The Gomeroi Gaaynggal Cohort: A Preliminary Study of the Maternal Determinants of Pregnancy Outcomes in Indigenous Australian Women

Kirsty G. Pringle1-3, Loretta Weatherall4, Celine Corbiset de Meaultsart1-3, Lyniece Keogh5-4, Stella Sands5-4, C. Caroline Blackwell1, Sharron Hall1-3, Donald Clausen5, Kenneth Apen6, Keith Hollebone6,7, T. Claire Roberts1, Sandra Eades8, Alex Brown9, D. Pathik W 10

1School of Biomedical Sciences and Pharmacy, University of Newcastle, Callaghan, Australia
2Mothers and Babies Research Centre, Hunter Medical Research Institute, New Lambton, Newcastle, Australia
3Priority Research Centre for Reproductive Sciences, University of Newcastle, Callaghan, Australia
4Gomeroi gaaynggal Centre, Faculty of Health, 2/1 Hinkler St, University of Newcastle, Tamworth, Australia
5Pathology North, New England, Johnston St, Tamworth, Australia
6Tamworth Rural Referral Hospital, Johnston St, Tamworth, Australia
7Robot Research Institute, University of Adelaide, Adelaide, Australia
8Baker IDI, 75 Commercial Rd, Melbourne, Australia
9South Australia Health and Medical Research Institute, North Terrace, Adelaide, Australia
10UC Irvine Development, Health and Disease Research Program, School of Medicine, University of California, Irvine, USA

Abstract

The life expectancy of Indigenous Australians is amongst the lowest of any population group within developed nations and chronic diseases collectively account for over 80% of the gap in life expectancy between Indigenous and non-Indigenous Australians. The Gomeroi gaaynggal cohort is a prospective, longitudinal maternal-infant cohort established to examine the origins of chronic disease in Indigenous Australians. This study aimed to determine the major antenatal factors associated with adverse birth outcomes (preterm delivery, low birth weight) and other pregnancy-related complications (gestational diabetes and hypertensive disorders of pregnancy) in Indigenous Australian women. Pregnant women who identified as Indigenous Australians or pregnant non-Indigenous women giving birth to an Indigenous infant were eligible to participate in the cohort (n=227). Physical measurements and biological sample collection (including blood and urine) were undertaken up to 3 times in pregnancy. Median weight and BMI of the cohort was 80.7 kg and 30.3 kg/m² at enrolment (median 23 weeks gestation). 43% reported smoking cigarettes during pregnancy. Of the 158 women in whom pregnancy outcomes were known, 43% had an uncomplicated pregnancy, 13.9% delivered preterm, 14.6% delivered a small-for-gestational age infant, 10% developed a hypertensive disorder of pregnancy, and 6.3% developed gestational diabetes. In addition, many women showed evidence of underlying renal dysfunction (proteinuria or albuminuria). The ratio of male to female offspring in this cohort was 1.38. Eighty-seven percent of preterm infants were male, as were 83.3% of babies from women with gestational hypertension. This skewed sex distribution was far higher than for those who had a healthy pregnancy outcome (59%). This study demonstrates that key factors including maternal obesity, exposure to cigarette smoke and underlying renal impairment, influence pregnancy outcome. Preliminary findings from this study also suggest that more male babies are born early and from complicated pregnancies in this Indigenous cohort.

Keywords: Indigenous; Preterm birth; Obesity; Small for gestational age; Preeclampsia; Gestational diabetes; Maternal renal health

Introduction

There is evidence that the origins of many chronic diseases can be traced all the way back to developmental conditions in utero. David Barker and colleagues provided epidemiological evidence that a poor intrauterine environment predisposes to early onset of chronic non-communicable diseases because a poor supply of nutrients programs structural and functional changes in the developing fetus that anticipate an extra-uterine environment with low nutrient availability [1]. Barker and others showed that low birth weight was associated with an increased risk of coronary heart disease, hypertension, stroke and type 2 diabetes mellitus in adult life [1]. Three reasons were proposed as to why people who are born small are more vulnerable to chronic disease. First, there is reduced functional capacity of key organs, such as the kidney; second, there are adverse alterations in metabolism and hormonal feedback; and third, they are more vulnerable to the adverse effects of environmental influences in later life [2].

