Abstract ID #55

Abstract Type:

Abstract Title: 3D MARKERS OF OVARIAN MORPHOLOGY OUTPERFORM 2D ULTRASONOGRAPHY AND ANTI-MÜLLERIAN HORMONE IN THE DIAGNOSIS OF PCOS

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ABSTRACT: OBJECTIVE: To contrast the diagnostic accuracy of 3D ultrasonographic markers of ovarian morphology to 2D ultrasonography and serum anti-Müllerian hormone (AMH) levels for detection of polycystic ovary syndrome (PCOS). Any gains in diagnostic accuracy when combining ovarian markers was also explored.

METHODS: 30 women with PCOS based on the National Institutes of Health (NIH) criteria and 30 age- and body mass index (BMI)-matched controls were evaluated. Transvaginal ultrasound scans (GE Voluson E or S Series; 5-12 MHz) and blood draws were conducted during the early follicular phase for women with regular cycles or at a random time for women with irregular cycles. Ovarian images were analyzed for the number of 2-9mm antral follicles in the entire ovary (FNPO), number of 2-5mm antral follicles (FNPO2-5mm) and 6-9mm antral follicles (FNPO6-9mm), and ovarian volume (OV) using 3D and 2D ultrasonography. 3D versus 2D ovarian markers were compared using Bland-Altman agreement statistics for matched-pair analysis. Diagnostic accuracy of ovarian markers for PCOS was determined by Receiver Operating Characteristic (ROC) curve analysis. Stepwise logistic regression analysis determined if combinations of ultrasonographic markers or AMH yielded greater diagnostic potential than single parameters.

RESULTS: 3D measurements of FNPO, FNPO2-5mm, and OV had greater diagnostic accuracy for PCOS compared to their 2D counterparts. The most accurate markers for PCOS were 3D FNPO (AUC=0.938) and 3D FNPO2-5mm (AUC=0.933), followed by 2D FNPO (AUC=0.922) and 2D FNPO2-5mm (AUC=0.906). Despite overall agreement between 3D and 2D FNPO measures, 3D ultrasonography overcounted FNPO2-5mm (2.00 ± 3.68, P=0.006) and undercounted FNPO6-9mm (-3.00 ± 3.49, P<0.001) in women with PCOS. AMH (AUC=0.898) had greater diagnostic accuracy than 3D and 2D OV (AUC=0.854 and 0.849, respectively), but remained inferior to both 3D and 2D follicle counts. The addition of OV or AMH did not improve diagnostic accuracy for follicle counts. However, the addition of AMH did substantially improve the diagnostic accuracy of 3D OV (AUC=0.918) and 2D OV (AUC=0.911).

CONCLUSIONS: 3D ultrasonographic markers of ovarian morphology outperformed 2D markers in the diagnosis of PCOS, with 3D markers of follicle excess being the most accurate measure overall. AMH had inferior diagnostic accuracy compared to FNPO across both modalities but was superior to OV. Addition of AMH improved the predictive power of OV on 2D and 3D ultrasonography thereby offering a robust alternative when image quality prevents an accurate assessment of follicle counts.

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Abstract ID #56

Abstract Type: Translational Science

Abstract Title: IDENTIFICATION OF NOVEL PCOS-RISK ALLELES BY LARGE-SCALE GENOME WIDE META-ANALYSIS PROVIDES NEW INSIGHTS INTO BIOLOGICAL MECHANISMS AND CLINICAL HEALTH OUTCOMES

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ABSTRACT: OBJECTIVE: To perform the largest genome-wide association study (GWAS) meta-analysis in women with polycystic ovary syndrome (PCOS) to identify novel genetic associations, biological pathways involved in the etiology, and to understand the clinical implications of genes involved in PCOS.

METHODS: A large fixed-effect, inverse-variance weighted meta-analysis was performed in 11,653 PCOS cases and 423,614 controls from 13 cohorts of European (86.5%), Hispanic (1.3%), African American (2.2%) and East Asian (10%). We performed an all ancestries combined and European only meta-analysis, using age-adjusted and age- and BMI-adjusted models. These results were then combined with previously published European GWAS meta-analysis summary data reaching a total of 21,570 PCOS cases and 523,971 controls. Secondary analysis included annotation of the identified variants and Summary-data-based Mendelian Randomization (SMR) in relevant tissues to link PCOS risk-alleles to genes of interest. Furthermore, potential associations between identified loci and other metabolic and endocrine phenotypes within PCOS were explored through additional polygenic risk score (PRS) analysis and MR-based analysis were performed to study the links between PCOS and other traits of interest.

RESULTS: In total, 19 loci were identified in the European meta-analysis, of which 7 loci were novel, and 12 loci replicated previously reported risk-alleles. The newly identified variants included for the first time the FTO gene, supporting the reported association between PCOS and BMI. No heterogeneity was observed between the different diagnostic criteria. Using SMR analysis we identified several potential effector genes acting through PCOS-relevant tissues, including the NEIL2 gene located at 8p23.1. Similar to the previous GWAS even more risk alleles could be linked to genes known play a role in reproductive hormonal pathways, including FSHβ, SHBG, INHBB and TEX41. Interestingly, several identified variants are in or near genes that play a role in DNA-repair mechanisms, such as NEIL2, MSH6, CHEK2 and RAD50, implicating the importance of these pathways in the pathophysiology of PCOS. Annotation of the identified PCOS loci with the publicly available GWAS results showed multiple associations with age at menopause, which was confirmed by additional post-GWAS analyses showing a causal association between PCOS and later age at menopause. Also, other PRS associated traits demonstrated an impact of PCOS-risk alleles on cardiovascular, metabolic and mental health outcomes in both men and women.

CONCLUSIONS: The current study identified novel PCOS-risk alleles, providing new insights into biological mechanisms involved in PCOS etiology. Moreover, the data provides evidence for links between PCOS-risk alleles and clinical as well as mental health outcomes in both men and women, emphasizing the broad impact of PCOS.

Abstract ID #57

Abstract Type: Clinical Science

Abstract Title: THE PREVALENCE OF THYROID DYSORDERS AND HYPERPROLACTINEMIA IN WOMEN WITH PCOS COMPARED TO CONTROLS

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ABSTRACT: OBJECTIVE: Ovulatory dysfunction is usually caused by an endocrine disorder, of which polycystic ovary syndrome (PCOS) is the most common cause. PCOS is associated with normal estrogen levels and can be characterized by oligo-/anovulation resulting in decreased progesterone levels. It is suggested that decreased progesterone levels may lead to more autoimmune diseases in women with PCOS. In addition to PCOS, hyperprolactinemia (HPRL) is also a common endocrine disorder in women of reproductive age and it is often claimed that there is an association between HPRL and PCOS. The aims of this study are to determine whether women with PCOS have 1) a higher prevalence of thyroid dysfunction, 2) an increase of anti-thyroid peroxidase antibodies (TPOab), and 3) a higher prevalence of hyperprolactinemia compared to controls.

METHODS: This retrospective cross-sectional study contains data of 1432 women with PCOS, who were diagnosed at a tertiary hospital (between 1993-2000), and 299 women without PCOS who conceived spontaneously and participated in a study between 2004-2007, of which 168 women gave birth to a child with a congenital heart disease and 131 women gave birth to a healthy child.

