

Project Proposal

Background

Affecting one in five young Australian women, and one in four Australian Indigenous women (1-4), PCOS is a common, under-recognised, and increasingly prevalent condition, with serious health and psychological impacts for women and their families (5-8). Whilst reproductive features are prominent, PCOS also has major metabolic (obesity, metabolic syndrome, gestational diabetes (GDM) type 2 diabetes (T2DM), cardiovascular risk factors (CVRF)) and mental health consequences including poor quality of life. Most of these complications are national health priorities (9, 10). PCOS identifies women from puberty with high reproductive and metabolic risks, who are prone to gain weight, which further exacerbates PCOS. These women are readily identifiable and are in need of targeted early prevention and management.

The prevalence of obesity is rising and adds considerably to the health and economic burden internationally. Excess weight, present in up to 70% of women with PCOS in many countries including Australia, further exacerbates incidence, prevalence and severity of the syndrome (11). PCOS is underpinned by insulin resistance (IR) which drives hyperandrogenism and plays a critical aetiological role in the reproductive and metabolic complications of the disorder (12). Independent of weight, women with PCOS have defective insulin activity (13) resulting in increased prevalence of GDM, impaired glucose tolerance (IGT), T2DM and increased CVRF (14) compared to women without PCOS. These are all further exacerbated by the rising prevalence of obesity.

There is an acknowledged lack of longitudinal studies to assess the natural history of the PCOS reproductive, metabolic and psychological features and the impact of BMI. In particular, further research examining metabolic complications of PCOS in a community-based cohort will further the understanding of PCOS natural history in this area. Further research addressing these important knowledge gaps is vital.

I will conduct longitudinal analysis using datasets from the ongoing Australian Longitudinal Study on Women's Health (ALSWH) commenced in 1995. Women were randomly selected from the national Medicare database and recruitment was based on mailed surveys. Three cohorts of Australian women aged 18–23, 45–50, and 70–75 years completed Survey 1 in 1996. Of these, 14,772 young women (aged 18-23 years) completed Survey 1 with over 60% retention through to survey 6. The study has recently been expanded by the addition of a new cohort in 2012-2013, with data collected from more than 10,000 women aged 18-23 years. This dataset provides a significant opportunity to study the natural history of PCOS across the lifespan.

I will expand my existing collaboration with the ALSWH investigators and will examine data from women with a diagnosis of PCOS compared to those not reporting PCOS. In this first community-based large scale prospective cohort study, PCOS prevalence, the interaction with demographic features, BMI and lifestyle factors will be examined along with predictors of PCOS over the 14 years of the study to date. PCOS complications including reproductive, metabolic and psychological features will be studied. Whilst I am familiar with this dataset from cross sectional data analysis from my PhD, here I will extend my technical skills to include longitudinal analysis and data linkage analyses. There are also now new opportunities to link to data on the PBS and MBS systems to ALSWH data to enable study on health care and medication utilisation. I will also utilise this dataset to learn and undertake advanced statistical modelling to study metabolic and reproductive features in PCOS and to focus on key determinants. I will be mentored by a series of highly experienced biostatisticians in this work.

Key objectives

To conduct longitudinal analyses using the outlined cohort to examine the:

- evolution of weight gain, metabolic features of PCOS including IR, CVRF

- prevalence, incidence and predictors of glycaemic complications in PCOS
- prevalence, incidence and predictors of hypertension and cardiovascular events in PCOS
- examine the role of BMI in contributing to metabolic complications of PCOS

Methods

A brief methodological description is included here. Data analysis will summarise continuous explanatory variables as means with standard errors and categorical explanatory variables as percentages. Differences in variables at baseline between subgroups of the study population will be tested using survey weighted univariable regression or the χ^2 test, as appropriate. Cross tabulation will be used to examine the relation between categorical explanatory variables and PCOS. Random intercepts models will be used to analyse the outcome event of interest and the main explanatory variables for each woman studied. To assess the effect of PCOS and BMI on the outcomes of interest, logistic regression analyses will be performed and will be adjusted for potential confounding covariates. The selection of variables will be based on identifying all measured clinical variables of known or suspected prognostic importance for the outcome of interest (and/or exhibiting a p value of less than 0.1 on univariate analyses). Given the deliberate oversampling from rural and remote areas, all statistical analyses will be survey weighted and adjusted by area of residence. All p-values will be calculated from two-tailed tests of statistical significance with a type I error rate of 5%. All analyses will be performed using Stata software version 11.0 (StataCorp, Texas, USA).

To enable me to complete the complex longitudinal analyses, modelling and data linkage studies available across these cohorts and linked datasets, I will build on my existing expertise in clinical reproductive endocrinology and in epidemiology and biostatistics and will complete further coursework and training through the School of Public Health and Preventive Medicine. I aim to complete advanced epidemiological research modules focused on epidemiology and biostatistics.

Significance of the proposal

This body of work aligns with some of the key areas for generation of new knowledge as identified by the PCOS Centre of Research Excellence. This work will help define the natural history of PCOS and metabolic complications in community-based cohorts. Ultimately, my work will definitively address important aspects of the natural history of PCOS, guiding screening, prevention, and treatment. This work should add considerably to the understanding of the aetiology and nature of PCOS which is essential to improving early diagnosis and progressing therapy to improve outcomes in PCOS.

This project will build on existing collaborations with the ALSWH team. This project grant will help support the research of a clinician researcher with a strong interest in PCOS, both in clinical practice and in research.

Expected outcomes

3 manuscripts are proposed from this work and are outlined below.

Title: Weight gain in women with Polycystic Ovary Syndrome: Longitudinal risk in Reproductive-Aged Women

Authors: Joham AE, Ranasinha S, Loxton D, Zoungas S, Teede HJ

Title: Type 2 Diabetes incidence and Polycystic Ovary Syndrome: Longitudinal risk of Type 2 Diabetes in Reproductive-Aged Women

Authors: Joham AE, Ranasinha S, Loxton D, Zoungas S, Teede HJ

Title: Hypertension incidence and Polycystic Ovary Syndrome: Longitudinal risk of Hypertension in Reproductive-Aged Women

Authors: Joham AE, Ranasinha S, Loxton D, Zoungas S, Teede HJ

Budget

\$8000 – statistical support

\$3000 – conference support

References

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