The concept of the developmental origins of adult health and disease is particularly relevant for Indigenous populations who experience chronic disease at significantly elevated rates. For Indigenous Australians, the prevalence of preterm and low birth weight babies is twice that of non-Indigenous Australian women [3]. Furthermore, the life expectancy of Indigenous Australians is amongst the lowest in the developed world and the burden of chronic disease remains a significant contributor to premature mortality and life expectancy differentials. Chronic disease in many Indigenous populations around the globe is considered to be at epidemic proportions. In Tiwi Islanders and other Northern Territory communities, Hoy et al. provided some evidence...
that fetal programming may well influence Indigenous Australian’s health [4]. Individuals who had lower birth weights had higher urinary albumin/creatinine ratios and blood pressures (BP) as young adults, with a more marked relationship in females than males [5]. Indigenous Australian adults who had low birth weights are more likely to die younger and the hospitalisation rates for cardiovascular disease (CVD) is also higher in this population [6].

Indigenous Australian babies born small have relatively small kidneys even compared with similarly small non-Indigenous babies [7]. Kidney size correlates with nephron number and individuals with a lower nephron number are thought to compensate by hyper-filtration, which predisposes to kidney failure. Luyckx et al. have demonstrated that adult Indigenous Australians also have fewer nephrons [8]. Thus the high prevalence of low birth weights among Aboriginal babies may place this population at an elevated risk for later development of renal failure, hypertension and CVD.

Prospective longitudinal cohort studies in Indigenous populations beginning in pregnancy are unfortunately rare despite their likely utility in exploring and explaining the causes and trajectories of poor health in these populations. We have been studying the pregnancy outcomes of Indigenous pregnant women in rural and remote regions of New South Wales, Australia. In this paper we describe our preliminary observations in 227 women of the Gomeroi gaaynggal Indigenous maternal/infant longitudinal cohort.

Method

Study design and setting

The Gomeroi gaaynggal study is a prospective, longitudinal cohort involving Indigenous and non-Indigenous women carrying Indigenous babies from the time of their pregnancy into early childhood (up to five years of age). Recruitment occurs primarily in Tamworth (n=174), a rural town of NSW, and Walgett (n=28), a remote town of New South Wales (NSW), Australia. The Indigenous families of Walgett and Tamworth of NSW live in relative poverty with the Aboriginal community of Tamworth having a socioeconomic index that puts them in the bottom 2% of the Australian economy, and Walgett is one of the poorest 3 communities in the state of NSW [9,10]. A small group of participants (n=25) were also recruited from Newcastle, a regional city of NSW. Newcastle is a relatively affluent area with its SEIFA index in the top 30% of regions in the country [10].

Ethics

Extensive community consultation was undertaken with the communities that were studied, to ensure that aims and design of the study met community and cultural protocols. The study has ethics approval from the Hunter New England Human Research Ethics Committee (Ref.no. 08/05/21/4.01), the NSW Human Research Ethics Committee (Ref. no. HREC/08/HNE/129), and the Aboriginal Health and Medical Research Council Ethics Committee (Ref. no. 654/08). No reimbursements or financial incentives were offered to participants at the request of the local Indigenous communities.

Recruitment

Pregnant women who identified as Indigenous Australians or pregnant non-Indigenous women with Indigenous partners were eligible to participate and could enrol at any stage in their pregnancy. In Australia, Indigenous participants identify as Aboriginal and/or Torres Strait Islander. Participants were recruited by Indigenous research assistants at antenatal clinic locations at all sites, including Indigenous antenatal birth centres and an Aboriginal Community Controlled service. All participants gave written, informed consent to participate in the study. Consent was given from the participant herself or from her guardian if the participant was under the age of 16. Each participant was given time to take information home to ensure their family members were also informed about the study. Here we report on data collected during pregnancy. The research team aimed to see participants once per trimester during pregnancy, with sample collections, physical measures and surveys occurring at times that suited participants (range: 6-40 weeks). Unless otherwise stated, data from all visits were used. Attendance at appointments can be sporadic for many reasons, including transport, health issues, work, and family commitments. Recruitment for the cohort is ongoing.

Physical and other measures

Data on Indigenous status was collected to ensure that one parent was Indigenous as it is a prerequisite for inclusion in the study. Antenatal medical history, birth history, family history and past obstetric history were all recorded. Pregnancy outcomes, as well as birth weight, height, head circumference, Apgar scores and admission to Neonatal Intensive Care Unit (NICU) were all obtained from hospital medical records when available. Pregnancy length and gestational age were calculated using first available ultrasound measurement.

Maternal blood pressure (BP) was taken using a Riecher re-champion® blood pressure machine and cuff (Jungingen, Germany). Participants’ self-reported pre-pregnancy weight and height were used to determine Body Mass Index (BMI). Anthropometric measures including weight, body fat percentage and visceral fat scores were measured using the In-Body 720™ bioelectrical impedance scales (Biospace Co., Ltd., Seoul, Korea).