RESULTS: The median age of women with PCOS was 28.2 years [interquartile range (IQR) 24.6 - 31.7] and 32.8 years [IQR 29.7 - 35.8] of the controls ($p<0.01$). Median BMI of women with PCOS was higher compared to the controls (25.2 kg/m2 [IQR 21.9 - 30.8] versus 24.4 kg/m2 [IQR 22.3 - 17.5]; $p<0.01$). The prevalence of thyroid diseases in PCOS women was similar compared to controls (1.9% versus 2.7%; $p=0.39$ for hypothyroidism, 3.2% versus 2.7%; $p=0.59$ for subclinical hypothyroidism, and 0.5% versus 0%; $p=0.99$ for hyperthyroidism). TSH levels and the prevalence of positive TPOab were the same in both groups (1.55 mIU/L versus 1.48 mIU/L; $p=0.54$ and 5.7% versus 8.7%; $p=0.12$). FT4 levels were higher in women with PCOS (18.1 pmol/L versus 17.7 pmol/L; $p<0.05$). The prevalence of HPRL was higher in PCOS patients (7.0% versus 3%; $p<0.05$) and in this group 0.5% had a pituitary abnormality, such as macroprolactinomas. All these results were adjusted for age and BMI.

CONCLUSIONS: The prevalence of thyroid diseases is not increased in women with PCOS. Although FT4 levels were significantly higher, they were well within the normal range. Hence, this finding is probably without any clinical relevance. Moreover, there was no difference in the prevalence of positive TPOab, indicating a similar risk for thyroid disease in women with PCOS versus controls. Although HPRL was more prevalent in PCOS patients this might be due to selection bias, because patients with HPRL are less likely to conceive spontaneously compared to our controls. However, as recommended in the guideline, thyroid diseases and HPRL should be excluded in women with symptoms of ovulatory dysfunction.

(No funding to declare.)

Abstract ID #58

Abstract Type: Clinical Science

Abstract Title: THE EXPERIENCE OF LIVING WITH POLYCYSTIC OVARY SYNDROME IN THE MILITARY

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ABSTRACT: OBJECTIVE: Polycystic ovary syndrome (PCOS) is the most prevalent reproductive endocrinopathy in women. PCOS symptoms and complications place a significant burden on servicewomen, negatively influencing their health, and hindering military operational and worldwide readiness. Common manifestations of PCOS include central adiposity, abnormal menstrual cycles, pelvic pain, increased facial and body hair, acne, and infertility. Despite Congressional recognition of the seriousness of PCOS, research in military PCOS populations is limited. Furthermore, current military policies do not address specific healthcare needs and challenges experienced by women with PCOS. Our purpose was to explore and describe servicewomen's experience of living with PCOS.

METHODS: Qualitative descriptive design using focus groups and individual interviews. Women with PCOS were recruited from three military locations. Data were analyzed using constant comparative content analysis with Nvivo12.

RESULTS: Air Force, Army, Navy, and Marine Corps women (N = 23) from 20 different occupational specialties participated. Three major themes emerged: (1) PCOS symptoms: PCOS was all-consuming, impacting every aspect of their lives, (2) Navigating the military healthcare system: challenges and facilitators within the military healthcare system, and (3) navigating PCOS as a servicemember: how the military environment including policies and work environment influenced their experience with PCOS. Thirteen sub-themes revealed challenges with accurate, timely diagnosis, access, trust, and continuity of healthcare, self-esteem and body image issues, and workplace harassment resulting in mental stress, due to symptoms such as facial hair, acne, painful, unpredictable menstrual cycles, and weight. A determination to "push through" to complete their unit mission was also identified.

CONCLUSIONS: Servicewomen living with PCOS have similar experiences regardless of duty title or service branch. Unlike their civilian counterparts, servicewomen face significant career-limiting consequences. The time to diagnosis (months to years) and managing onerous symptoms negatively influence health and unit cohesiveness, degrading mission readiness. Future studies are needed to further elucidate military-specific challenges and resilience-promoting factors experienced by these women. Research is also needed to facilitate development of evidence-based policies and identify effective strategies that support the health and readiness of these servicewomen and inform future healthcare policy and programs.

(Tri-Service Nursing Research Program: N18-B05)

Abstract ID #59

Abstract Type: Translational Science

Abstract Title: SERUM METABOLOMICS PROFILE AFTER ORAL MACRONUTRIENT CHALLENGES: INFLUENCE OF OBESITY AND POLYCYSTIC OVARY SYNDROME

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ABSTRACT: OBJECTIVE: Metabolomics is a powerful tool to characterize organism phenotypes and can facilitate the identification of altered metabolites and molecular pathways in pathophysiological states. Metabolites are small intermediates or end products of cellular metabolism which reflect the response to endogenous and exogenous factors. In this regard, sex hormones and obesity are important modulators of whole-body metabolism, and obese individuals and women with polycystic ovary syndrome (PCOS) present with metabolic alterations that may also manifest in the postprandial period. Hence, we investigated the effect of obesity and sex hormones on the serum metabolomics profile after single macronutrient challenges in a series of young adults.

METHODS: Seventeen non-hyperandrogenic control women, 19 women with PCOS, and 19 healthy men —equally distributed in obese and non-obese subgroups— were submitted to isocaloric oral glucose, lipid, and protein loads. Serum samples were obtained at baseline, 1h and 2h after glucose and protein ingestion, or at 2h and 4h in the lipid challenge. Thirty-five low-molecular-weight polar metabolites were determined by 1H-NMR. Postprandial net changes were expressed as areas under the curve (AUC). The influence of macronutrient, group (women, PCOS, men), obesity, and their interactions on each metabolite were evaluated by univariate GLM for repeated measures analysis.

RESULTS: Twelve metabolites (glycine, alanine, proline, threonine, serine, asparagine, glutamine, glutamic acid, ornithine, isobutyric acid, citrate, and glycerol) showed different AUCs among macronutrient loads, although neither obesity nor sex hormones exerted any influence. In contrast, the AUCs of 3-hydroxybutyric and pyroglutamic acids were lower in men compared with either control or PCOS women. Remarkably, we observed numerous interactions between group, and/or obesity, and/or macronutrient for several molecules, indicating that the effect of obesity was different (or even the opposite) in control and PCOS women compared with men, and depending on the type of macronutrient. These metabolites included, among others, branched-chain and aromatic amino acids, lysine, methylhystidine, beta-glucose, and acetone. Furthermore, patients with PCOS exhibited a specific and unique response —different from that of women and men— for pyruvate, tryptophan, creatine, and betaine. Finally, five metabolites (2-oxoisovaleric acid, creatinine, carnitine, acetate, and choline) showed no differences among the distinct macronutrient challenges and no effect of obesity, sex, or PCOS.

CONCLUSION: Altered postprandial metabolomic profiles in women with PCOS point to worse metabolic flexibility that is exacerbated by obesity.

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Abstract ID #62

Abstract Type: Clinical Science

Abstract Title: DO ALLOSTATIC LOAD AND METABOLIC SYNDROME CONTRIBUTE TO MENTAL HEALTH OUTCOMES IN WOMEN WITH POLYCYSTIC OVARY SYNDROME?

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ABSTRACT: OBJECTIVE: Polycystic ovary syndrome (PCOS), is associated with reduced health-related quality of life (QOL) and increased risk for depression and anxiety. These associations are partly due to the stressful and stigmatizing nature of PCOS symptoms, including hirsutism and negative body image stemming from BMI. However, the impact of the cumulative wear and tear in the stress response system (i.e. allostatic load (AL)), and of metabolic syndrome on these QOL outcomes is unknown. We assessed how AL and metabolic syndrome relate to physical and mental health related QOL in women with PCOS.

METHODS: We performed a secondary analysis of baseline data from a randomized control trial (OWL-PCOS) in women with PCOS defined by Rotterdam criteria. Physical and mental health related QOL were assessed by the SF36 and PCOSQ. AL was calculated using the 12 factors: IGF-1, HDL, LDL, triglycerides, fasting glucose, fasting insulin, creatinine, systolic blood pressure, diastolic blood pressure, heart rate, waist-to-hip ratio, and BMI. High risk categories were calculated as the 75th percentile for all factors except for HDL in which the 25th percentile was used. An AL index was calculated for each participant as the sum of the number of factors in the risk category (0-12), with higher scores indicating more physiological dysregulation in the stress response system. We defined a high level of AL as an ALI of ⍰4, based on convention. Metabolic syndrome was classified as meeting 3 of 5 NIH criteria. Wilcoxon rank sum tests were used to assess differences in QOL measures between high vs low AL, and with vs without metabolic syndrome. All analyses were performed in RStudio version 2022.07.1.

