to determine the incidence and disease severity of COVID-19 in women with PCOS compared to those without PCOS. Categorical outcomes were analyzed using chi-square test and continuous outcomes with student's t-test. Data was restricted to reproductive aged women for additional analyses. Preliminary unadjusted results are presented here in anticipation of completing multivariable regression analyses.

RESULTS: We identified 46,820 women with PCOS amongst 3.41 million females in the dataset. Mean BMI (in kg/m2) in those with PCOS was 36.9 +9.78 vs 28.7 +8.52 in those without PCOS (p<0.001). Of these, 39,353 women with PCOS and 2.78 million without PCOS had confirmed laboratory testing for COVID-19. Fewer women with PCOS tested positive for COVID-19 (20.2%) compared to females without PCOS (24.9%, p<0.001). Of those who tested positive, using the WHO severity classifications, more women with PCOS had mild disease (85.7%) versus females without PCOS (83.9%, p<0.001). Despite a higher BMI, women with PCOS had the same likelihood of moderate disease (13.8% vs 14.1%, p=0.509) and severe disease (0.3% vs 0.4%, p=0.125) compared to those without PCOS. Women with PCOS were also less likely to die from COVID-19 (0.2% vs 1.7%, p<0.001).

When restricting to the 1.29 million females who were reproductive aged (18-49 years), fewer women with PCOS tested positive for COVID-19 (20.3%) compared to those without PCOS (26.8%, p<0.001). Of those who tested positive, 86.4% of those with PCOS had mild disease compared to 90.4% of those without PCOS (p<0.001). Women with PCOS were more likely, however, to have moderate disease (13.3% vs 9.2%, p<0.001) but not severe disease (0.3% vs 0.2%, p=0.181) or death (0.1% vs 0.2%, p=0.283).

CONCLUSIONS: Our findings suggest PCOS diagnosis is not associated with a higher incidence of severe COVID-19 disease or death in women with documented positive COVID-19 test results. This is the first study in the US evaluating incidence of COVID-19 in the PCOS population and distribution of disease severity as compared to women without PCOS. As the COVID-19 pandemic continues to have a tremendous impact on national health, it is vital to understand the precise independent risk of COVID-19 associated with PCOS.

ID #27 Type: Clinical Science

TITLE: VARIABLE DISCRIMINATORY POWER OF OVARIAN MARKERS ACROSS LIFESPAN WARRANT AGE-SPECIFIC PCOS CRITERIA

AUTHORS: Pea J (1), Jarrett BY (1), Vanden Brink H (1), Brooks ED (1), Hoeger KM (2), Spandorfer SD (3), Pierson RA (4), Chizen DR (4), and Lujan ME (1)

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(4) Department of Obstetrics, Gynecology and Reproductive Sciences, University of Saskatchewan, Saskatoon, SK, Canada

OBJECTIVE: To determine whether changes in ovarian morphology across the reproductive lifespan warrant age-specific ultrasonographic diagnostic criteria for PCOS.

METHODS: 102 women with PCOS based on the NIH criteria and 116 regular cycling, normoandrogenic controls aged 18-48 were prospectively evaluated. Ovarian ultrasound images were analyzed for ovarian area (OA), ovarian volume (OV), and number of 2-9mm antral follicles in both a single cross-section (FNPS) and the entire ovary (FNPO). Two-step hierarchical clustering using age and ultrasonographic markers of PCOS was used to identify age-stratified groups. Correlations between ovarian markers and age were assessed by Spearman's rank correlation coefficients for each phenotype and within each age group. Diagnostic accuracy of ovarian markers for PCOS was determined by Receiver Operating Characteristic (ROC) curve analysis.

RESULTS: Two-step hierarchical clustering generated three reproductive age groups: Early (ERA; 18-24yo), Middle (MRA; 25-30yo), and Late (LRA; 31-48yo). Age negatively correlated with follicle counts (FNPS, FNPO, and FNPO2-5mm) in the control group (ρ = -0.38, p = 0.0001, ρ = -0.26, p = 0.0091, ρ = -0.22, p = 0.0262, respectively) with variation in strength and directionality of associations noted across age groups. In contrast, no associations between age and follicle counts were observed in the PCOS group. Age-specific associations were also not detected between age and ovarian size (OA, OV) in the control and PCOS groups. Age-specific diagnostic thresholds for FNPS, OA, OV, and FNPO were superior versus thresholds generated across the entire group; OA and OV exhibited the greatest diagnostic potential in the ERA (AUC = 0.815 and 0.747, respectively) and MRA groups (AUC = 0.877 and 0.866, respectively). In the LRA, FNPO was the most accurate diagnostic marker (AUC = 0.898).

CONCLUSIONS: Certain ultrasonographic markers of ovarian morphology exhibit age-related changes in diagnostic accuracy which differ between control women and women with PCOS. These findings support the use of ovarian size for younger women and follicle counts in older women in the ultrasonographic diagnosis of PCOS.

(This study was funded by the National Institutes of Health Grant [R01HD09374, R56HD089962, UL1 TR000457-06, 4T32DK007158-41] and the Canadian Institute of Health Research [FRN 146182].)

ID #13 Type: Clinical Science

TITLE: HYPERTENSION, OBESITY AND MATERNAL AGE NEGATIVELY ASSOCIATED WITH REPRODUCTIVE OUTCOMES IN PCOS

AUTHORS: Tay CT (1,2), Loxton D (3), Bahri Khomami M (1,2), Teede H (1,2), Joham AE (1,2).

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OBJECTIVE: This study investigates the lifetime reproductive outcomes and the relationship of family size aspiration (FSA) achievement with metabolic, psychiatric and reproductive history in women with and without polycystic ovary syndrome (PCOS).

METHODS: A cross-sectional study was conducted on survey data collected from 1996 to 2018 in the cohort of community-recruited women born 1973-78 from the Australian Longitudinal Study of Women's Health. 9034 women with (n=778) and without PCOS (n=8256) were included. The outcomes of the study were family size aspiration (FSA) achievement, nulliparity and total number of live births. Main explanatory variables examined were self-reported PCOS status, history of metabolic, psychiatric and reproductive conditions. X2 tests were used to examine the difference in prevalence between groups. Logistic regression analyses were performed to assess the relationship between PCOS, metabolic condition history, psychiatric condition history and reproductive history and achievement of FSA.

RESULTS: Women with and without PCOS had similar FSA but significantly less women with PCOS than without achieved their FSA (53.08% vs 60.47%, p<0.001). Higher proportion of women with than without self-reported PCOS were nulliparous (37.15% vs 31.64%, p=0.002) and the median total number of live births was also lower in women with than without self-reported PCOS (1 vs 2, p<0.001). After controlling for sociodemographic factors, negative associations were observed between FSA achievement and PCOS 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 0.69-0.90), history of in-vitro fertilisation use (adjusted OR 0.49, 95% CI 0.38-0.63) and maternal age at first childbirth (adjusted OR 0.92, 95% CI 0.91-0.93) remained 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.

ID #9 Type: Clinical Science

TITLE: LEVERAGING NORTHERN EUROPEAN POPULATION HISTORY: NOVEL LOW FREQUENCY VARIANTS FOR PCOS

AUTHORS: Pujol-Gualdo N (1,2), Tyrmi JS (3,4,5), Arffman RK (1), Kurra V (6), Papunen LM (1), Sliz E (3,4,5), FinnGen, EstBB Research Team, Piltonen TT (1), Laisk T (2), Kettunen J (3,4,5,7), Laivuori H (8,9,10)

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(10) Institute for Molecular Medicine Finland, Helsinki Institute of Life Science, University of Helsinki, Helsinki, Finland;

OBJECTIVE: To leverage genetic information of two neighboring and well-characterized populations in Europe – Finnish and Estonian – to provide a basis for a new understanding of the genetic determinants of polycystic ovary syndrome (PCOS).