Sample collection

Venepuncture was conducted by a trained Indigenous Australian research assistant, or a Hunter Area Pathology Service (HAPS) technician in Newcastle, and collected into lithium-heparin or EDTA tubes as appropriate and placed on ice until centrifugation at 4°C. Samples were processed by Pathology New England, Tamworth, NSW or HAPS, Newcastle, NSW. Spot urine samples were collected from each participant and kept at room temperature prior to aliquoting and storage at -20°C.

Laboratory measurements

Urinary and plasma creatinine, albumin and protein were measured using Siemens Flex reagent cartridges for the respective proteins, while electrolytes were measured using a Siemens V-Lyte integrated multisensor and all read using a Siemens Dimension Vista 1500 chemistry analyser at Hunter Area Pathology Service (Newcastle, NSW, Australia). Plasma samples were also assessed for exposure to cigarette smoke by a semi-quantitative commercial competitive enzyme immunoassay (EIA) kit for cotinine according to manufacturer’s instructions (Bio Quant Cotinine ELISA, CA. Catalog No. BQ 096D), as described previously [11].

Pregnancy outcomes

Pregnancy and birth outcomes were not recorded in 55 women, and these were excluded from further analyses. Women were classified as having an uncomplicated pregnancy if they had no pre-existing pathologies (diabetes, essential hypertension, nor kidney disease), remained normotensive (<140 and/or <90 mmHg prior to labour), showed no proteinuria, delivered a live born baby at or after 37 weeks of...
gestation who was not small or large for gestational age and had no other sign of pregnancy complications. Gestational hypertension was defined as new onset hypertension (systolic BP ≥ 140 mmHg and/or diastolic BP ≥ 90 mmHg) on at least 2 occasions, after 20 weeks’ gestation and before the onset of labour. These women had no evidence of proteinuria. Women were classified as preeclamptic if they had gestational hypertension with proteinuria (urinary protein ≥ 300 mg/24 h or spot urine protein/creatinine ratio ≥ 3 mg/mmol creatinine or urine dipstick protein ≥ ++). Gestational diabetes was defined as a fasting plasma glucose of ≥ 5.5 mmol/l or a 2 hour level ≥ 8.0 mmol/l following a 75 g oral glucose tolerance test (OGTT). Women were classified as having proteinuria or albuminuria if they had a spot urine protein/creatinine ratio ≥ 30 mg/mmol or spot urine albumin/creatinine ≥ 3 mg/mmol, respectively on more than one occasion and no evidence of hypertension. Small for gestational age (SGA) was defined as birth weight less than the 10th customized centile, and large for gestational age (LGA) as birth weight greater than the 90th customized centile, both adjusted for maternal height, booking weight, ethnicity, parity and infant gestation and sex according to GROW [12]. Preterm birth was classified as birth of live infant prior to 37 weeks of gestation. Women often suffered from more than one of the pathologies and they were allocated to each pathology group (for example, to both preeclampsia and SGA).

Statistical analysis

Stata 11.1 for PC (StataCorp LP, College Station, TX) was used for statistical analyses. Clinical characteristics were analysed by Mann–Whitney Rank Sum test and Kruskal-Wallis one-way analysis of variance, as appropriate. Kruskal-Wallis one-way analysis of variance was used to assess the effect of women's health on the birth outcomes, using Bonferroni's method for multiple comparison analyses.

Data are presented as median (IQR) unless otherwise stated. BMI was calculated from height and self-reported pre-pregnancy weight. Women were classified as smokers if they self-reported smoking cigarettes at any time in their pregnancy. BMI, Body Mass Index; VFA, Visceral Fat Area; BP, Blood Pressure.

Table 1: Maternal descriptive at enrolment.

|                      | All women | n=213 |
|----------------------|-----------|-------|
| Age, years           | 24.5 (21.1, 29) | 185   |
| Height, cm           | 164 (160, 167)  | 66    |
| Weight, kg           | 80.7 (67, 92.2) | 66    |
| BMI, pre-pregnancy    | 26.7 (22.1, 33.6) | 64    |
| Percentage body fat  | 40.4 (34.3, 46.9) | 66    |
| VFA, cm²              | 144.5 (103.7-182.3) | 66    |
| Diastolic BP, mmHg    | 62 (60, 70)    | 85    |
| Systolic BP, mmHg     | 110 (100, 119) | 85    |
| Smokers, %            | 43          | 128   |
| Number of past pregnancies | 3 (2, 5)      | 88    |
| Number of miscarriages| 0 (0, 1)     | 85    |
| Number of live children| 2 (1, 4)      | 88    |

GA, Gestational Age; NICU, Neonatal Intensive Care Unit.