RESULTS: Among 90 women with PCOS, the mean age was 29 years old, the majority of which were White (84%), non-Hispanic (93%), nulliparous (83%) and not on any medications for depression (97%) or anxiety (98%). Thirty-six women had high AL and 27 women had metabolic syndrome. Women with high AL, had significantly higher summary scores on the SF36 Mental Component ($p = 0.012$) and lower scores on the SF36 Physical Component ($p = 0.001$), indicating higher mental health QOL and lower physical health QOL. On the PCOSQ, women with high AL had higher Emotional Wellbeing scores ($p = 0.013$), but no differences in Physical Wellbeing and General Wellbeing scores. Women with metabolic syndrome had lower SF36 Physical Component summary scores ($p=0.039$), indicating lower physical health related QOL.

CONCLUSION: These findings suggest that among the constellation of symptoms experienced by women with PCOS, AL and metabolic syndrome are not primary drivers of adverse mental health outcomes in this population.

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Abstract ID #63

Abstract Type: Clinical Science

Abstract Title: DEPRESSION, ANXIETY & FATIGUE AMONG BLACK WOMEN WITH PCOS WITH AND WITHOUT HYPERTENSION

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ABSTRACT: OBJECTIVE: Polycystic ovary syndrome (PCOS) is associated with increased risk for depression and anxiety, partly driven by BMI, hirsutism, and genetic factors. Although PCOS increases the odds of hypertension (HTN) by 1.5, the co-occurrence of PCOS + HTN in relation to symptoms of depression and anxiety is not well understood. Furthermore, few studies focus solely on these symptoms in Black women with PCOS. Here, we examine the impact of HTN on depression, anxiety, and fatigue symptoms in Black women with PCOS.

METHODS: We preformed preliminary data analysis of a single cohort study of symptoms in adult Black women with PCOS or with PCOS + HTN. Both diagnoses were obtained from medical records. Depressive symptoms were measured by the PROMIS Depression short-form and the CESD-10. Anxiety was measured by the PROMIS Anxiety short-form and the state scale of the State-Trait Anxiety Inventory (STAI). Fatigue was measured by the PROMIS Fatigue short-form and the Multidimensional Fatigue Inventory (MFI). Wilcoxon rank sum tests were used to assess differences in symptoms between PCOS vs PCOS + HTN. All analyses were performed in RStudio version 2022.07.1.

RESULTS: Among 32 Black women with PCOS, the mean age was 34.7 years old, and the mean BMI was 39.8. Nine of the 32 women had PCOS + HTN. Women with PCOS + HTN demonstrated higher fatigue on the MFI ($p = 0.015$), more severe depression on the PROMIS Depression ($p = 0.039$) and CESD-10 ($p = 0.046$), and more severe anxiety symptoms on the STAI ($p = 0.007$). For those with PCOS + HTN, mean scores exceed cut points for clinical depression on the CESD-10 and clinical anxiety on the STAI. Women with PCOS + HTN also demonstrated a trend for higher fatigue on the PROMIS Fatigue as well as higher anxiety on the PROMIS Anxiety.

CONCLUSION: Our findings highlight that the co-occurrence of HTN and PCOS in Black women may contribute to the severity of depression, anxiety, and fatigue symptoms. Our study also points toward the need to better understand the symptom experience of minority groups with PCOS, including racial, ethnic, sex, and gender.

(Funding: 1P30NR-18090 [Pilot PI: LN])

Abstract ID #64

Abstract Type: Clinical Science

Abstract Title: INCREASED RISK OF DIABETES ACROSS THE REPRODUCTIVE AGE RANGE IN WOMEN WITH PCOS: A TERRITORY-WIDE RETROSPECTIVE ANALYSIS FROM THE HONG KONG DIABETES SURVEILLANCE DATABASE

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ABSTRACT: OBJECTIVE: Polycystic Ovary Syndrome (PCOS) is associated with insulin resistance, hyperandrogenism, and dyslipidemia, but the progression of type 2 diabetes mellitus in Chinese women with PCOS have only been investigated in clinic-based study population. Therefore, a population-based longitudinal study can help establish the overall risk of diabetes progression in Chinese women with PCOS.

METHODS: This territory-wide, retrospective cohort study evaluated data extracted from the Hong Kong Diabetes Surveillance Database (HKDSD) between year 2000 and 2019. The subjects were women with PCOS (n=3978) identified based on the ICD-9 code for PCOS diagnosis, whilst women without PCOS served as controls (n=39780). Women with PCOS were age-matched at a ratio of 1:10 to a set of non-PCOS controls. Primary outcome was the first record of incident diabetes. Crude rates for diabetes were presented, and time to diabetes was analyzed using Cox proportional hazard models.

RESULTS: The mean follow-up was 6.3 ± 4.2 and 7.0 ± 4.3 years in women with PCOS (baseline mean age: 28.53 ± 7.39 years old) and controls (baseline mean age: 28.93 ± 7.62 years old), respectively. In the cohort of women with PCOS, the crude incidence rate of diabetes was 21.48 per 1000 person-years (95% CI 19.56 -23.40) compared with 3.51 (95% CI 3.29-3.73) in the control cohort. The crude hazard ratio for the development of diabetes in Chinese women with PCOS was 6.25 (95% CI: 5.60-6.98, $p<0.001$). All participants were further stratified by age groups (≤19, 20-29, 30-39 and ≥40 years old). The incidence rate of diabetes was significantly higher in women diagnosed with PCOS than that of the age-matched control cohort, especially if PCOS was diagnosed at a younger age. Although the excess risk of developing diabetes decreased with increasing age at diagnosis, it remained significantly higher in women with PCOS across all age groups. Nevertheless, diabetes was diagnosed on average 5 years earlier in women with PCOS compared to control counterpart (mean onset of diabetes in PCOS: 34.65 ± 8.13 vs control: 39.61 ± 9.38, $p<0.001$).

CONCLUSIONS: The risk of developing diabetes is markedly increased in Chinese women with PCOS compared with women without PCOS. Women diagnosed with PCOS at a younger age have the highest relative risk of developing diabetes when compared to non-PCOS women, suggesting regular glycaemic status screening might be required in order to detect diabetes at an early stage.

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Abstract ID #65

Abstract Type: Clinical Science

Abstract Title: REPRODUCTIVE FEATURES CAPTURED WITHIN THE FIRST GYNECOLOGICAL YEAR PREDICT PERSISTENT MENSTRUAL IRREGULARITY AT TWO YEARS POST-MENARCHE

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ABSTRACT: Introduction: Assessment of ovarian features are discouraged in the diagnosis of PCOS in adolescence owing to a lack of normative data and historically poor image quality via transabdominal ultrasonography. However, we have recently shown that ovarian morphology is adequately resolved via transabdominal ultrasound in adolescents and that follicle number and ovarian size reflect circulating AMH within the first gynecological year. Whether ovarian features at this early gynecological stage predict menstrual cycle status at two-years post-menarche (2YR-PM) is unknown.

Objective: To determine whether ovarian features assessed at 6-10 months post-menarche (PM) predict menstrual cycle status at 2YR-PM.

Methods: Menstrual records of 19 adolescent females who were evaluated at 6-10 months PM were collected as a part of a prospective cohort study. Menstrual cycle status was determined at 2YR-PM as regular (three previous inter-menstrual intervals within 21-45 days) or irregular (at least one of the three previous inter-menstrual intervals <21 or >45 days). At 6-10 months PM, participants underwent a fasting blood draw, anthropometry, bioimpedance, and a transabdominal ultrasound of the ovaries. Differences in reproductive and metabolic features at 6-10 months PM were contrasted in those who were regular versus irregular at 2YR-PM via Mann-Whitney U-Tests. Whether reproductive features assessed at 6-10 months PM predicted menstrual cycle status at 2YR-PM was determined via logistic regression analyses.

