

Pregnancy and Birth Cohorts for Biomarkers, Metabolic and Pregnancy Outcomes Evaluation: A Summary of Pre-conception, Prenatal and Postnatal Cohorts in KK Women's and Children's Hospital

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ABSTRACT

Pregnancy cohort studies are important as they can help us better understand health conditions during pregnancy and later in life after birth. This article summarises the cohorts which are predominantly based in KK Women's and Children's Hospital.

Keywords: Pregnancy, Pre-conception, Birth Cohort, Biobank, Biomarkers

INTRODUCTION

KK Women's and Children's Hospital (KKH), previously known as Kandang Kerbau Maternity Hospital, is celebrating her 160th anniversary in this year of 2018. As the largest Singapore

medical facility in pregnancy and delivery service, KKH has actively promoted pregnancy research over the past 70 years.¹⁻² KKH is also involved in significant obstetric practice changing trials, including one of the most renowned international studies - Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study. As one of the 15 study centres worldwide, KKH enrolled 1,787 patients for HAPO data analyses.³ Furthermore, KKH was involved in the landmark MAGPIE Trial Study, on the use of magnesium sulphate as a prophylaxis for eclampsia.⁴ These two international trials have radically changed the clinical management of gestational diabetes and pre-eclampsia worldwide. KKH was also put on the global map for obstetric research as a key collaborator of the international trial of PROGNOSIS ASIA, involving the use and validation of novel serum biomarkers sFlt-1 and PIGF in preeclampsia.⁵

There is now a growing interest in the development and establishment of pregnancy & birth cohorts, in recognition of the importance of the periconceptional, in utero and peripartum environments on later life health outcomes.^{6,7} Barker et al in 1993 was the first to develop of the concept of

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fetal programming as an origin of adult disease (the Barker hypothesis).⁸ Gluckman et al in 2006 further expanded the developmental origins of health and disease concept, which considers a broad range of exposures during early life and adult diseases.⁹ There is also the concept of epigenetics, where heritable changes in gene expression potential not involving changes in DNA, as a result of early life exposures, can lead to adult disease.¹⁰

Even though there has been a lot of interest in birth cohorts, it is only recently (since 2008) that KKH is involved in large well characterized birth cohorts with bio-banking capability, including for metabolic evaluation and also biomarker discovery, development and validation. We can better understand trans-generational health conditions during pregnancy and later in life after birth, through pregnancy and birth cohorts covering pre-conception, prenatal (antenatal) and postnatal phases. This article summarizes the cohorts which are predominantly conducted in KK Women's and Children's Hospital, which are also distinctive as they comprised our 3 major Asian ethnicities (Chinese, Indian & Malay) in Singapore.

PREGNANCY AND BIRTH COHORTS (PRE-CONCEPTION, PRENATAL AND POSTNATAL PHASES) IN KKH

There are currently 4 significant birth cohorts predominantly based in KKH. They are the Growing Up in Singapore Towards Healthy Outcomes (GUSTO) birth cohort; Singapore PREconception Study of long-Term maternal and child Outcomes (S-PRESTO) pre-conception birth cohort; Neonatal & Obstetric Risk Assessment (NORA) / Pregnancy Events Collaborative Study (PECO) antenatal birth cohorts; and the Integrated Platform for Research in Advancing Metabolic Health Outcomes of Women and Children - BIOMarkers Assessment Study (IPRAMHO-BIOMA) antenatal birth cohorts. All four pregnancy cohort groups with their respective biobanks has strong capabilities for indepth evaluation of metabolic diseases, biomarkers and pregnancy outcomes.

GUSTO

GUSTO, a cohort of >1000 mother-child dyads studied from 10 weeks' gestation onwards, is one

of the most intensively phenotyped Asian birth cohorts ever conducted. The GUSTO mother-offspring cohort included first-trimester pregnant women aged between 18 and 50 years old residing in Singapore between June 2009 and September 2010. The cohort patients were recruited mainly from KKH (>80% of the antenatal patients) and also from National University Hospital of Singapore (NUH).

It is funded from Developmental Pathways to Health and Disease: Metabolic, Neurodevelopment and Related Outcomes. (NRF2007BMS-TCR003-020). This Translational & Clinical Research (TCR) Flagship programme in metabolic disease, awarded in 2008, focuses on developmental pathways that affect health outcomes across the population. GUSTO is now, globally, one of the most intensively studied perinatal cohorts and allows an assessment of how the perinatal environment affects subsequent metabolic, neurodevelopmental and other phenotypes of mother and child. GUSTO children have been followed up to the age of 8 since the cohort started. GUSTO has a high rate of publications which include those that helped change clinical practice.¹¹⁻¹⁶

S-PRESTO

S-PRESTO study comprises >350 pregnancies where women were intensively studied and bio-sampled starting before conception, with a further ~600 similarly studied and sampled women who did not conceive. The study is funded by National Medical Research Council (NMRC/TCR/012/2014). S-PRESTO began recruitment in February 2015, and 1056 patients have been recruited all in KKH since the end of 2017, and 377 pregnancies have resulted. Of these 169 has since delivered. There is an ongoing follow up of this cohort at the moment. Data will be analysed later this year when a significant number of patients have delivered in order to assess outcomes.

NORA / PECO

NORA / PECO are two very similar KKH cohort studies, funded by the NMRC Programme Project Grant (NMRC/PPG/KKH/2010) from 2010-2014 and A* STAR Gap Funding for membrane vesicle-

associated biomarker discovery platform for high risk pregnancy from 2013 to 2015 respectively. NORA and PCEO established a combined antenatal birth cohort and biobank of >1000 patients. All the patients were delivered in KKH and cohorts have been useful for assessing trajectories of biomarkers in pregnancy. The unique feature of both cohorts, is that biosamples were taken at 4 time-points in the antenatal period, allowing norms and trajectories of hormones and biomarkers to be established in our Asian population.¹⁷ It helped established reference standards for various pregnancy hormones & metabolic biomarkers in Singapore.¹⁸⁻¹⁹ The cohort validated novel extracellular vesicles (EV) biomarkers of preeclampsia.²⁰

IPRAMHO-BIOMA

This KKH study is funded by (NMRC CGAug16C008) since 2017. Thus far a total of 373 pregnancies (where routine OGTT was performed) has been characterised with biobanking of serum and plasma biosamples at 24-28 week time-point during routine OGTT. The study recruitment is still ongoing.

CHALLENGES AND VALUE OF ANTENATAL COHORT STUDIES

There are challenges in conducting cohort studies. Besides the need for appropriate funding and adequate resources, patient engagement and consent are important. In NORA cohort study, only about a third consented to participate

among those screened and approached.²¹

Based on GUSTO, NORA & KKH cost effectiveness data on screening for gestational diabetes¹⁶, our team initiated a change in a few-decade-old clinical practice of Singapore - implementation of universal/routine GDM screening & adoption of new IADPSG Criteria in both Singapore hospitals KKH & Singapore General Hospital (SGH). This had made significant impact in improving metabolic care for pregnant women. Our unique sets of bio-banked samples and data from GUSTO, S-PRESTO, NORA/PECO & IPRAMHO-BIOMA cohorts are valuable resources for various research studies including those studies on metabolic outcomes, biomarker discovery & validation, and population norms & health.

CONCLUSION

Developmental concepts and hypotheses have provided the rationale for assembling birth cohorts in KKH and the world. Current worldwide interest in trans-generational population metabolic health make it essential for us to invest in and develop good cohort studies, to shed light for improving population health.

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