METHODS: We conducted a three-stage case-control genome-wide association study (GWAS). In the discovery phase, we performed a GWAS comprising of a total of 797 cases and 140,558 controls from the FinnGen study. For validation, we used an independent dataset from the Estonian Biobank, including 2,812 cases and 89,230 controls. Finally, we conducted a joint meta-analysis of 3,609 cases and 229,788 controls from both cohorts.

RESULTS: In total, we identified three novel genome-wide significant variants associating with PCOS. Two of these novel variants, rs145598156 (p=3.6 × 10−8, OR=3.01 [2.02-4.50] MAF=0.005) and rs182075939 (p=1.9 × 10−16, OR= 1.69 [1.49-1.91], MAF=0.04), were found to be enriched in the Finnish and Estonian populations and are tightly linked to a deletion c.1100delC (r2= 0.95) and a missense I157T (r2=0.83) in CHEK2. The third novel association is a common variant near MYO10 (rs9312937, p= 1.7 × 10−8, OR=1.16 (1.10-1.23), MAF=0.44). We also replicated four previous reported associations near the genes ERBB4, DENND1A, FSHB and ZBTB16.

CONCLUSIONS: We identified three novel variants for PCOS in a Finnish-Estonian GWAS. Using isolated populations to perform genetic association studies provides a useful resource to identify rare variants contributing to the genetic landscape of complex diseases such as PCOS.

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ID #10 Type: Basic Science

TITLE: GLUT4 MRNA EXPRESSION IN ADIPOSE TISSUE AFTER METFORMIN WITHDRAWAL IN PCOS: IS THERE LEGACY EFFECT?

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OBJECTIVE: Metformin induces GLUT-4 mRNA expression in insulin target tissues in PCOS. It is not clear how long the metformin treatment in obese PCOS should last and how long its metabolic cellular impact is sustained after its withdrawal. We aimed to compare the effect of metformin withdrawal on GLUT-4 mRNA expression in subcutaneous adipose tissue after prior short and long term treatment in obese PCOS women.

METHODS: We conducted longitudinal study including 24 overweight/obese PCOS women aged 32.5 (28.25–42.25) years, who had been treated with metformin monotherapy 1000 mg BID for at least one year prior the inclusion. They were divided into ST group (N = 11) that was treated with metformin for one year (1 (1–1) years) and LT group (N = 13) that had been continuously treated with metformin for at least 3 years (5 (3–9) years). They were followed from the day after they discontinued metformin up to 6 months after metformin withdrawal. At baseline and after 6 months, all patients underwent history check-up and anthropometric, endocrine and metabolic assessments. Biopsy of subcutaneous adipose tissue followed by quantitative PCR analysis was performed to determine GLUT-4 mRNA expression.

RESULTS: We found no time/effect differences in GLUT-4 mRNA expression in ST (2-dCt at baseline 0.42 (0.16–0.48) vs 2-dCt after 6 months 0.31 (0.22–0.56), p = 0.594) and no time/effect difference in LT group (2-dCt at baseline 0.24 (0.14–0.39) vs 2-dCt after 6 months 0.25 (0.20–0.38), p = 0.382). There was also no difference in GLUT-4 mRNA expression between both groups at baseline and after 6 months. In ST users, withdrawal of metformin resulted in regain of body weight and BMI. In LT users withdrawal resulted in a significant increase in weight, BMI, androstenedione and decreased menstrual frequency. By contrast, waist circumference, VAT, IR as assessed by HOMA-IR and the parameters of glucose homeostasis, remained stable in both groups.

CONCLUSIONS: In summary, 6 months after metformin withdrawal, GLUT-4 mRNA expression remained stable, regardless of the prior treatment duration. The results imply some metabolic treatment legacy of metformin at least 6 months after withdrawal. To the best of our knowledge, this is the first study that compared consequences of metformin withdrawal on GLUT-4 mRNA expression in ST and LT prior users.

(This research was funded by Slovenian Research Agency, grant numbers #P3-0298 and P1-0170.)

ID #29 Type: Translational Science

TITLE: CONVERSION OF CLASSICAL AND 11-OXYGENATED ANDROGENS BY AKR1C3 IN A MODEL OF PCOS ADIPOCYTES

AUTHORS: Paulukinas RD (1), Mesaros CA, Ph.D. (1), and Penning TM, Ph.D. (1)

Affiliation: (1) Department of Systems Pharmacology and Translational Therapeutics & Center of Excellence in Environmental Toxicology, University of Pennsylvania, Philadelphia, PA, United States;

OBJECTIVE: The source of androgens and the androgen profile that constitutes androgen excess (AE) in PCOS is uncertain. Aldo-keto reductase family 1 member C3 (AKR1C3) catalyzes the conversion of peripheral androgens and is induced by insulin in adipocytes. The 11-oxygenated androgens were reported as the dominant androgens of PCOS and may be an alternative source of AE. AKR1C3 converts the following: Δ4-androstene-3,17-dione (4AD) to testosterone (T), 5α-androstane-3,17-dione (5AD) to 5α-dihydrotestosterone (DHT), 11-ketoandrostene-3,17-dione (11K-4AD) to 11-ketotestosterone (11K-T), and 11-ketoandrostane-3,17-dione (11K-5AD) to 11-ketodihydrotestosterone (11K-DHT). The purpose of this study is to elucidate the conversion of both classical and 11-oxygenated androgens by insulin-induced AKR1C3 in a model of PCOS adipocytes.

METHODS: We developed a stable-isotope-dilution liquid chromatography high resolution mass spectrometric assay for the quantification of both classical and 11-oxygenated androgens in differentiated Simpson-Golabi-Behmel Syndrome adipocytes. Cells were treated with 4AD, 11K-4AD, or 11β-hydroxy-androstene-3,17-dione (11β-OH-4AD), the adrenal precursor to 11K-4AD. Androgens were derivatized with Girard P to enhance sensitivity and specificity. Analyte peaks were quantified using calibration curves of analyte to internal standard ratios versus pg of standard.

RESULTS: Our data suggests that 11β-OH-4AD is converted to 11K-4AD, which is then converted by insulin-induced AKR1C3 to 11K-T. The conversion of 11K-4AD to 11K-T was AKR1C3 dependent since a panel of AKR1C3 inhibitors blocked 11K-T formation. We found that 11K-T is deactivated to 11β-hydroxy-testosterone (11β-OH-T) and 11K-4AD can be back converted to 11β-OH-4AD by HSD11B1. This suggests that HSD11B1 protects the androgen receptor (AR) by converting potent 11-keto-androgens to their less potent 11β-hydroxy-counterparts.

CONCLUSIONS: Both classical and 11-oxygenated androgens may be sources of AE in PCOS by their intracrine formation in adipocytes. 11K-T may be deactivated by HSD11B1, suggesting that the occupancy of the AR by 11K-T is tightly regulated by this enzyme. Our work elucidates the role of AKR1C3 in the formation of both classical and 11-keto-androgens in a model of PCOS adipocytes and supports AKR1C3 as a potential therapeutic target in mitigating the AE of PCOS.