Table 2: Birth outcomes.

|                      | All Babies | Females | Males |
|----------------------|------------|---------|-------|
| GA at delivery, wks  | 39.1 (37.5, 40.1) | 39.1 (38.4, 40.2) | 39 (37.2, 40.1) | 98 |
| Birth weight, g      | 3170 (2810, 3550) | 3093 (2815, 3535) | 3250 (2780, 3585) | 98 |
| GROW centile         | 40.3 (14.7, 71.3) | 38.3 (14.5, 64.9) | 40.3 (16.5, 74.7) | 94 |
| Length, cm           | 49 (47.5, 51)    | 49 (48, 50)       | 49.5 (47, 51)     | 83  |
| Head circumference, cm | 34.5 (33.5, 35.5) | 34.2 (33.5, 35)  | 34.5 (33.5, 35.5) | 87  |
| NICU, %              | 27          | 21.7     | 30.4   | 92   |

Results

Participant characteristics

227 participants were recruited to the study between February 2010 and December 2014. 12 participants withdrew and 2 miscarried early in pregnancy leaving 213. Twenty-five women were recruited in Newcastle, 174 in Tamworth and 28 in Walgett, NSW, Australia. 76.1% of the women in the study identified as Indigenous, many of these had a partner who was also Indigenous (25.8%). 11.7% of mothers were not Indigenous but they had an Indigenous partner; for the remaining 12.2%, parental Indigenous status was not recorded. Due to the low numbers recruited in Newcastle and Walgett, participants from all three locations are examined as a whole. It should be noted that due to the nature of the study and the population of women who participated, not all variables were collected for each participant.

The participant characteristics are outlined in Table 1. The women in the cohort were relatively young; with a median age of 24.5 years on enrolment (range: 13.8–40.9 years); they had a median gestational age at enrolment of 23 weeks. The median weight and BMI of the cohort at enrolment was 80.7 kg (IQR: 67.0–92.2 kg) and 30.3 kg/m² (IQR: 24.4–34.8 kg/m²), respectively, and their percentage body fat was 40.4% (34.3–46.9%). 27.2% of women were in the healthy range for BMI (18–25 kg/m²), while 19.7% were overweight (25–30 kg/m²) and 53% were obese or morbidly obese (>30 kg/m²). Using self-reported pre-pregnancy height and weight to calculate BMI (n=59), 8.47% were underweight, 32.2% were in the healthy range for their BMI, 20.3% were overweight, 15.2% were classified as obese, and 23.7% morbidly obese (i.e., 59.2% overweight or obese). Almost half of the women (43%) reported smoking cigarettes during pregnancy and 50/97 women (51.5%) had detectable levels of cotinine in their serum.

Women participating in the study were also asked about their previous pregnancy history. On average women in the cohort had 4 previous pregnancies and 2.7 live children with many women reporting a history of miscarriages, stillbirths and/or elective terminations of pregnancy.

Pregnancy and birth outcomes

Information on the infants at birth is described in Table 2. Seven (3.3%) of the women in the study were carrying twins and the ratio of males to females in the cohort was 1.38. The median birth weight was 3170 g (IQR: 2810–3550 g) and median gestational age at delivery was 39.1 weeks (IQR: 37.6–40.1 weeks) resulting in a median adjusted birth weight centile of 40.3. There was no difference in the timing of delivery or growth parameters between male and female infants (Table 2). Twenty-seven percent of all infants were admitted to neonatal intensive care nurseries (NICU); more males than females (30.1% vs. 21.7%) were admitted to NICU but this was not statistically significant.

Of the 158 women where birth outcomes were known, 68 (43%)...
had uncomplicated pregnancies. Nine women (5.7%) had pre-existing hypertension or diabetes, 22 (13.9%) delivered preterm, 23 (14.6%) delivered a baby who was small for gestational age (SGA), 16 (10.1%) delivered a large for gestational age infant (LGA), 10 (6.3%) developed gestational diabetes, and 16 (10.1%) developed gestational hypertension or preeclampsia. In addition, many women in the study had evidence of underlying renal dysfunction, with 20 (12.7%) having proteinuria and 21 (13.3%) having albuminuria in the absence of hypertension. Interestingly, 20/23 babies (87%) who were born preterm were male and 5/6 babies (83.3%) born to mothers who developed gestational hypertension were also male. This skewed sex ratio was much higher than that seen in those who had uncomplicated pregnancies (59% male) or any other pathology (50-57% male).