Results: At 2YR-PM, 6/19 adolescents met the criteria for regular menstrual cycles and 13/19 met the criteria for irregular menstrual cycles. There were no differences in the metabolic profile nor in clinical or biochemical measures of androgens status at 6-10 months PM between those who ultimately achieved regular vs irregular menstrual cycles ($P>0.05$). However, adolescents with irregular menstrual cycles at 2YR-PM had higher LH concentrations (4.8 [3.5-5.5] vs 3.0 [2.4-3.8] mIU/mL; $P=0.025$), AMH (5.6 [5.1-7.3] vs 3.0 [1.6-4.5] ng/mL, $P=0.023$), and tended to have higher numbers of antral follicles 2-5mm in diameter (FNPO 2-5mm) (19 [14-25] vs 10 [7-16], $P=0.06$) at 6-10 months PM. The likelihood of regular menstrual cycles at 2YR-PM decreased with higher AMH (Odds Ratio 0.49 [0.24-0.98], $P=0.01$), LH (OR: 0.33 [0.13-1.09], $P=0.019$) and tended to decrease with greater FNPO 2-5mm (OR: 0.89 [0.76-1.03], $P=0.05$) at 6-10 months PM.

Conclusion: Ovarian features and serum LH may serve as early, clinically feasible biomarkers of future persistent menstrual irregularity with defective folliculogenesis preceding metabolic and androgenic derangements in the timeline to aberrant reproductive maturation. Whether adolescents with persistent menstrual irregularity meet criteria for PCOS will be determined upon conclusion of the cohort study.

[NIH: R21-HD095372; CIHR: Postdoctoral Fellowship #171268]

Abstract ID #66

Abstract Type: Clinical Science

Abstract Title: PCOS DIAGNOSIS AND DIFFERENT PHENOTYPES IN A LARGE POPULATION-BASED DATASET: THE USABILITY OF SERUM AMH AS A SURROGATE FOR PCOM

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ABSTRACT: OBJECTIVES: Serum anti-Müllerian hormone (AMH) levels correlate with the ovarian antral follicle count and thus could be used in the identification of polycystic ovarian morphology (PCOM). The main aim of the study was to investigate different cut-offs for serum AMH levels in polycystic ovary syndrome (PCOS) characterization in a large population-based study setting.

METHODS: A longitudinal population-based birth cohort study including 5889 females born in 1966. AMH concentrations were measured from all available serum samples taken at age 31 years (n=2917) using the electrochemiluminescence immunoassay (Elecsys®). By using different concentration cut-offs, the AMH data was then combined with questionnaire data on oligo-amenorrhea and hirsutism as well as biological measurement of hyperandrogenism at age 31 years to identify women with PCOS.

RESULTS: The addition of AMH as a surrogate marker for PCOM increased the number of women fulfilling at least two PCOS features in accordance with the Rotterdam criteria. The prevalence of PCOS increased from 5.2% to 5.9% when using the highest AMH cut-off, based on the 97.5% quartile (10.35 ng/ml), and to 13.6% when using the recently proposed cut-off of 3.2 ng/ml. When using the latter cut-off value, the distribution of PCOS phenotypes A, B, C and D were 23.9%, 4.7%, 36.6% and 34.8%, respectively. The prevalence of PCOS was 16.9% if the self-reported history of PCOS diagnosis by age 46 was also included. Compared with the controls, all PCOS groups with different AMH concentration cut-offs showed significantly elevated T, FAI, luteinising hormone (LH), LH/follicle stimulation hormone-ratio, body mass index, waist circumference and homeostatic model assessment of insulin resistance values, as well as significantly decreased SHBG values.

CONCLUSIONS: Our results support the use of AMH as a surrogate for PCOM in large populations where transvaginal ultrasound is not feasible and paves way for facilitated PCOS diagnostics in healthcare. AMH measurement from archived samples also enables retrospective PCOS diagnosis when combined with gynaecological history.

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Abstract ID #67

Abstract Type: Clinical Science

Abstract Title: COMPARING ROTTERDAM AND NIH CRITERIA: WOMEN WITH PCOS HAVE INCREASED RISK FOR CARDIOVASCULAR DISEASES REGARDLESS OF DIAGNOSTIC CRITERIA USED

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ABSTRACT: OBJECTIVES: Polycystic ovary syndrome (PCOS) is associated with many cardiovascular disease (CVD) risk factors. However, it has remained debatable, whether the presence of multiple CVD risk factors translates to increased number of CVD events. The purpose was to study whether PCOS increases the risk of CVD events regardless of the diagnostic criteria of PCOS.

METHODS: A prospective, longitudinal, population-based cohort, which has been followed since the birth in 1966. Women were classified as having PCOS either according to NIH criteria (n=149) or Rotterdam criteria (n=395) at the age of 31. The study population was re-examined at age 46. The register data linkage for major adverse cardiovascular events (MACE) including angina pectoris (AP), myocardial infarction (MI), stroke, heart failure, and cardiovascular mortality was followed up to age 53.

RESULTS: During the 22-year follow-up both women with NIH-PCOS and Rotterdam-PCOS had a significantly higher risk for cardiovascular events compared to controls. The BMI-adjusted hazard ratio (HR) for the MACE in Rotterdam-PCOS group was 2.74 (1.61–4.67) and 3.24 (1.71–6.14) in NIH-PCOS group. The Cum Hazard curves began to diverge already at the age of 35 years and the number of new CVD events dramatically increased at age 53. As regards of the individual CVD endpoints, when compared to controls, AP and MI were significantly more prevalent in both women with NIH-PCOS (AP: 3.9% [n=5/129] versus 0.7% [n=13/1781], p=0.005 and MI: 4.1% [n=6/147] versus 0.8% [n=16/2051], p=0.002) and Rotterdam-PCOS (AP: 2.8% [n=10/355] versus 0.7% [n=9/1277], p=0.003 and MI: 2.3% [n=9/390] versus 0.7% [n=10/1518], p=0.007).

CONCLUSIONS: According to our population-based data, PCOS should be considered as a significant risk factor for cardiovascular diseases. Future follow-up will show how the risk of CVD events develops during the postmenopausal years.

(This study was funded by the Academy of Finland (315921, 321763, Profi6 336449), Sigrid Juselius Foundation, the Medical Research Center Oulu, the Novo Nordisk Foundation and Roche Diagnostics International Ltd. The NFBC1966 31-year follow-up received financial support from the University of Oulu Grant no. 65354, Oulu University Hospital Grant no. 2/97, 8/97, Ministry of Health and Social Affairs Grant no. 23/251/97, 160/97, 190/97, National Institute for Health and Welfare, Helsinki Grant no. 54121 and Regional Institute of Occupational Health, Oulu, Finland Grant no. 50621, 54231. The NFBC1966 46-year follow-up received financial support from University of Oulu Grant no. 24000692, Oulu University Hospital Grant no. 24301140 and European Regional Development Fund (ERDF) Grant no. 539/2010 A31592. The data generation, curation and manpower were also supported by the EU H2020 grants).

Abstract ID #68

Abstract Type: Clinical Science

Abstract Title: ANTI-MULLERIAN HORMONE (AMH) BASED PHENOTYPING OF PCOS WOMEN

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ABSTRACT: OBJECTIVE: The original description of PCOS was based on the cystic morphology of the ovaries. Serum Anti Mullerian Hormone (AMH) concentration reflects follicular reserve of the ovaries and high AMH concentrations correlate with PCO morphology. The presence of three different definitions and four different phenotypes of PCOS indicates heterogeneity of the syndrome. Our goal was to examine if phenotyping based on serum AMH can help to understand the mechanisms underlying the clinical heterogeneity.