(Supported by DOD grant and P30ES013508 to TMP and T32ES019851 to RDP)

ID #50 Type: Basic Science

TITLE: OXIDATIVE STRESS AND WHITE ADIPOSE TISSUE IN A RAT MODEL OF POLYCYSTIC OVARY SYNDROME

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OBJECTIVE: Polycystic Ovary Syndrome (PCOS) is the most common endocrinopathy in reproductive-age women. It is characterized by androgen excess; 80% of this population is obese. As white adipose tissue (WAT) expands through hypertrophy, there is increased hypoxia and reactive oxygen species (ROS). However, the effect of female androgen excess on WAT is poorly understood. Hyperandrogenemic female (HAF) rat model of PCOS have 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/90days). At 3 months of DHT, upon euthanasia, heparinized plasma was collected 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 SOD (SOD2). Complex IV (CIV) activity, a marker of oxidative phosphorylation capacity, was measured by respirometry. Adipocyte area was quantified from 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 copper reducing equivalents, P<0.05). In sWAT, HAF had increased frequency of adipocytes at 500 µm2 (20.5 ± 2.2 vs 12.7 ± 2.5 %, P<0.01) and decreased frequency at 1300 µm2. However, in vWAT, HAF had decreased frequency of adipocytes at 300 µm2 and increased frequency at 900 µm2 (16.5 ± 1.6 vs 11.7 ± 1.4 %, P<0.01). sWAT SOD1 protein (0.69 ± 0.06 vs 1.00 ± 0.09, P<0.05) expression was decreased in HAF with no change in vWAT. SOD2 protein expression was unchanged in sWAT and vWAT. HAF had decreased CIV activity in sWAT (197 ± 24 vs 273 ± 24 nmol e-/min/mg of protein, P<0.05) but not in vWAT.

CONCLUSIONS: In summary, HAF rats had decreased TAC, suggesting increased ROS. Furthermore, androgens downregulated SOD1 protein and CIV activity only in sWAT with no change in vWAT. Surprisingly, hyperandrogenemia only caused hypertrophy of vWAT adipocytes while decreasing adipocyte size in sWAT. These data suggest that hyperandrogenemia has a differential effect on sWAT and vWAT, and that sWAT 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: NIGMS P20GM121334 and P20GM104357, NIDDK R21DK11350 and F30DK127527, NHLBI P01HL51971)

ID #39 Type: Basic Science

TITLE: DEEP LEARNING MODEL ANALYSIS OF LEUCOCYTE COUNTS AND PROLIFERATION IN NON-PCOS AND PCOS ENDOMETRIUM

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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 LH+ 7–9 (10 control, 16 PCOS) and LH+ 10–12 (7 control, 9 PCOS) secretory phase were collected during 2014–2019. Samples were stained with antibodies for CD8+ T cells, CD56+ 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 (AINO, Aiforia). First AINO 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 (n = 11) vs. proliferative phase controls (n =18) 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 CD68+ cells in the epithelium (controls vs. PCOS, median [IQR] 0.92 [0.75–1.51] vs. 1.97 [1.12–2.68], p = 0.025) and fewer leucocytes in the stroma (CD8% 3.72 [2.18–4.20] vs 1.44 [0.77–3.03], p = 0.017; CD56% 6.36 [4.43–7.43] vs. 2.07 [0.65–4.99] p = 0.003; CD68% 4.57 [3.92–5.70] vs 3.07 [1.73–4.59], 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 remarkably from the controls, which might indicate that gaining ovulatory cycles normalizes PCOS endometrium allowing more normal leucocyte environment prior implantation. Deviant endometrial leucocyte populations seen in anovulatory women with PCOS could interrelate 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 Juselius Foundation, Academy of Finland, the Orion Research Foundation sr, the Finnish Medical Association, Emil Aaltonen foundation and the Swedish Research Council.)

ID #11 Type: Clinical Science

TITLE: A REVIEW OF THE NHANES DATASET TO IDENTIFY INDIVIDUALS WITH PCOS

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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 1) 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 20-40 years were included; exclusions were menopause, 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 #12 Type: Clinical Science

TITLE: PCOS with metabolic syndrome & psychological distress.

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Objective; to identify and compare the possible relationship between psychological distress among PCOS women and associated risk of metabolic syndrome, contributing this psychological distress".

Introduction; Psychological distress correlates polycystic ovary syndrome (PCOS), are the source of profound morbidities and decreased quality of life. Body images & pathogenesis of PCOS are associated with physical, metabolic and psychological disturbances. 33% of PCOS women suffer from metabolic syndrome (MS), which may results CVD, diabetes, cancer. Depression and anxiety are more in MS, but these are often overlooked and undiagnosed. So our study tried to identify the possible relationship between psychological distress among PCOS and associated risk of metabolic syndrome, contributing the psychological disorders.

Method & material; this prospective cross sectional study was conducted among 120 young PCOS patients from ZHSWMCH between 1st January 2020 to 1st June 2021. Diagnosis of PCOS was done with Rotterdam criteria. MS =50 were chosen from them, diagnosed by IDFC. PCOS without metabolic syndrome A=70. All participants completed the 12-item version of General Health Questionnaire (GHQ-12), 36-item, Beck Depression Inventory and State-Trait Anxiety Inventory to measure current mental states.

Results: 38% of PCOS women suffered from some psychological disturbances. PCOS women with MS, had marked incidence of mental distress (80%) According to GHQ-12.

PCOS with MS had more mental distress than PCOS with out MS [80%vs

35.7%, p= <.0001]. Incidence of Depression {7.1%vs 38%, p=.002], Anxiety [28.6% vs. 56%,p=<.002} and Bipolar [0 vs3%,p=<0.002] were much in PCOS with MS. Again eating disorder {74% vs. 55.7%,p=<0101] was higher in PCOS with MS but was not statistically significant.

Conclusion: Despite high prevalence of psychological distress among PCOS women, it is a neglected entity; PCOS women suffer from mental distress significantly, this distress is more evident in PCOS with MS which is undoubtedly stigmatizes and lowers their quality of their life. Again Metabolic syndrome in PCOS not only affect mental health, it is associated with long-term complications like CVD, DM and endometrial cancer. Therefore meticulous assessment of "metabolic syndrome" and "mental health" is very important for all PCOS women even they don't have these symptoms, so that we may institute holistic treatment earliest to prevent the devastating consequences.

ID #14 Type: Clinical Science

TITLE: METABOLOMICS PROFILE OF YOUNG ADULTS: INFLUENCE OF SEX, FUNCTIONAL HYPERANDROGENISM AND OBESITY

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OBJECTIVE: Metabolites are 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. We aimed 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 19 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 alanine 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-oxoisocaproic and 2-oxoisovaleric acids, isoleucine, valine, lactate, alanine, acetone, pyruvate, creatine, lysine, ornithine, glycerol, glucose, methylhistidine, tyrosine and tryptophan) and 7 decreased (isobutyric and pyroglutamic 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 (leucine, isoleucine, valine, 2-oxoisocaproic and 2-oxoisovaleric acids, pyruvate, lysine, ornithine, glucose, methylhistidine and creatinine). 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.

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ID #15 Type: Clinical Science

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

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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 (i.e., nonbinary or 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 perceived 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 #16 Type: Clinical Science

TITLE: CAN WE JUST USE SCOFF TO PREDICT EATING DISORDERS IN WOMEN WITH PCOS? – TESTING THE RECOMMENDATIONS

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OBJECTIVE: Women with Polycystic ovary syndrome (PCOS) have a higher risk of developing disordered eating (DE) and clinical eating disorders (ED), compared to women without PCOS. The SCOFF and EDE-Q are identified as screening tools for DE/EDs in the 2018 International PCOS guidelines. The SCOFF has been tested in women in the general population but is yet to be tested in women diagnosed with PCOS. Therefore, the aim of this study was to test the ability of the SCOFF questionnaire to identify to the same degree as the EDE-Q and hence the proportion of people who indicate eligibility for further treatment.

METHODS: An online cross-sectional survey of Australian women with PCOS (n=501) was conducted in August 2017 to March 2018. Participants completed the EDE-Q, SCOFF and a demographic questionnaire. Three separate logistic regression models were conducted to examine the predictive validity of the SCOFF. The first included a dichotomous variable of EDE-Q indicating treatment required (≥3 and >3) as the outcome and the SCOFF dichotomous variable of likely diagnosis for an ED as the predictor. The second model used the EDE-Q DE cut off (≥1.52) as the outcome and used the same SCOFF dichotomous variable as the predictor. Finally, a step-wise multiple regression was used to examine the ability of the SCOFF components (Sick, Control, One Stone, Fat and Food) to predict the EDE-Q global score. The percentage of cases correctly classified by the model was identified through the percentage of accuracy classification. All analyses were conducted in SPSS V26, Chicago, USA. Statistical significance was set at $p<0.05$.