**Maternal factors affecting pregnancy outcome**

Women who delivered babies who were preterm had significantly higher cotinine levels in pregnancy than those who delivered at term (P=0.009), but their BMIs, blood pressures, and plasma glucose levels were no different (Table 3). Women who delivered preterm also had higher urinary protein/creatinine (P=0.002) and urinary albumin/creatinine ratios in pregnancy compared with women with uncomplicated pregnancies (P=0.01). Mothers who delivered SGA infants did not differ from women with appropriately grown infants in any maternal physical or biochemical measure (Table 4). In contrast, women who delivered babies who were LGA had significantly higher plasma glucose levels (P<0.001) and higher systolic blood pressures (P=0.033, Table 4) in pregnancy than those who delivered appropriately grown infants.

| Table 3: Maternal and infant parameters in women delivering preterm or with uncomplicated pregnancies. |
|-----------------------------------------------|-----------------|-----------------|-----------------|-----------------|
|                                       | Uncomplicated | Preterm Births |
|-----------------------------------------------|-----------------|-----------------|-----------------|-----------------|
| **Babies**                                   |                |                |                |                |
| Birth weight, g                              | 3398           | 2998           | 3635           | 68             | 2720           | 2300           | 2900           | 22             | 0.000***       |
| GA at delivery, wks                          | 39.3           | 38.5           | 40.3           | 68             | 35.5           | 34.4           | 36.2           | 22             | 0.000***       |
| Length of baby, cm                           | 50             | 48             | 51             | 64             | 47.5           | 46.5           | 48.5           | 14             | 0.0003***      |
| Head circumference, cm                       | 34.5           | 33.5           | 35.5           | 65             | 33             | 31.5           | 34             | 17             | 0.001***       |
| **Mothers**                                  |                |                |                |                |
| Maternal age, years                          | 24.2           | 21.7           | 28.9           | 67             | 24.2           | 21.3           | 30.7           | 19             | 0.771          |
| BMI, pre-pregnancy                           | 26.5           | 20.6           | 30.6           | 32             | 27.4           | 23.6           | 30.1           | 6              | 0.548          |
| % Body fat                                   | 41.6           | 33.2           | 48.4           | 69             | 39.5           | 35.6           | 46.6           | 24             | 0.679          |
| Cotinine, ng/mL                              | 0.5            | 0.0            | 79             | 57             | 153            | 0.6            | 217           | 15             | 0.009***       |
| Diastolic BP, mmHg                           | 85             | 60             | 74             | 87             | 60             | 60             | 71.5           | 24             | 0.169          |
| Systolic BP, mmHg                            | 110            | 100            | 120            | 87             | 110            | 104            | 119           | 24             | 0.699          |
| Plasma glucose, mmol/L                       | 4.2            | 3.7            | 4.9            | 121            | 4.1            | 3.6            | 5             | 37             | 0.054          |
| Protein/creat, mg/mmol                       | 11.8           | 8.6            | 15.7           | 112            | 16.3           | 10.9           | 27            | 37             | 0.002**        |
| Albumin/creat, mg/mmol                       | 1.0            | 0.7            | 1.6            | 114            | 1.5            | 0.8            | 2.9           | 37             | 0.010**        |

Bonferroni post-hoc, *p ≤ 0.05, **p ≤ 0.01, ***p ≤ 0.001. Data are from 68 women with uncomplicated pregnancies and 23 women who delivered preterm. Maternal age and BMI (from height and self-reported pre-pregnancy weight) were recorded at enrolment; all other maternal parameters include data from all pregnancy visits. BMI, Body Mass Index; BP, Blood Pressure; creat, Creatinine; GA, Gestational Age.