METHODS:

Subjects: The EPIC EMR was used to retrospectively review the charts of 123 patients who were referred to the PCOS clinic at the UC Davis Medical Center. Patients who did not meet the Rotterdam Criteria for PCOS, who were on were on hormonal contraception, or diagnosed with a different pathology (i.e. congenital adrenal hyperplasia, pituitary tumor, premature ovarian failure) were excluded. The remaining 92 patients were included in the final analysis. Variables: Anthropometric data (age, BMI), sex/adrenal steroids (testosterone, SHBG, bio-available-T, free-T, DHEA-S,17OHP), pituitary hormones (LH, FSH, prolactin) and metabolic (HgA1C, total-cholesterol, HDL-C, LDL-C and triglyceride) were collected.

RESULTS:

The distribution for AMH was skewed to right and therefore a rank-based quartile classification was used. AMH concentrations (ng/mL) in these quartiles were: 1st: 2.4±1.3 (n = 31); 2nd: 5.2±0.6 (n = 14); 3rd: 7.8±0.9 (n = 24) and 4th: 18.9±10.7 (n = 23). Age did not differ among groups. The following variables differed significantly ($p < 0.05$) in the highest AMH group (4th) when compared with the other quartiles (1st, 2nd, or 3rd) using non-parametric pairwise tests: BMI: Highest AMH group was thinner (BMI:27.1±5.9) vs. (range:28.9±6.2 to 30.5±6.5); had higher testosterone (ng/dL): (52.6±27.8) vs (29.6±13.4 to 34.9±17.7); had higher free-testosterone (ng/dL): (8.0±6.8) vs. (4.9±±2.7 to 5.4±3.0); had higher 17OHP (ng/dL): (86.7±58.8) vs. (36.8±22.2 to 46.2±39.2); had higher HDL-C (mg/dL): (56.7±13.6) vs. (44.4±5.8 to 46.4±8.7).

CONCLUSIONS:

The phenotyping based on serum AMH concentrations demonstrated that the PCOS women with highest serum AMH differ from the rest: They are thinner and have higher androgen levels. They appear to have more favorable metabolic profiles. AMH-based phenotyping may help to understand the differences between various clinical presentations of PCOS, and potentially guide the treatment approaches.

Abstract ID #69

Abstract Type: Clinical Science

Abstract Title: SEXUAL DIMORPHISM IN CARDIOMETABOLIC RISK IN OFFSPRING OF MOTHERS WITH PCOS

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ABSTRACT: OBJECTIVE: PCOS is a common condition with endocrine-metabolic dysfunction, and is highly heritable. Yet, there is limited research on how offspring are affected, and the age of onset, if any. We established a cohort of women with PCOS and matched controls along with their offspring to evaluate the effects of maternal PCOS on the offspring, as well as any differential impact between boys and girls.

METHODS: Among Chinese women from our PCOS registry (diagnosed based on the 2003 Rotterdam diagnostic criteria), we invited those who have children to participate in a follow-up study, and evaluated both the mothers and their sons (PCOSs) and daughters (PCOSd). For controls, we recruited women from the Hyperglycaemia and Adverse Pregnancy Outcome (HAPO) Study, who did not have PCOS or GDM, together with their sons (Cs) and daughters (Cd), for comparison. All offspring aged 15-25 years were included in the current analysis, and all have undergone a detailed assessment with questionnaire, anthropometric assessment, a standardized 75g OGTT for glycemic status evaluation and biochemical tests. Difference between groups were evaluated using independent sample t-test or Mann-Whitney U test for continuous variables, while Chi-square (X2) or Fisher's exact tests were used for categorical variables.

RESULTS: A total of 21 PCOSs and 18 PCOSd (mean age 19.86 ± 3.98 and 18.33 ± 2.30, respectively) as well as 26 Cs and 45 Cd (mean age 17.27 ± 0.67 and 17.58 ± 0.84, respectively) were recruited to date. We noted a high prevalence of menstrual irregularity in PCOSd when compared with Cd (PCOSd: 8/18 (44.4%) vs Cd: 7/44 (15.9%), $p<0.005$). We also found that the frequency of elevated androgen levels was 8/18 (44.4%) and 11/33 (33.3%) in PCOSd and Cd, respectively ($p=0.433$). PCOSd were significantly more centrally obese than Cd (PCOSd: 5/18 (27.8%) vs Cd: 2/45 (4.4%), $p=0.007$). Yet, such significant difference was not observed when comparing between PCOSs and Cs. There was no significant difference in the prevalence of dyslipidemia (PCOSs: 13/21 (61.9%) vs Cs: 9/21 (42.9%), $p=0.217$; PCOSd: 3/18 (16.7%) vs Cd: 5/34 (14.7%), $p=0.852$), hypertension (none for both PCOSs and Cs; PCOSd: 1/18 (5.6%) vs Cd: 1/45 (2.2%), $p=0.465$) and metabolic syndrome (AHA/NHLBI) (PCOSs: 3/21 (14.3%) vs Cs: 0/26; Pd: 2/18 (11.1%) vs Cd: 0/45) in both gender between offspring of mothers with and without PCOS. There is a trend towards higher frequency of glucose abnormalities when comparing PCOSd vs Cd (PCOSs: 2/21 (9.5%) vs Cs: 1/21 (4.8%), $p=0.549$; PCOSd: 4/18 (22.2%) vs Cd: 2/34 (5.9%), $p=0.079$), although there was no significant difference.

CONCLUSIONS: PCOSd have increased risk of menstrual irregularity and central obesity compared to Cd. No difference in cardiometabolic traits were observed between PCOSs and Cs. Our preliminary results shed some light on the potential long-term cardiometabolic burden on PCOSd.

Abstract ID #70

Abstract Type: Basic Science

Abstract Title: WOMEN WITH POLYCYSTIC OVARY SYNDROME (PCOS) HAVE POORER WORK ABILITY AND HIGHER DISABILITY RETIREMENT RATE AT MIDLIFE- A NORTHERN FINLAND BIRTH COHORT 1966 STUDY

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ABSTRACT: OBJECTIVE: Polycystic ovary syndrome (PCOS), the most common endocrinopathy in women, presents with multiple comorbidities and warrants attention beyond gynecological aspects. This was the first general population-based study to evaluate work ability, participation in working life, and disability retirement in middle-aged women with PCOS and in non-PCOS controls.

METHODS: Women with PCOS (n=280) and women without PCOS symptoms or diagnosis (n=1573) were identified in the Northern Finland Birth Cohort 1966 and were evaluated for self-rated work ability and potential confounders at age 46. Incidence rate ratios (IRRs) for disability and unemployment days were extracted from national registers during a prospective two-year follow-up. Lastly, we assessed hazard ratios (HRs) for disability retirement between 16 and 52 years of age from national registers.

RESULTS: The women with PCOS reported poorer ability to work at age 46, especially due to poorer health. During the two-year follow-up period, the affected women gained on average an additional month of disability and unemployment days, corresponding to a 25% higher risk for both disability (IRR [95% CI] 1.25 [1.22–1.27]) and unemployment days (IRR [95% CI] 1.26 [1.23–1.28]) in models adjusted for health and socioeconomic factors. Lastly, we found a two-fold higher cumulative risk for disability retirement by age 52 compared to non-PCOS women (HR [95% CI] 1.98 [1.40–2.80]), which remained after adjusting for confounding factors.

CONCLUSIONS: PCOS is associated with lower participation in working life as early as midlife. Our results contribute to increased understanding of the association between PCOS and multimorbidity and disability.