RESULTS: Women had a mean age of 30.5 years, with the majority experiencing oligoanovulation (67.7%) and hirsutism (74.5%). The sample had a mean global EDE-Q score of 2.30 (±1.12) and a mean SCOFF score of 1.57 (±1.57). The EDE-Q considered 27.3% (n=137) of women to be at high risk for an ED and needing further treatment, whilst 71.5% (n=358) were classified as having DE. In comparison, the SCOFF screened 49.1% (n=246) of women as having a possible ED and correctly identifying 73% of those with symptoms warranting treatment and 72% of those with DE.

CONCLUSIONS: This analysis shows that up to 27% of DE and ED cases may go undiagnosed or unrecognised with the use of the SCOFF tool. Therefore, in juxtaposition to the international guidelines the SCOFF questionnaire is not recommended, instead it is recommended to use the EDE-Q to screen for DE and ED.

ID #17 Type: Translational 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 exogenous hyperinsulinism resulting from subcutaneous 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 stablished 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 participants 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-β-estradiol, DHEA-S, δ-4-androstenedione, basal and stimulated 17-hydroxyprogesterone, total testosterone, SHBG and calculated free testosterone, at their follicular phase of the menstrual cycle). An ovarian ultrasound was performed to assess polycystic ovarian morphology. We used Stata software v16 (StataCorp LLC) for statistical analysis.

RESULTS. At recruitment, mean age of participants was 30.3 ± 8.7 yrs, mean duration of T1D was 14.9 ± 9.7 yrs and mean BMI was 23.7 ± 3.9 kg/m2. Mean A1c was 7.2 ± 1.4%. The prevalence of all PCOS phenotypes (Rotterdam/ESHRE-ASRM criteria) was 23.3% (95% CI: 15.8–33.1%); of hyperandrogenic PCOS (AE-PCOS criteria) 16.7% (10.1–25.7%), and of classic PCOS (NIH criteria) 14.4% (95%CI: 8.6–23%). Univariate regression model showed significant results for age (OR: 0.91, p=0.004), premenarcheal diagnosis of T1D (OR: 3.06, p=0.038) and insulin dose (OR: 9.54, p=0.046) as predictors of PCOS. After introducing these variables into a multivariate regression model, only age (OR: 0.89, p=0.024) 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.

ID #19 Type: Clinical Science

TITLE: CHARACTER STRENGTHS OF WOMEN WITH POLYCYSTIC OVARY SYNDROME

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OBJECTIVE: The health sector has recently showed 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 (CSs) between patients with and without polycystic ovary disease (PCOS) and find the association between biological (testosterone levels) and psychological factors (CSs).

METHODS: A total of 100 women divided into PCOS (50) and non-PCOS (50) groups who presented to the gynecological clinics 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-72. Univariate and multivariable analyses were performed to examine the association of CSs between the two groups and its predictors.

Univariate and multivariable analyses were performed to examine the association of CSs 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 activational influences of testosterone on the character strengths of the sample population.

Of the 24 CSs, 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 patients. 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)

ID #20 Type: Clinical Science

TITLE: Investigation of the mechanism of action of duodenal mucosal resurfacing in PCOS. The DOMINO study.

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BACKGROUND: Duodenal mucosal resurfacing (DMR) is a novel day-case endoscopic intervention which results in weight loss-independent reductions in HbA1c in patients with type 2 diabetes mellitus (T2DM). We hypothesized that DMR works by increasing insulin sensitivity and we aimed to investigate the mechanism of action of DMR through longitudinal metabolic phenotyping in humans

METHODS: Thirty-two insulin-resistant women with polycystic ovary syndrome (PCOS) and obesity were randomised in a double-blinded manner to DMR or sham endoscopy. They underwent measurements of insulin sensitivity using euglycaemic hyperinsulinaemic clamps, insulin secretion using oral glucose tolerance tests and reproductive function using weekly reproductive hormone profiles and ovarian ultrasonography (follicular tracking) for 6 months post-intervention.

RESULTS: A small increase in total body insulin sensitivity measured by the clamp was observed in both groups at week 12. An increase in insulin sensitivity, as measured by HOMA-IR, was observed in both groups at week 24. There was an increase in the number of menses (median 2 DMR, 0.5 sham). There were no significant differences between the two groups in these outcomes or insulin secretion.

CONCLUSIONS: These findings suggest that DMR does not work by increasing insulin sensitivity in euglycaemic, insulin resistant women with PCOS. The procedure may exert its effects only in the context of hyperglycaemia or pathologically hyperplastic, insulin-desensitised duodenal mucosa. Future studies could examine the effect of DMR in people with T2DM in whom an insulin sensitising effect might be more pronounced, but also explore the reduction of intestinal glucose absorption as an alternative mechanism of action.

ID #22 Type: Clinical Science

TITLE: CARDIOMETABOLIC PROFILE IN WOMEN WITH POLYCYSTIC OVARY SYNDROME IN LATIN AMERICA: SYSTEMATIC REVIEW

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OBJECTIVE: Polycystic ovary syndrome (PCOS) is an endocrine disorder that commonly affects women of childbearing age and has been associated with metabolic and reproductive abnormalities. Only a few studies have investigated metabolic traits in women with PCOS in Latin America. Therefore, we conducted a systematic review to provide an overview of the available evidence on the metabolic profile of Latin American women with PCOS. METHODS: We searched Embase, Medline, and Cochrane Central Register of Controlled Trials databases for cross-sectional, case-control, or cohort studies focusing on populations of countries in South and Central America and Mexico, published until October 31, 2019. We selected studies that reported the diagnostic criteria for PCOS. In the absence of a control group, we included studies if they reported relevant metabolic data. RESULTS: Of the 4878 records identified, 41 studies were included in the systematic review. Sample sizes ranged from 10 to 288 in PCOS groups and from 10 to 1500 in control groups. The prevalence of phenotypes A and B (classic PCOS) ranged from 65.8% to 87.5% as reported in studies from Argentina, Brazil, and Chile. Metabolic syndrome ranged from 33.3% to 44.0% for phenotype A, from 15.0% to 58.0% for phenotype B, from 11.9% to 36.0% for phenotype C, and from 14.2% to 66.0% for phenotype D. Women with PCOS had higher body mass index, waist circumference, blood pressure, glucose, and homeostasis model assessment index as well as a more adverse lipid profile than those without PCOS. CONCLUSIONS: Evidence from the present systematic review suggests that anthropometric and metabolic profiles are worse in women with PCOS who live in different Latin American countries than in women without PCOS living in the same region. Additional studies assessing metabolic comorbidities, such as diabetes, and distinct PCOS phenotypes in different Latin American countries are warranted and may produce invaluable information for primary and secondary prevention of PCOS in the region. This systematic review was registered in PROSPERO (CRD42016038537).
(Funding: CNPq, Fapergs, Brazilian National Institute of Hormones and Women's Health).

ID #23 Type: Clinical Science

TITLE: COMPARISON OF THREE AMH ASSAYS WITH AMH AND FOLLICLE NUMBER IN PATIENTS WITH PCOS

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OBJECTIVE: Polycystic ovary syndrome (PCOS) is an endocrine disorder including polycystic ovarian morphology (PCOM). Anti-Müllerian hormone (AMH) levels correlate with the number of follicles (TFC) in the ovary. In PCOS, this is reflected by increased AMH levels and therefore AMH is suggested as a proxy for PCOM. However, lack of a golden standard limits direct comparison of different assays. In addition, little is known about the inter-assay correlation in PCOS. Hence, this study aims to investigate the correlation between different AMH assays and TFC in PCOS patients.