| Table 4: Maternal and infant descriptive in SGA, LGA or uncomplicated pregnancies. |
|-----------------------------------------------|-----------------|-----------------|-----------------|-----------------|
|                   | UNCOMPROMISED  | SGA             | LGA             |
|-----------------------------------------------|-----------------|-----------------|-----------------|-----------------|
| **Babies**                                   |                |                |                |                |
| Birth weight, g                              | 3398           | 2998           | 3635           | 68             | 2498           | 2170           | 2750           | 26             | 0.000***       | 4260           | 4008           | 4575           | 16             | 0.000***       |
| GA at delivery, wks                          | 39.3           | 38.5           | 40.3           | 68             | 39             | 37.3           | 39.6           | 25             | 0.022*         | 39.8           | 37.6           | 40.5           | 16             | 1              |
| Length of baby, cm                           | 50             | 48             | 51             | 64             | 47             | 46.5           | 48             | 17             | 0.000***       | 52             | 50             | 53.5           | 11             | 0.010**        |
| Head circumference, cm                       | 34.5           | 33.5           | 35.5           | 65             | 33             | 31.3           | 34.5           | 20             | 0.000***       | 37             | 35.3           | 37.3           | 12             | 0.003**        |
| **Mothers**                                  |                |                |                |                |
| Maternal age, years                          | 24.2           | 21.7           | 28.9           | 67             | 25.3           | 20.8           | 29             | 22             | 1              | 23.4           | 21.2           | 28.7           | 16             | 1              |
| BMI, self-reported                           | 26.5           | 20.6           | 30.6           | 32             | 24.7           | 21.3           | 33.8           | 8              | 1              | 34.3           | 21             | 37.3           | 6              | 0.248          |
| % Body fat                                   | 41.6           | 33.2           | 48.4           | 69             | 46.1           | 27.7           | 54.1           | 11             | 1              | 43.4           | 37.1           | 52.5           | 20             | 1.792          |
| Cotinine, ng/mL                              | 0.5            | 0.0            | 79             | 57             | 61             | 36.9           | 101            | 21             | 0.287          | 0              | 0.0            | 1.1            | 13             | 0.296          |
| Diastolic BP, mmHg                           | 65             | 60             | 74             | 87             | 69.5           | 60             | 76.5           | 24             | 1              | 69             | 61             | 75            | 25             | 0.754          |
| Systolic BP, mmHg                            | 110            | 100            | 120            | 87             | 110            | 106            | 122            | 24             | 1              | 120            | 112            | 127           | 25             | 0.033*         |
| Plasma glucose, mmol/L                       | 4.2            | 3.7            | 4.9            | 121            | 4.05           | 3.8            | 4.6            | 30             | 1              | 5.2            | 4.3            | 6.5            | 35             | 0.000***       |
| Protein/creat, mg/mmol                       | 11.8           | 8.6            | 15.7           | 112            | 14.2           | 8.07           | 19.6           | 26             | 0.597          | 10.8           | 8.47           | 18.9           | 31             | 0.632          |
| Albumin/creat, mg/mmol                       | 1.0            | 0.7            | 1.6            | 114            | 2              | 0.7            | 4              | 26             | 0.718          | 1              | 0.7            | 2.4            | 31             | 1              |

Citation: Pringle KG, Weatherall L, de Meaultsart CC, Keogh L, et al. (2015) The Gomeroi Gaaynggal Cohort: A Preliminary Study of the Maternal Determinants of Pregnancy Outcomes in Indigenous Australian Women. J Preg Child Health 3: 211. doi:10.4172/2376-127X.1000211
Six women in the study (3.8%) developed gestational hypertension. These women had higher median BMI's ($P=0.017$), higher median body fat percentages ($P=0.003$), higher plasma glucose levels ($P=0.001$) and tended to deliver babies who had higher GROW adjusted birth weight centiles ($P=0.058$) than those with uncomplicated pregnancies (Table 5). Ten women (6.3%) developed preeclampsia during their pregnancy; two of these delivered preterm, one at 29.6 weeks and the second at 35.6 weeks, the latter case was considered severe and the woman was diagnosed with HELLP syndrome. Pre-eclamptic women had similar BMI’s and plasma glucose levels but their body fat percentages were greater than those of women with uncomplicated pregnancies ($P=0.033$, Table 5). Pre-eclamptic women delivered approximately 1-2 weeks earlier on average ($P=0.001$) and had babies with lower birth weights (median: 2850 g, $P<0.001$) and lower customised birth weight centiles (median: 12.75, $P=0.016$) than those with uncomplicated pregnancies.

Several women in the study had pre-existing Type 1 (n=3) or Type 2 (n=4) diabetes mellitus and 10 women (6.3%) developed gestational diabetes during their pregnancy. Women with gestational diabetes delivered earlier than women with uncomplicated pregnancies ($P<0.009$, Table 6) but there were no differences in the infant growth variables. In addition, women with gestational diabetes did not differ from women with uncomplicated pregnancies with respect to BMI and percentage body fat but they had significantly higher plasma glucose levels ($P<0.01$) and higher protein/creatinine and albumin/creatinine ratios in pregnancy ($P<0.05$ and $P<0.001$, respectively, Table 6).

### Table 5: Maternal and infant parameters in women with uncomplicated pregnancies or from those who developed gestational hypertension or preeclampsia.