Abstract ID #71

Abstract Type: Clinical Science

Abstract Title: EVIDENCES VII – ONGOING PROOF OF CONCEPT STUDY OF SAROGLITAZAR IN TREATMENT OF NAFLD IN WOMEN WITH PCOS

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ABSTRACT: BACKGROUND: The association between polycystic ovary syndrome (PCOS) and non-alcoholic fatty liver disease (NAFLD) is well documented and believed to be due to associated metabolic risk factors. NAFLD prevalence in PCOS is estimated to be between 25.4% and 68.8%. Saroglitazar Magnesium, a dual PPAR α/γ agonist, demonstrated lipid and glucose lowering effects with good safety profile in various clinical studies. In Letrozole-induced PCOS animal models, repeated doses of Saroglitazar magnesium reduced cystic follicle, improved insulin sensitivity, increased serum FSH, decreased LH/FSH ratio, decreased serum testosterone, and normalized ovary weight.

OBJECTIVE: We are currently conducting a proof of concept study to evaluate the efficacy and safety of Saroglitazar Magnesium 4 mg in adult females (≥ 18 years) women with well characterized PCOS and NAFLD by measuring the magnetic resonance imaging proton-density fat-fraction (MRI-PDFF). The secondary objectives are changes in alanine aminotransferase (ALT) aspartate aminotransferase (AST), liver stiffness measurement (LSM), controlled attenuation parameter (CAP), serum-glucose, body mass index (BMI), body weight, lipid-profile, sex hormone binding globulin (SHBG), ovarian function and free androgen index (FAI).

METHODS: Multicentre, phase 2a, randomized, double-blind, placebo-controlled study is currently ongoing across eight centres in US (NCT03617263) and Mexico. 90 eligible patients with ALT level ≥ 38 U/L & hepatic fat fraction ≥10% by MRI-PDFF are randomly assigned to either Saroglitazar Magnesium 4 mg or placebo arms in 1:1 ratio for 24 weeks.

RESULTS: Of the 122 subjects (mean age of 29.9 ± 7 years) who have been screened from December 2018 to August 2022, 51 (41.8%) subjects have been randomized so far. Major reason of screening failure was ALT < 38 U/L in 58 (86.6%) patients. Subjects with screen failures had significantly lower mean ALT levels (27.6 ± 20.6 U/L vs 53.6 ± 44.5 U/L, $p<0.001$), lower AST levels (21.8 ± 18.2 U/L vs 36.0 ± 28.4 U/L, $p=0.002$), lower FAI (1.13 ± 0.97 vs 1.66 ± 1.16, $p=0.007$) and higher SHBG (66.7 ± 80.1 vs 42.6 ± 50.4, $p=0.045$) compared with subjects without screen failures at baseline. No other significant differences were observed. Of 51 subjects enrolled, 45 (88.2%) patients were obese, 37 (72.5%) had hyperinsulinemia, 47 (92.2%) had Hyperandrogenism, 8 (15.7%) had impaired fasting glucose and 5 (9.8%) patients had dyslipidaemia.

CONCLUSION: This is the only prominent ongoing interventional study in US for treatment of NAFLD in women with PCOS. Above baseline data will help endocrinologist, gynaecologist and hepatologist in better collaboration and awareness of the disease amongst PCOS patients. The results of this clinical trial will provide a strong basis for long term evaluation and potential management and treatment of patients with PCOS and NAFLD.

Abstract ID #72

Abstract Type: Basic Science

Abstract Title: LH/CG RECEPTOR ACTIVATION PROTECTS MICE FROM DIET-INDUCED OBESITY

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ABSTRACT: OBJECTIVE: Epidemiologic data suggests negative association of LH levels with body mass index in women with PCOS, girls with central precocious puberty, and menopausal women. Here we are testing the hypothesis if LH has a direct action on adipose tissue.

METHODS: In vitro: qPCR, RNA sequencing, western blotting, Sanger sequencing, RNA scope, Immunohistochemistry, AlexaFluor-488-labeling for binding studies, siRNA Knockdown, Elisa

In vivo: Body weight measurement, qNMR, GTT on C57BL/6 mice fed on high-fat-diet and Lhcgr knockdown mouse line

RESULTS: We confirmed the presence of LHCGR in mouse genital and inguinal fat pads, adipose-derived stromal vascular cells, as well as in differentiated and undifferentiated 3T3.L1 murine adipocytes by qPCR, RNAscope in situ hybridization, and immunohistochemistry. Sanger sequencing showed that the extracellular domain of LHCGR in genital fat depot was identical to the ovarian receptor. Similarly, we identified LHCGR in human subcutaneous and visceral fat depots. Binding of intraperitoneally injected AlexaFluor-488-labeled hCG was found not only in mouse ovary, but also in genital and subcutaneous fat pad, further confirming the presence of LHCGR in adipose tissue. This binding could be competitively displaced in 3T3L1 cells using unlabeled hCG. LH, hCG and ORG43553 activated ERK1/2 in a dose-dependent manner in undifferentiated and differentiated 3T3.L1 cells, suggesting that the adipose LHCGR is fully functional. LH and hCG reduced adipogenic differentiation in 3T3L1 cells, which is further confirmed by RNA sequencing.

High-dose LH, hCG, or small molecule LH/CGR agonist ORG43553 that was injected twice-a-week into 14-month-old C57BL/6 male mice protects them from diet-induced obesity and reduces leptin levels. The testosterone levels were elevated in mice treated with LH or hCG, but not with ORG43553. We determined the anti-obesity action of LH/hCG is independent of testosterone, as blocking the androgen receptor using flutamide yielded similar results. Importantly, male LHCGR knockout mice on a high-fat diet treated with LH failed to display a reduction in adiposity, confirming the in vivo specificity of action. Furthermore, our data phenocopied LHCGR haploinsufficiency in mice.

CONCLUSIONS: We demonstrated that LH/CG receptors are present and fully functional in adipose tissue, and that high-dose intermittent activation of LHCGR in mouse fat depots protects mice from diet-induced obesity.

Abstract ID #73

Abstract Type: Clinical Science

Abstract Title: PCOS IS ASSOCIATED WITH AN INCREASED INCIDENCE OF CO-MORBIDITIES IN A CANADIAN POPULATION COHORT

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ABSTRACT: OBJECTIVE: PCOS is the most common metabolic-endocrine disorder that can impact health and quality of life over a lifespan. It is important we understand the scope of health outcomes that impact the health and quality of life of those with PCOS in order to improve health care in this population. The aim of this study was to determine the incidence of co-morbidities in PCOS compared to an age-matched population.

METHODS: We conducted a retrospective observational case-control study in those diagnosed with PCOS and age-matched controls using the Alberta Health Services Health Analytics database from 2002-2019 in Alberta, Canada.

RESULTS: The incidence of high blood pressure, high blood lipids, diseases of the heart, kidney, gastrointestinal tract, pre-diabetes, eating disorders, mental illness, depression-anxiety, rheumatoid arthritis, respiratory infections and all cancers was 20-40% ($p<0.0001$) higher in PCOS (n=16531) compared to controls (n=49335). Overweight-obesity, non-alcoholic liver disease, Type 1 diabetes (T1D) and T2D had a 3-fold greater incidence in PCOS ($p<0.0001$). Cardiovascular disease and cerebrovascular disease were 60% higher in PCOS compared to controls ($p<0.0001$).

CONCLUSION: These findings indicate PCOS is associated with a significantly greater incidence of co-morbidities and adverse health outcomes. This data provides evidence of the potential economic health care burden and lower quality of life in those with PCOS. The data may also indicate a need to improve education of patients and clinicians in raising awareness of health risks and implementation of preventative health care in this high-risk population.

This work was funded by the Women and Children's Health Research Institute and University of Alberta Medical Research Foundation.