METHODS: AMH levels were measured in 1660 PCOS patient by three different assays: (1) Modified Gen II AMH ELISA; (2) picoAMH assay; and (3) Fully automated Elecsys AMH plus assay. Patients were divided in three subgroups based on a previously reported range of AMH cutoff values for PCOM: low (<2.80 ng/ml), mid (2.80–7.04 ng/ml) and high AMH level (>7.04 ng/ml). Passing Bablok regression was used for the comparison between assay methods. Spearman's rank was used to assess the correlation between AMH and TFC.

RESULTS: The inter-assay correlations over the total range of AMH levels were: Gen II vs Elecsys: 0.81; picoAMH vs Gen II: 0.81; picoAMH vs Elecsys: 0.94. Stratification in three AMH subgroups revealed an AMH level dependent inter-assay correlation. A strong inter-assay correlation was present in both the low and high AMH subgroups, ranging from 0.62–0.86. The correlation in the mid AMH level subgroup was only moderate, with correlation coefficients ranging between 0.28–0.56.

A positive correlation was present between AMH levels and TFC, with correlation values ranging from 0.57–0.62. Subgroup analysis showed that only in patients with AMH levels <2.80 ng/ml, the correlation with follicle count was moderate (0.36–0.55). With AMH levels above 2.80 ng/ml the correlation with follicle count decreased in all three assays, resulting in correlation coefficients ranging from 0.18–0.38.

CONCLUSIONS: In conclusion, in our cohort of PCOS patients both the inter-assay correlation and the correlation between AMH level and follicle count depend on range of serum AMH level. While a high AMH level may reflect the presence of PCOM, our results suggest that it does not accurately reflect the total number of follicles in PCOS. This once more emphasizes the need of a standardization of AMH measurement for an accurate interpretation of AMH in clinical practice.

ID #24 Type: Clinical Science

TITLE: EFFECT OF COVID-19 PANDEMIC ON SLEEP IN PATIENTS WITH PCOS

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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 Polycystic Ovarian Syndrome (PCOS). METHODS: longitudinal study conducted with 20 patients with PCOS by the Rotterdam criteria from the PCOS Outpatient Clinic of Hospital São Vicente de Paulo (HSVP), 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 risk, 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 31.8±6.1 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=0.08). 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=0.004). 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 #25 Type: Clinical Science

TITLE: ASSESSING INDIRECT AND INTANGIBLE COSTS OF PCOS IN THE U.S.

AUTHORS: Delau O (1), Yadav S (2), Patterson W (3), Ottey S (3), Azziz R (4-7)

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OBJECTIVE: Polycystic Ovary Syndrome (PCOS) is the most common endocrine-metabolic disorder in reproductive-aged women affecting 10-15% of unselected reproductive-aged 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:GH). 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 presenteeism, 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 Dollars). Intangible costs will be assessed by calculating quality of life years (QALY) 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.)

ID #26 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 underlaying 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 615 pregnant women with PCOS were included from two RCTs randomizing women to metformin (n=299) or placebo (n=316), from first trimester to delivery. Serum was sampled at gestational weeks 10 (n=596), 19 (n=575), 32 (n=552) and 36 (n=541). Twenty-two cytokines were measured using a bead-based multiplexed immunoassay system, 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 (RM-ASCA+) 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 eotaxin (p<0.01), the inflammatory cytokines interleukin (IL)-17 (p=0.03) and IL-12 (p=0.04), the anti-inflammatory cytokine IL-4 (p=0.04), granulocyte colony-stimulating factor (G-CSF) (p=0.04), and fibroblast growth factor-basic (FGF-b) (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=0.01).

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 immune mobilization, possibly protecting against infections in pregnancy.

(Supported by NTNU, Research council of Norway, Novo Nordisk foundation and St. Olav's 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 abnormality of reproductive-aged women today, affecting 10-15% of unselected reproductive-aged women worldwide, and represents a significant financial burden to our health care. In the U.S. alone, costs associated with direct medical care, excluding management of mental health disorders and indirect and intangible costs, are estimated to approximate $8 billion yearly (in 2020 USD). Women with PCOS have increased odds of developing moderate and severe depression, anxiety, eating disorders, and other mental health conditions, in part due to biochemical changes, constant concerns regarding physical appearance, and social stigma from hirsutism, obesity, and infertility. We aim to determine the excess costs associated with mental health disorders in women with PCOS vs. controls through a systematic review of pre-existing literature. An ongoing goal is to estimate the economic burden of PCOS as completely as possible to allow for a more accurate prioritization of the disorder as a public health interest.

METHOD: We have initiated a study to assess the economic burden of mental health disorders. We will systematically review U.S based case-control studies focusing on mental health disorders in PCOS patients. A comprehensive meta-analysis of comparative studies reporting mental health disorders would be performed. While there are many mental health complications associated with PCOS, for the purpose of this economic burden analysis, we will only consider those disorders that have been most consistently and strongly associated with PCOS, including depression, anxiety, and eating and mood disorders. We will then determine the excess direct costs of mental health disorders in adolescents and adult women due to PCOS in US dollars. Preliminary data on the excess economic burden of PCOS related to mental health disorders in the U.S. will be presented.

ID #31 Type: Clinical Science

TITLE: CHANGES IN PCOS PHENOTYPE WITH WEIGHT LOSS ARE ASSOCIATED WITH BASELINE FREE ANDROGEN STATUS

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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-PCO, 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 1–2lbs of weight loss per week. Weight and menstrual cycle status were monitored at least twice-weekly. Anthropometry, dual x-ray absorptiometry, transvaginal 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=8) was defined by transition to a less severe 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 Wilcox signed-rank test and differences across groups by Kruskal-Wallis tests.

RESULTS: At baseline, 48% of participants were classified as Frank, 43% Non-Androgenic, 9% Non-PCO and none had Ovulatory PCOS. Post intervention, participants classified as Frank, Ovulatory, Non-Androgenic or Non-PCO changed to 44%, 26%, 22% and 4% respectively. One participant (4%) lost their PCOS designation. All participants experienced significant decreases in weight, waist and hips 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%, -6.3%, respectively ($p=0.19$). Baseline free androgen index (FAI) ($p=0.041$) 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 ($p=0.025$) 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 useful biomarker to predict phenotypic change in response to weight loss. (NIH R01HD09374, 4T32DK007158-41, 5R25GM125597-03; CIHR FRN146182).

ID #32 Type: Basic Science

TITLE: CLINICAL VERSUS SELF-ASSESSMENT OF HIRSUTISM

AUTHORS: Oliveira TF(1), Oliveira T(1), Gonçalves BA (2),Santana DC(2), Rocha AL(3), Azevedo RC(1),Reis FM(3), Cândido AL(2),Comim FV(2)

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OBJECTIVE: The modified Ferriman Gallwey (mFG) performed by a trained investigator has been considered the best method to identify hirsutism. Recent evidence from the literature has suggested other approaches to establish the diagnosis of excessive hair growth, such as the self-assessment of mFG. The aim of our study was to compare the performance of patient self-reported mFG versus clinician mFG in a PCOS outpatient clinic.

METHODS: Patients (n=48) were selected and answered a questionnaire providing sociodemographic, clinical, and anthropometric information. These women were also asked if they were bothered by excess hair. The score of nine areas of mFG was assessed by two blind trained investigators (Kappa index>90%). Descriptive statistics were used. The study (in progress) was approved by the Local Ethics Committee. For this research, we employ the new proposed cutoffs for mFG scale: >= 6 for South American women, as suggested by the Clinical Practice Guideline of the Endo Society (2018), or >= 4 accordingly with the work of Azziz et al. (2020).