| UNCOMPPLICATED | GESTATIONAL HYPERTENSION | PREECLAMPSIA |
|---------------|---------------------------|--------------|
| **Babies**    |                           |              |
| Birth weight, g | 3398 (2998, 3635)         | 3480 (3195, 3550) | 6 | 1 | 2850 (2680, 3055) | 10 | 0.000*** |
| GA at delivery, weeks | 39.3 (38.5, 40.3) | 38.4 (36.5, 40) | 6 | 0.226 | 38.3 (37.5, 38.5) | 10 | 0.001*** |
| GROW centile | 48 (24.3, 66.5) | 74.9 (51.6, 97.9) | 6 | 0.058 | 12.8 | 3.2, 29 | 10 | 0.016 * |
| Length of baby, cm | 50 (48, 51) | 48.5 (48, 51) | 5 | 1 | 47 | 47.485 | 8 | 0.009** |
| Head circumference, cm | 34.5 (33.5, 35.5) | 35 | 33.5, 35.5 | 5 | 1 | 33.78 | 33, 34 | 10 | 0.004** |
| **Mothers**    |                           |              |
| Maternal age, years | 24.2 | 21.7, 28.9 | 67 | 26 | 20.8, 32.3 | 4 | 1 | 26 | 21.6, 30.4 | 10 | 1 |
| BMI, pre-pregnancy | 26.5 | 20.6, 30.6 | 32 | 0 | 35.6 | 23.4, 41.4 | 5 | 0.291 |
| % body fat | 41.6 | 33.2, 48.4 | 69 | 51.4 | 50.4, 55 | 7 | 0.003** | 48.8 | 43.8, 54.1 | 13 | 0.033* |
| Cotinine, ng/mL | 0.5 | 0.79 | 57 | 0.45 | 0.1, 0.8 | 2 | 1 | 0.05 | 0.811 | 4 | 1 |
| Diastolic BP, mmHg | 65 | 60, 74 | 87 | 59 | 58, 61 | 3 | 1 | 72 | 70, 90 | 13 | 0.004** |
| Systolic BP, mmHg | 110 | 100, 120 | 87 | 113 | 108, 115 | 3 | 1 | 120 | 110, 137 | 13 | 0.046* |
| Plasma glucose, mmol/L | 4.2 | 3.7, 4.9 | 121 | 5.3 | 4.6, 7.2 | 10 | 0.000*** | 4.05 | 3.0, 5 | 16 | 1 |
| Protein/creat, mg/mmol | 11.8 | 8.6, 15.7 | 112 | 19.4 | 10.9, 34.6 | 13 | 0.035** |
| Albumin/creat, mg/mmol | 1 | 0.7, 1.6 | 114 | 2.5 | 1.3, 3.1 | 13 | 0.004*** |

### Table 6: Maternal and infant parameters in women with uncomplicated pregnancies or in those who developed gestational diabetes.

| UNCOMPPLICATED | GESTATIONAL DIABETES |
|---------------|-----------------------|
| **Babies**    |                       |
| Birth weight, g | 3398 (2998, 3635) | 68 | 3288 | 3100, 3550 | 10 | 0.673 |
| GA at delivery, weeks | 39.3 | 38.5, 40.3 | 68 | 38.3 | 38.3, 38.5 | 10 | 0.009*** |
| GROW centile | 48 | 24.3, 66.5 | 68 | 50.1 | 35.7, 68.1 | 10 | 0.58 |
| Length of baby, cm | 50 | 48, 51 | 64 | 48.8 | 47.5, 49.5 | 8 | 0.127 |
| Head circumference, cm | 34.5 | 33.5, 35.5 | 65 | 33.8 | 32.5, 35.3 | 8 | 0.239 |
| **Mothers**    |                       |
| Maternal age, years | 24.2 | 21.7, 28.9 | 67 | 32.5 | 20.1, 33.1 | 9 | 0.231 |
| BMI, pre-pregnancy | 26.5 | 20.6, 30.6 | 32 | 32.4 | 23.4, 33.4 | 5 | 0.23 |
| % body fat | 41.6 | 33.2, 48.4 | 69 | 46.7 | 39.1, 50.9 | 8 | 0.113 |
| Cotinine, ng/mL | 0.5 | 0.79 | 57 | 0 | 0.4, 9 | 0.225 |
| Diastolic BP, mmHg | 65 | 60, 74 | 87 | 63.5 | 60, 77.5 | 16 | 0.993 |
| Systolic BP, mmHg | 110 | 100, 120 | 87 | 112 | 110, 124 | 16 | 0.306 |
| Plasma glucose, mmol/L | 4.2 | 3.7, 4.9 | 121 | 5 | 4.5, 7.3 | 15 | 0.004*** |
| Protein/creat, mg/mmol | 11.8 | 8.6, 15.7 | 112 | 19.4 | 10.9, 34.6 | 13 | 0.035** |
| Albumin/creat, mg/mmol | 1 | 0.7, 1.6 | 114 | 2.5 | 1.3, 3.1 | 13 | 0.004*** |

Mann–Whitney Rank Sum test; **p ≤ 0.05, ***p ≤ 0.01. Data are from 68 women with uncomplicated pregnancies and 10 with gestational diabetes. Maternal age and BMI (from height and self-reported pre-pregnancy weight) were recorded at enrolment; all other maternal parameters include data from all pregnancy visits. BMI, Body Mass Index; BP, Blood Pressure; creat, Creatinine; GA, Gestational Age.
Discussion

Given the substantial evidence linking adverse intrauterine and early infancy events with poorer health over the course of life, the importance of prioritising the health of women of childbearing age and mothers of young children is critical for closing the gap in life-expectancy between Indigenous and non-Indigenous Australians. This study aimed to determine antenatal maternal factors associated with the delivery of preterm and low birth weight babies and pregnancy complications (e.g., gestational diabetes and hypertensive disorders of pregnancy) in Indigenous Australian women. This study of the Gomeroi gaaynggal cohort has demonstrated that several key factors influence pregnancy outcomes in this population. These include maternal obesity, exposure to cigarette smoke and the existence of underlying renal impairment.