Abstract ID #74

Abstract Type: Clinical Science

Abstract Title: EARLY ATHEROSCLEROSIS IN HIGH-RISK YOUNG WOMEN WITH AND WITHOUT PCOS

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ABSTRACT: OBJECTIVE: Polycystic Ovary Syndrome (PCOS) is associated with increased cardiometabolic risk factors and incidence of cardiovascular disease (CVD). Currently, early screening of dyslipidemia, atherosclerotic CVD (ACVD) and heart function are not routine in the primary care of high-risk young women with and without PCOS. The aim of this study was to provide evidence-based research to aid the development of assessment guidelines for early detection of dyslipidaemia, cardiac dysfunction and ACVD in high-risk young women with and without PCOS.

METHODS: A case-control study in high-cardiometabolic risk (body mass index (BMI>25) women aged 25-45 years with and without PCOS, matched for age and body mass index, and healthy weight controls was conducted. The main outcome measures included blood lipids, apoB-lipoproteins, carotid intima-media thickness (cIMT), carotid plaque and cardiac function using ultrasound and 2D/3D echocardiography.

RESULTS: High-risk women with (n-45) and without PCOS (n=20) had a 25% higher total apoB, 30% higher non-HDL-C and 50% higher triglycerides compared to age-matched health weight controls (n=10). PCOS tended to have higher plasma triglycerides, total ApoB, non-HDL-C and remnant cholesterol compared to BMI-matched controls Those with PCOS had a significantly lower HDL-C compared to both BMI-age-matched and health-weight controls. Carotid plaque was 3- and 8-fold higher in those with PCOS compared to BMI-matched and healthy weight controls, respectively. Those with PCOS and BMI-matched controls had increased cIMT by 15% and early left ventricular global longitudinal strain by 10%, compared to healthy-weight controls.

CONCLUSIONS: High-risk PCOS and BMI-matched controls have early impairment in global cardiac function and increased ACVD, and this is associated with an atherogenic dyslipidemic profile. These results suggest early primary prevention screening and a risk-stratification model may be warranted in this high-risk population of young women to reduce risk of premature development and incidence of CVD.

This research is funded by Women and Children’s Health Research Institute and Mazankowski Heart Research Institute

Abstract ID #75

Abstract Type: Clinical Science

Abstract Title: FACTORS INFLUENCING DEVELOPMENT OF PCOS IN PREMENOPAUSAL WOMEN WITH TYPE 1 DIABETES.

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ABSTRACT: OBJECTIVE. Polycystic ovary syndrome (PCOS) is common in women with type 1 diabetes (T1D). Although reported prevalence rates vary according to diagnostic criteria used for PCOS, rates up to 49% have been described. However, not all women with T1D develop hyperandrogenic traits and factors that influence the occurrence of PCOS have not been well stablished yet. Results of previous studies are controversial regarding the paper of insulin dose, treatment modality, body mass index or premenarcheal diagnosis of PCOS. We aim to assess the factors associated to the occurrence of PCOS in premenopausal women with T1D.

METHODS. Cross-sectional study. For this analysis, we included 103 patients with T1D, 23 diagnosed with PCOS by ESHRE-ASRM/Rotterdam criteria (22.3%) and 80 T1D women without PCOS (77.7%). Patients were 18 to 45 years-old and they had been 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. We performed a comparison between both groups (DM1-PCOS and DM1-without PCOS) for factors such as age, chronic glycemic control (HbA1c and time in range, TIR), total insulin dose, body mass index (BMI) and premenarcheal diagnosis of T1D. We used Stata software v23 (StataCorp LLC) for statistical analysis.

RESULTS. Mean age was 26.4 ± 7.5 yrs in DM1-PCOS group and 31.4 ± 8.7 in DM1-without PCOS (P = 0.016). Results were not significant for mean duration of T1D (14.2 ± 6.5 yrs in DM1-PCOS and 15.1 ± 9.9 in DM1-without-PCOS, P = 0.665), although premenarcheal diagnosis of T1D was more common in T1D-PCOS group (65.2% in T1D-PCOS vs 46.3% in T1D-without PCOS, P < 0.001). Also, we found no statistically significant differences for BMI (23.4 ± 4.2 kg/m2 in T1D-PCOS vs 24 ± 4.3 kg/m2 in T1D-without-PCOS, P = 0.528), HbA1c (7.11 ± 1.3% in T1D-PCOS vs 7.37 ± 1.4% in T1D-without PCOS, P = 0.428) or TIR (66.8 ± 15.1 in T1D-PCOS vs 63.9 ± 19.1% in T1D-without PCOS, P = 0.545). Regarding insulin dose, patients with T1D and PCOS had higher daily total insulin dose (0.71 ± 0.36 U/kg/day vs 0.58 ± 0.19 U/kg/day in those without PCOS, P = 0.026).

CONCLUSIONS. In our study, premenopausal women with T1D and PCOS were younger, had a more common premenarcheal diagnosis of T1D and used higher insulin doses compared to T1D women without PCOS.

Abstract ID #76

Abstract Type: Basic Science

Abstract Title: LUTEINIZING HORMONE KNOCKOUT ALLEVIATES ANXIETY IN AGED, BUT NOT IN YOUNG MICE

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ABSTRACT: OBJECTIVE: Experimental data support the association of luteinizing hormone (LH) - age related increase in post-menopausal and women suffering from PCOS to increase levels of anxiety and depression. However, the role of LH in neuropsychiatric disorders has not yet been characterized. Here we identify an anxiolytic phenotype in a model of a luteinizing hormone/human chorionic gonadotropin receptor knockout (LHCGR-KO) that implicated LHCGR as potential a target for the anxiety elderly.

METHODS: We establish a behavioral test battery for assessing anxiety and memory in both young (12-weeks) and aged (22-weeks) male and female WT and LHCGR-KO mice.(B6;129X1-Lhcgrtm1Zmlei/J). Behavioral testing included a Dark/Light box (DLB) task for anxiety, a Y-Maze spontaneous alternation task for short term spatial memory, a novel object recognition (NOR) test for long term recognition memory and a fear conditioning contextual and cued memory for anxiety-related memory. We used RNAscope, a technology that allows the detection of mRNA at single-transcript level, together with protein level validation, to document LHCGR transcripts in 401 brain regions, nuclei and sub–nuclei using the Atlas for the Mouse Brain in Stereotaxic Coordinates.

RESULTS: We found no effect of LHCGR -KO on anxiety in the DLB, short- or long-term memory in the Y-Maze and NOR as well as on contextual fear memory in young male or female mice but improved cued fear conditioning for both sexes. However, we show an age-related elevation of anxiety in the DLB task and a decline in long term memory in the NOR task, in aged females, but not in aged males. The knockout of LHCGR resulted in reducing anxiety in the DLB test but not improving the long-term memory in the NOR test for aged females. In addition, the LHCGR -KO aged female mice showed reduced freezing behavior under a different context and under the same context, pre-and post-conditioning cue in the fear conditioning test. Thus, supporting the reversal of increased anxiety but not of a memory decline shown for aged female mice. In line with the behavioral results, our RNAscope studies identified LHCGR in the amygdala, a vulnerable region in anxiety.

CONCLUSIONS: Our study established a comprehensive behavioral battery to provide evidence on of the role of LHCGR in alleviating age-related anxiety in females and suggest the development of new therapeutic strategies for targeting elevated LH levels in conditions such as post-menopausal and PCOS.

Abstract ID #77

Abstract Type: Clinical Science

Abstract Title: WOMEN WITH PCOS EXPERIENCE DIFFERENT MENSTRUAL CYCLE EXPERIENCES THAN CONTROLS DURING THE PANDEMIC

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ABSTRACT: OBJECTIVE:

Although increasing studies are now reporting reproduction in women with Polycystic Ovary Syndrome (PCOS), none have described menstrual cycle-related experiences. Our objective was to explore this by standardized daily Menstrual Cycle Diary©. Specifically, we compared PCOS "cases" with matched controls. We hypothesized in PCOS vs controls: greater levels of depression and lower levels of self-worth but similar levels of outside stress.