RESULTS: Overall, participants' age and BMI were respectively (mean +- SEM) 30.7 +- 1.15 years and 33.5 +- 1.52 kg/m2. Patients that complained about excessive hair growth were 54%, and 37.1% reported alopecia. All women with more than one area of removed hair or submitted to hair discoloration, which may potentially affect the classification as hirsute (clinician mFG >= 4) or non-hirsute (clinician mFG < 4), were excluded from the group analysis. No differences in age, ethnic group, BMI, abdominal circumference, and menstrual cycles were observed between hirsute and non-hirsute women. Both groups complain similarly about increased hair growth (61.3% of hirsute against 52.94% of non-hirsute women). The mean +- SEM for the clinician mFG was 7.04 +- 0.79 in the hirsute women and 1.16 +- 0.27 in non-hirsute women ($p< 0.001$). The self-assessment of mFG show increased scores for both groups 16.3 +- 2.26 in Hirsute group versus 9.43 +- 1.61 in non-hirsute group ($p=0.027$). Despite the substantial difference between self-reported to clinician mFG scores mean (around 7.6 points), the correlation between these two mFG tools was 0.662. Similar results between these two groups were observed when the cutoff of mFG to establish hirsutism was >= 6.

CONCLUSIONS: Our partial results confirm previous reports of an overestimation of self-assessed mFG score in comparison to clinician mFG.

ID #33 Type: Clinical Science

TITLE: DISTINCT ANDROGEN AND IMMUNE PROFILES IN PREGNANT WOMEN OF HYPER- AND NORMOANDROGENIC PCOS PHENOTYPE

AUTHORS: Stokkeland LMT (1,2), Giskeødegård GF (3), Ryssdal M (1,2), Jarmund AH (1,2), Løvvik TS (1,4), Schmedes AV (5), Iversen AC (1,2), Vanky E (1,4).

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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), androstendione (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 pregestational 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 T and FTI at all measured times points in pregnancy (p-values < 0.05). Cytokine profiling revealed that HA-PCOS women show higher levels of fibroblast growth factor-basic (FGF-b), interleukin (IL)-2, IL-1β and IL-8 throughout pregnancy. Longitudinal cytokine profiling and androgen analyses are both equally able to separate women of HA- and NA-PCOS phenotype. When assessed by BMI classes, the difference in cytokine profile between HA- and NA-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. Serum cytokine profiling reveals novel differences between pregnant HA- and NA-PCOS women, and the lack of correlation to androgen levels may reflect distinct underlying processes contributing to the phenotype difference. Combined assessment of immunological changes and androgens therefore provide new and valuable knowledge and may lead to more targeted care in pregnancy for women with PCOS.

(Supported by NTNU, The Research Council of Norway and St. Olavs hospital).

ID #34 Type: Clinical Science

TITLE: PSYCHOLOGICAL INTERVENTIONS FOR DEPRESSION IN WOMEN WITH PCOS: SYSTEMATIC REVIEW AND META-ANALYSIS

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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(Ovid), Web of Science, Coachrane, 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 52 weeks and involved between 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 2.10) 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 sessions 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.

ID #35 Type: Clinical Science

TITLE: PREVALENCE OF POLYCYSTIC OVARY SYNDROME IN TYPE 1 DIABETES. A SYSTEMATIC REVIEW AND META-ANALYSIS.

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OBJECTIVE. An increased prevalence of functional hyperandrogenism – including 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-OVID and Embase databases (Open Science Framework registry for systematic review protocols https://osf.io/6cv9p/). Studies published up to March 29 2021 were considered. We selected cross-sectional or prospective studies that reported, in patients with T1D, prevalence data on PCOS according to current definitions and different phenotypes, and/or prevalence rates of other related traits [hirsutism, hyperandrogenaemia, oligo-amenorrhea, and/or polycystic ovarian morphology (PCOM)]. Two independent researchers performed study selection and data extraction. We used Stata 16 for statistical analyses.

RESULTS. We selected 18 studies (989 women) reporting the prevalence of PCOS and/or other hyperandrogenic traits. Regarding bias, 11 studies were considered of low-risk, and the remaining 7 studies were considered intermediate-risk. The pooled prevalence of PCOS when considering all possible phenotypes (ESHRE-ASRM criteria) in T1D was 26% (95% CI: 19–35%; 13 studies, 684 women). Pooled prevalence of classic PCOS (NIH criteria: hyperandrogenism and ovulatory dysfunction) was 16% (95% CI: 10–22%; 9 studies, 614 women). Pooled prevalence of hyperandrogenic PCOS (AE-PCOS criteria: hyperandrogenism plus ovulatory dysfunction and/or PCOM) was 27% (95% CI: 15–42%; 5 studies, 329 women). Hirsutism (24%), hyperandrogenaemia (30%), oligomenorrhea (23%), and PCOM (35%) were also highly prevalent in women with T1D. Heterogeneity was high in almost all these meta-analyses.

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

ID #36 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 murinometric and metabolic parameters (included an oral glucose tolerance test OGTT) and hormonal profiles analyzed by liquid chromatography-tandem mass spectrometry (LC-MS/MS).

RESULTS: Our results showed that PA-females presented with lower weaning weight, body mass index (BMI), and increased anogenital 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 estrone 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.

(Grants PI15/01686 and PIE16/00050 from ISCIII. IRYCIS & CIBERDEM).

ID #38 Type: Clinical Science

TITLE: EFFECTS OF METFORMIN ON FOLISTATIN AND OXYNTOMODULIN LEVELS IN PCOS

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Objective: Polycystic Ovary Syndrome (PCOS) is the most common endocrinopathy in women of reproductive age, with a prevalence of up to 15%. It is a complex disease with metabolic, reproductive and psychological changes. Metformin is an insulin-sensitizing hypoglycemic drug and is widely used in the treatment of PCOS. Oxyntomodulin is a polypeptide hormone in incretin family and causes weight loss in obese patients, lower food intake and increases energy expenditure. Follistatin is a glycoprotein hormone found in follicular fluid and ovaries that inhibits FSH secretion by neutralizing the action of activins and is increased in conditions of insulin resistance. The study performed was a secondary analysis, randomized double-blind clinical trial and aimed to evaluate the levels of follistatin and oxyntomodulin before and after the use of metformin (1500mg/day) for 60 days and possible relationships with comorbidities associated with the syndrome.

Methods: Forty-five patients with PCOS were recruited, divided into one group that received metformin (n=21) and one group who received placebo (n=24). Blood levels of oxyntomodulin and follistatin were evaluated by ELISA tests. At the end of the study, 20 patients were evaluated, 5 (25%) from the group using metformin and 15 (75%) from the placebo group.

Results: Women using metformin presented mean follistatin values 1.53 ± 0.21 (median 1.44) before treatment and 1.58 ± 0.19 (median 1.51) after treatment, while placebo group had mean values to 1.40 ± 0.13 (median 1.34) before treatment and 1.42 ± 0.13 (median 1.39) after treatment. Metformin group obtained mean values of oxyntomodulin to 23.72 ± 9.92 before treatment and 27.31 ± 9. after treatment. Placebo group had mean values of oxyntomodulin before and after treatment to 21.56 ± 7.28 (median 24.03) and 23.90 ± 11.99 (median 21.93). There was no significant difference in the variation in follistatin and oxyntomodulin levels between the metformin and placebo. There was a significant difference (p=0.004) in follistatin levels among participants with hyperandrogenic and non-hyperandrogenic phenotype. There was no significant difference in oxyntomodulin levels in different phenotypes.

Conclusions: Use of metformin for 60 days did not alter follistatin and oxyntomodulin levels; there was a significant difference between the follistatin values in hyperandrogenic and non-hyperandrogenic phenotypes.

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 phenotypical, 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 1991 and June 2021. Data was available on anthropometric measurements, ultrasound measurements and an endocrine assessment for each visit. Multilevel linear and logistic regression was applied for longitudinal analyses.

RESULTS: A total of 596 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 not having PCOS. Serum levels of testosterone, androstenedione, dehydroepiandrosterone sulfate, 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.

ID #41 Type: Clinical Science

TITLE: Altered bile acids are related to BAs synthesis route in lean PCOS: potential role of androgen

AUTHORS: Yuchen Zhu, Chang Shan, Yi Zhang, Jie Yu, Yushan Li, Jiarong Fu, Tao Tao

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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 serum bile acid profile had 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 steroid 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 serum bile acid profiles and assessed associations of bile acid including selected ratios with steroid metabolism and diagnosis, 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 chenodeoxycholic 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 depletion or downregulation of CYP8B1 and indicated the bile acid alternative pathway was activated, strongly negative associated with free androgen index (FAI).

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 exploring the potential pathophysiological mechanisms of bile acid metabolism in different phenotypes of polycystic ovary syndrome would be necessary.

FUNDING: This work was supported by the National Natural Science Foundation of China (8217030752); the Medical Guidance Science and Technology Support Projects of Shanghai Municipal Science and Technology Commission (18411968700); and the Natural Science Foundation of Shanghai (12ZR1417800).

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 reduce inflammation, inhibit androgen production, and regulate metabolic pathways. Here, we evaluated the therapeutic mechanism of hMSC through extracellular vesicles (EV), also known as exosome, 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 (Exosome) to androgen producing H293R cells, and analyzed androgen producing gene expression. For in vivo experiment, Exosome were injected directly into ovary of Letrozole (LTZ) induced mouse PCOS model. Exosome effect in androgen producing cells or PCOS model mice was assessed by analyzing steroidogenic gene expression (quantitative real-time polymerase chain reaction [qRT-PCR] and body weight change, serum hormone levels, and fertility by pup delivery

RESULTS: Exosome significantly reduced gene expression Cyp11a1 (0.75±0.03 fold), Cyp17a1 (0.58±0.04 fold), and Dennd1 (0.72±0.06 fold) in H293R cells. In our in vivo model, increased body weight in PCOS mice were significantly decreased after Exosome treatment. In addition, average size of adipocyte also decreased in Exosome treated (4426±2660 um2) mice compared to PCOS mice (9030±5797um2). Moreover, abnormal serum hormone levels in PCOS mice such as testosterone, FSH, and LH were reversed by Exosome 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 Exosome 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 (Exosome) 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 #43 Type: Clinical Science

TITLE: AMH, LH and FSH hormone levels through-out cycle phase in ovulatory and anovulatory women with PCOS

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OBJECTIVE: Hormonal imbalance is characteristic to polycystic ovary syndrome (PCOS). Here, we investigated AMH, LH and FSH serum levels in ovulatory and anovulatory women with PCOS and compared them to controls in different cycle phases. We also evaluated the association between AMH levels and clinical status.

METHODS: Participants were recruited in the Oulu University Hospital, Finland. Women in the PCOS group – divided into ovulatory (PCOS-OV, n=84) and anovulatory (PCOS-anOV, n=14) subgroups ¬ – -were selected by tracing their former PCOS diagnosis from the health records. The control group (Ctrl-OV, n=72) consisted of healthy volunteers. Participants underwent blood sampling and clinical examinations according to their menstrual cycle days (CD) measured by urine LH surge (CD 2-4, LH+2-3, LH+7-8, LH+10-11). 92 participants gave repeated samples over several cycles. Serum AMH, LH and FSH concentrations and metabolic parameters were measured.

Serum hormone levels were analyzed as log-transformed. The cycle phase differences were analyzed with linear mixed regression model. Correlations between AMH and ovarian parameters were estimated by linear regression models. For AMH cut-off values to predict PCOS, receiver operator curve (ROC) was generated.

RESULTS: As expected, serum AMH concentration was higher in PCOS compared to controls, being highest in PCOS-anOV. AMH did not have major fluctuation during menstrual cycle in ovulatory PCOS or control women. When comparing cycle phases separately, AMH levels were higher in women with PCOS in all phases except in LH+2–3 days. Also, LH levels were higher in women with PCOS, being significant in whole group analysis and when comparing anovulatory samples to control CD2–4 samples. Early cycle (CD2-4) FSH was significantly lower in PCOS compared to controls.

AMH and AFC and AMH and ovarian volume correlated positively in both groups, (p=0.018, p>0.05, respectively). AMH and endometrium thickness correlation was positive in control group, but negative among women with PCOS (p=0.001).

We visually evaluated repeatedly measured AMH levels and they remained stable withing individuals in 3-month timeline. Cut-off values for AMH were 3.64 ng/ml for women <age 36 years (sensitivity 0.83, specificity 0.70), and 1.38 ng/ml for women > 36 years (sensitivity 0.94, specificity 0.48).

CONCLUSIONS: Ovulatory women with PCOS have lower AMH values than anovulatory counterparts yet higher than in controls. High AMH persists stable in all cycle phases and at least for 3 consecutive cycles. When using AMH in clinical practice to estimate PCOS, different cut-offs should be used for women under and over 36 years.

Funding: Sigrid Juselius foundation, Orion Research Foundation, Laboratoriolääketieteen Edistämissäätiö

ID #44 Type: Translational Science

TITLE: DOES POLYCYSTIC OVARY SYNDROME (PCOS) AFFECT MALE GERMLINES TRANGENRATIONALLY?

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Objective: Our 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 Chilean 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 obese lineages, respectively, but with stronger phenotype in the obese lineage. Small non-coding RNAs (sncRNAs) sequencing of sperm from F1 and F3 male offspring revealed common differential expressed sncRNAs (DEsncRNAs) across generations in androgenized, obese, and obese and androgenized lineages, with distinct regulatory patterns among lineages. Three of the predicted targets of piRNA and miRNAs 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 germline changes by sncRNAs.

ID #45 Type: Basic Science

TITLE: INFLUENCE OF METFORMIN ON HYPERANDROGENISM IN WOMEN WITH PCOS: A META-ANALYSIS OF CLINICAL TRIALS

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OBJECTIVE: The excess of insulin observed in Polycystic Ovary Syndrome (PCOS) is directly related to the increased production of androgen hormones. Thus, the use of metformin to control hyperinsulinism could lead to a reduction of hyperandrogenism in these patients. The aim of this study was to evaluate the effects of metformin treatment on markers of hyperandrogenism 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 $p<0.05$ with 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: 3,694 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: -0.63 (95% CI: -1.18 to -0.09) points; $I2 = 86\%$; p-value for heterogeneity: <0.00001] were observed in both of 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).

ID #47 Type: Clinical Science

TITLE: ANDROGENIC STATUS DURING REPRODUCTIVE AGE AND CARDIOMETABOLIC PROFILE YEARS LATER IN WOMEN WITH PCOS

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OBJECTIVE: The prevalence of cardiovascular risk factors is increased in women with polycystic ovary syndrome (PCOS). It seems that women with hyperandrogenism are more prone to develop CVD. However, studies assessing PCOS characteristics during reproductive age in relation to cardiometabolic profile later in life are lacking. The aim of this study was to determine whether hyperandrogenism at time of PCOS diagnosis is associated with differences in cardiometabolic profile during post-reproductive years.

METHODS: We compared the cardiometabolic profile of 130 women with PCOS after the age of 45, with their endocrine profile (43 normoandrogenic and 87 hyperandrogenic), which was assessed during their reproductive years. Anthropometrics, insulin, glucose, lipid levels, prevalence of metabolic syndrome, type II diabetes, carotid intima media thickness (CIMT) and coronary artery calcification scores (CACs) were measured.