METHODS:

This is a single-cycle prospective case-control study using data from the 112 community-dwelling women ages 19-35 years with approximately month-apart, spontaneous (not on hormonal contraception) menstrual cycles in the Menstruation Ovulation Study 2 (MOS2); all data were collected early in the SARS-CoV-2 pandemic. Six women self-reported PCOS. We matched them with random participants in a 3:1 ratio within 5-years of age, and by BMI category. We did not adjust for ovulatory characteristics, given that 63% of all MOS2 cycles had ovulatory disturbances1. We described data while testing hypotheses by Mann-Whitney U and Chi-Square Tests. We also described Principal Component Analysis (PCA) patterns versus published mean 11-month data in normally ovulatory normal-weight women2. Data were analyzed using SPSS version 28.

RESULTS:

As expected, women living with PCOS (n=6) and controls (n=18) were similarly aged in the early 30s, with non-different mean BMI's in the low overweight range. PCOS women were more white than East Asian and other ethnicities. Mean menstrual flow (ml/day) was significantly higher in controls than PCOS ($p=0.009$) with no difference in days of flow ($p>0.721$). There was also no significant difference in duration of cramps ($p>0.812$), cramp intensity ($p>0.415$) nor front breast tenderness ($p>0.250$).

Our hypotheses of lower feelings of self-worth and higher feelings of depression with similar perceived outside stresses were not confirmed. Women with PCOS had significantly higher ($p>0.001$) feelings of depression than controls. There was no significant difference in feelings of self-worth; however, women with PCOS experienced significantly greater ($p>0.001$) outside stressors than controls.

PCA patterns showed six rather than the expected five 'Factors', and, except for "Negative Moods" in Factor 1, differed importantly in Factor loading structure from previous data in ovulatory women. Most interesting is that cramps and flow were not on the same factor but that "stretchy" cervical mucus loaded positively with increase in sex.

CONCLUSIONS

In conclusion, women with PCOs experience less menstrual flow/day than matched controls. They also experienced greater outside stresses, had more depression and similar feelings of self-worth as did the controls during the SARS-CoV-2 pandemic.

REFERENCES

Prior JC et al. Endocrine Society podium presentation, 2022.

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Abstract ID #78

Abstract Type: Basic Science

Abstract Title: Associated Risk of PCOS Comorbidities

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ABSTRACT: OBJECTIVE: Women with polycystic ovarian syndrome (PCOS), the most common endocrine disorder in women of reproductive age, are at risk for a number of cardiometabolic comorbidities. Little information is known about the long-term health risks that are associated with PCOS as many studies do not follow PCOS patients longitudinally. Metformin, a drug traditionally used to treat patients with type 2 diabetes (T2D), has many off-label uses and early evidence has also shown metformin to have a protective effect on coronary arteries. We hypothesize that women with PCOS are at increased risk for developing cardiovascular disease (CVD) and that metformin can play a protective role in disease progression.

METHODS: We leveraged a large longitudinal cohort from the Penn Medicine electronic health record (EHR). Out of 2,514,400 women, 24,850 had at least one PCOS diagnosis. We calculated the relative risk for women with PCOS being diagnosed with comorbidities such as obesity and T2D, as well as six different CVD: cardiomyopathy, hypertensive heart disease, thrombotic disease, congestive heart failure, cerebrovascular accident, and ischemic heart disease. Finally, we determined the relative risk that women with PCOS who were also prescribed metformin had for being diagnosed with cardiometabolic comorbidities. Controls were identified as women not diagnosed with PCOS, metformin, or comorbidities.

RESULTS: We found that 1% of women had at least one PCOS diagnosis and while 30% and 11% of PCOS patients had also been diagnosed with obesity and T2D respectively, there was a low prevalence of CVD diagnoses (an average of 1.37%). These results were mirrored overall by relative risk, where women with PCOS were 4.35 and 1.66 times more likely to also be diagnosed with obesity and T2D respectively. Interestingly, patients with PCOS were 1.48 times more likely to be diagnosed with thrombotic diseases (obstetric embolism and pulmonary embolism). We found that overall, women with PCOS who were also prescribed metformin had low risk for being diagnosed with both T2D and CVD comorbidities. However, the opposite was true for obesity; the relative risk was determined to be 1.43.

CONCLUSIONS: In a large longitudinal cohort of women diagnosed with PCOS, we showed that a PCOS diagnosis is associated with a high risk for obesity, T2D, and thrombotic diseases such as obstetric and pulmonary embolisms. We observed an increased risk of obesity, and a decreased risk of T2D and all six CVD classes associated with PCOS patients who were also prescribed metformin. The results from this work add to both the established and emerging role of metformin as a preventative drug for women diagnosed with PCOS who are at risk for cardiometabolic diseases. Due to the high prevalence of CVD in women, future work is needed to uncover the molecular and genetic pathways underlying the off-label use of metformin in PCOS and other high-risk women.

Abstract ID #80

Abstract Type: Clinical Science

Abstract Title: Influence of metformin on hyperandrogenism biochemical markers in women with polycystic ovary syndrome: A systematic review and meta-analysis of randomized clinical trials

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ABSTRACT: OBJECTIVE: Insulin resistance is closely related to hyperandrogenism in patients with Polycystic Ovary Syndrome (PCOS). The treatment of PCOS includes drugs, such as metformin, an insulin-sensitizing drug, which can improve this clinical symptom. The aim of the study was to investigate the effects of metformin treatment on biochemical markers of hyperandrogenism in PCOS.

METHODS: The design followed the recommendations of the Cochrane Handbook and literature searches were performed in MEDLINE, CENTRAL, Embase, CINAHL, WOS, and Scopus databases, until April 2022, for randomized clinical trials that evaluated the effects of metformin treatment on the levels of hyperandrogenic biochemical markers in women over 18 years of age with PCOS. The study protocol was registered on the PROSPERO under the identification CRD42021235761. The primary outcome was considered as changes in the initial and final values of the androgenic biomarkers evaluated by the primary studies, namely: androstenedione; DHEAS; Free Androgen Index - FAI; SHBG; free testosterone and; total testosterone. To assess changes in the levels of hyperandrogenism biochemical markers, the values obtained at the beginning and at the end of each study were extracted and applied in the meta-analysis using the random effect and the results presented as SMD with 95% CI. The heterogeneity of the outcomes was explored with sensitivity analysis. The risk of bias was assessed from the Rob 2.0 and the certainty of evidence for each outcome was assessed from GRADE approach.

RESULTS: Search performed in electronic databases, gray literature and reference lists resulted in 3,694 records. After a complete reading of the studies, 18 primary studies were included in the qualitative analysis and 17 studies in the quantitative analysis. Were evaluated 866 patients diagnosed with PCOS, being 427 allocated to the intervention group, and 439 in the placebo group. Was observed a significant reduction in total testosterone levels in the metformin-treated group when compared to the control group SMD: -0.48 (-0.95 to -0.01) points; I2=86%; p=<0.00001. FAI values for sensitivity analysis were also regulated by metformin treatment SMD: -0.40 (-0.66 to -0.13) points; I2=0%; p=0.59 and total testosterone levels when compared to the control group SMD: -0.29 (-0.46 to -0.11) points; I2 =0%; p=0.47.

CONCLUSIONS: Metformin probably proved effective in reducing total testosterone levels and FAI values. The results also consistently suggest that SHBG and free testosterone levels are not affected by metformin treatment. The certainty of the body of evidence was classified as moderate. More primary studies should be developed to confirm the findings, combining the joint assessment of biochemical and clinical markers, in patients diagnosed with PCOS under metformin treatment in randomized placebo controlled clinical trials.