RESULTS: The median age during the follow-up assessment was 47.3 years in the normoandrogenic group and 47.1 years in the hyperandrogenic group (P=0.39). Hyperandrogenic women at time of PCOS diagnosis had a higher BMI (30.1 (IQR 26.1 - 34.9) versus 24.1 (IQR 22.0 - 29.0), P<0.01) and a higher waist/hip ratio (0.89 (IQR 0.84 - 0.93) versus 0.83 (IQR 0.79 - 0.90), P<0.05) at their follow-up visit. Also, they had a more unfavorable cardiometabolic profile, including a higher prevalence of hypertension (51.7% versus 18.6%, P<0.01) and metabolic syndrome (29.9% versus 9.3%, P<0.05). CIMT and CACs were not significantly different between the two groups. Both within the normoandrogenic and hyperandrogenic group, a BMI≥25 kg/m2 during initial screening was negatively associated with the cardiometabolic profile during follow-up, in particular with the prevalence of hypertension and metabolic syndrome. The presence of both hyperandrogenism as well as a BMI≥25 kg/m2 increased these negative associations even further.

CONCLUSIONS: Women with PCOS with hyperandrogenism or a BMI≥25 kg/m2 during reproductive age had the worst cardiometabolic profile during their post-reproductive years, with the most risk if both factors were present. It is important to know which women with PCOS during reproductive age are more prone to develop CVD later in life so they can be adequately monitored and screened lifelong.

ID #48 Type: Translational Science

TITLE: THE ROLE OF B CELLS IN IMMUNE CELL ACTIVATION IN POLYCYSTIC OVARY SYNDROME

AUTHORS: Angelo Ascani (1), Sara Torstensson (1), Sanjiv Risal (1), Haojiang Lu (1), Gustaw Eriksson (1), Congru Li (1), Katalin Sandor (1), Martin Helmut Stradner (2), Camilla I Svensson (1), Barbara Obermayer (2), Elisabet Stener-Victorin (1)

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OBJECTIVE: Age-associated double negative (DN) B memory cells are associated with higher disease activity in autoimmune diseases. We characterized B cell phenotypes in women with and without Polycystic Ovary Syndrome. Thereafter we transferred purified IgG extracted from serum of hyperandrogenic women with PCOS to mice to establish whether self-reactive B cells have a causal effect on the development of a PCOS-like profile in mice.

METHODS: First, we characterized B cell subsets in serum of hyperandrogenic women with PCOS and in women without PCOS (controls). Second, purified IgG from serum of women with PCOS or controls was intraperitoneally injected into wild type (WT) female mice. Reproductive function was tested by measuring anogenital distance and estrous cyclicity. Body weight was recorded so as EchoMRI for analyses of fat and lean mass, metabolic cages and oral glucose tolerance tests. Serum sex steroids were tested by liquid chromatography mass spectrometry. Flow cytometric analyses was performed on whole blood, spleen, lymph node, ovary, endometrium, visceral adipose tissue, omentum for main populations of immune cells.

RESULTS: Immunophenotypic analyses showed a significant remodeling of B cell repertoire in women with PCOS compared with controls. The frequency of DN B memory cells was higher in PCOS patients (P=0.002), with declined IgD+ B memory cells (P=0.01). Preliminary results from the transfer of human IgG into female WT mice showed an increase of DN B cells, particularly DN2 subset with CD21- phenotype, and higher frequencies of active naïve cells and neutrophils, notably in the ovaries in mice receiving IgG from women with PCOS and weigh more than control mice (P<0.05). No effect was seen on circulating sex steroids, anogenital distance or estrous cyclicity.

CONCLUSIONS: Women with PCOS display an increased peripheral expansion of DN B cells. Exposing mice with IgG from women with PCOS rapidly induced an altered immune cell profile and metabolic phenotype. The follow-up experiment with transfer of purified B cells from prepubertal hyperandrogenic mouse model into B cell deficient mice, will define the overall impact of androgen exposure on B cell phenotypes. These results indicate that PCOS may represent a state of inflammatory-cell hypersensitivity, persistent antigen stimulation and chronic inflammation, resulting in remodeling of the lymphocytes.

ID #49 Type: Translational Science

TITLE: RHESUS MACAQUE: MODEL FOR POLYCYSTIC OVARY SYNDROME & ENDOMETRIOSIS

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OBJECTIVE: Polycystic ovary syndrome (PCOS) and endometriosis (ENDO) cause pain, subfertility and metabolic dysfunction. ENDO increases the risk of certain ovarian cancer (EAOCs). Our nonhuman primate (NHP) model knocks down hypothalamic estrogen receptor alpha (ERα) in adult female rhesus macaques to investigate pathogenic mechanisms common to PCOS, ENDO and EAOC.

METHODS: The Wisconsin National Primate Research Center (WNPRC) maintains a rhesus colony with well-documented incidence of ENDO. ERα was knocked down in the hypothalamus (hypoERαKD) of a group of adult female monkeys. Monkeys were monitored 24-36 months for metabolic changes, menstrual patterns and endocrine outcomes. After necropsy, hemotoxylin & eosin (H&E) slides of uterus, cervix, fallopian tube, and ovary from formalin fixed paraffin embedded tissues were reviewed by human and veterinary pathologists. Slides underwent immunohistochemical staining (IHC) for PAX-8, Wilm's Tumor 1 (WT-1), ERα and progesterone receptor (PR).

RESULTS: Eleven female monkeys were evaluated, six hypoERαKD and five controls. Age at necropsy and characteristics associated with rhesus ENDO were comparable. HypoERαKD monkeys demonstrated 22% weight gain at 24 months compared to 12% gain in controls (control median weight 9.1 kg, hypoERαKD 10.4 kg, $p<0.05$). Menstrual cycles were comparable between groups, but mean luteal phase progesterone (control 3.6ng/mL; hypoERαKD 2.4ng/mL, $p=0.013$) and peak luteal progesterone (control 5.7ng/mL; hypoERαKD 3.6ng/mL, $p=0.004$) were diminished in hypoERαKD. Luteinizing hormone ($p<0.01$) and androstenedione ($p<0.01$) were increased in the follicular phase/anovulatory period of hypoERαKD. ENDO was present in 4/6 (67%) hypoERαKD and 1/5 (20%) controls. HypoERαKD expressed ENDO within the uterus (n=2), cervix (n=1), fallopian tube (n=2), ovary (n=2) and colon (n=1). One control exhibited ENDO in the uterus. WT-1 was expressed in epithelium and stroma of ENDO from both groups, ERα was only expressed in control ENDO, while PAX-8 was expressed as expected from human studies. One EAOC was identified in a hypoERαKD with ENDO.

CONCLUSION: Our NHP model increases ENDO penetrance and demonstrates PCOS-like characteristics. Rhesus and human ENDO and EAOC were comparable by gross and histologic examination. Results suggest diminished ERα activity in the neuroendocrine hypothalamus may predispose adult female NHP to ENDO and hyperandrogenic PCOS-like traits. (NIH R01 DK121559, NIH R25 GM083252)

ID #51 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, 2003 and December 31st, 2020, from 9 Mass General Brigham institutions with 1) a PCOS ICD-9/10 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 HA and OD but without 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 AE or OA between ages 25-34. Among the patients with a PCOS ICD code, there were 2065 who had additional codes for AE and OA. Among these 2065, the leading feature of AE was hirsutism (46.2%), followed by acne (38.7), and alopecia (15.9%). Among the 4636 lacking the PCOS code who met Rotterdam, the leading feature of AE was acne (68.4%), followed by alopecia (26.3%), and hirsutism (11.9%).

Conclusion: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.

ID #6 Type: Translational Science

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

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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 underrepresented in the literature. While early diagnosis is crucial in mitigating comorbidities, a robust literature points to lengthy diagnosis timeframes, 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 incivility, a form of interpersonal 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 control 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.

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 (57/79, 72%) over a decade ago (48/79, 61%) and enrolled obese/overweight women (57/77, 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, 65%) and allocation bias (49/79, 62%). Only 27 were registered prospectively (27/79, 34%). Two-thirds evaluated a dietary intervention (70/79, 88%), most commonly a hypocaloric diet (32/70, 46%); 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 LSI 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.