It is known that Indigenous women give birth at significantly younger ages compared with their non-Indigenous counterparts. Studies report that almost half of Indigenous women deliver before the age of 25 [13]. This study is in line with these findings with a median age (at enrolment) of 24.5 years with many women also having had previous pregnancies. In contrast to previous reports [14] we found no difference in maternal age between our women with uncomplicated pregnancies and those with complicated pregnancies; this suggests that a younger maternal age is unlikely to have contributed to the poor perinatal outcomes seen in this cohort.

Almost half of the women in the study (43%) reported smoking cigarettes during their pregnancy; this is reflected in the prevalence of detectable cotinine levels (51.5%). This is similar to other Indigenous Australians around the country [3,13]. As reported previously [13,15], exposure to cigarette smoke (as measured by serum cotinine) was associated with preterm birth (Table 3) with the mothers delivering preterm having significantly higher levels of cotinine than controls. Unfortunately, despite efforts to promote smoking cessation in Indigenous pregnant women, all tested intervention programs have, to date, been unsuccessful [16]. Clearly this is one area that needs to be improved, and more needs to be done in consultation with Indigenous people to influence the rates of smoking in Aboriginal and Torres Strait Islander communities.

Elevated BMI is a known risk factor for a number of pregnancy complications including preeclampsia and GDM [17]. Almost 60% of the women in the Gomeroi gaaynggal cohort were overweight, obese or morbidly obese (>25 kg/m²) according to self-reported pre-pregnancy weight and height, and 6.3% of women developed gestational diabetes. This is very similar to previous studies but higher than that reported for non-Indigenous pregnant women, where 49% were overweight or obese and the prevalence of GDM was 3-5.5% [17-21]. Thrill and Callaway also reported that the prevalence of GDM, hypertensive disorders of pregnancy and high birth weight is associated with overweight or obesity in both Indigenous and non-Indigenous Australians, however the prevalence of preterm birth and hypertension in pregnancy was lower in overweight Indigenous women compared with non-Indigenous women [17]. There was no evidence for this in the current cohort, that is, the preterm, SGA, LGA and GDM mothers did not differ from those with uncomplicated pregnancies with respect to BMI and percentage body fat. This may be due to the low numbers in our pregnancy pathology groups as in an earlier publication on this cohort (n=123) we have demonstrated a significant positive correlation between maternal BMI and birth weight [15] as is seen in Indigenous and non-Indigenous Australians [17] and internationally [22]. Women with hypertensive disorders of pregnancy did, however, have higher BMIs and/or body fat percentages than women with uncomplicated pregnancies (Table 5).

The adverse impact of obesity and gestational diabetes is highlighted by the data showing that women with GDM had higher protein/creatinine and albumin/creatinine ratios in pregnancy, suggesting that these women also had renal damage. Women who develop GDM have a very high risk of developing type 2 diabetes post-partum, and Indigenous women experience the highest risk [23,24]. The high rates of renal impairment in this population of Australian Indigenous women (13.3%) suggests that they will be at high risk of renal damage should they subsequently develop diabetes. Developing interventions that improve maternal weight prior to conception that can influence pregnancy outcomes is critical, as are programs to prevent the development of type 2 diabetes and kidney disease.

The rates of preterm birth (13.9% vs. 12.7%) and SGA (14.6% vs. 14%) were similar to those reported for Indigenous Australians in urban New South Wales, Australia [13] and nationally but much higher than those of non-Indigenous Australian women (7.7% overall in 2012 [3]). Women delivering preterm had higher protein/creatinine and albumin/creatinine ratios compared with those with healthy pregnancy outcomes (Table 3). This may be due to either the higher prevalence of obesity or the higher rates of cigarette smoking in this cohort, as both obesity and cigarette smoking are known to cause the up-regulation of pro-inflammatory factors that can contribute to kidney damage [25]. We have previously demonstrated that analysis of a subset of women in this cohort showed significantly elevated levels of plasma C-reactive protein (CRP, a marker of inflammation) which was positively associated with maternal BMI and cotinine levels [15].

Perhaps the most surprising finding from the study is the male/female birth ratio of 1.38. This is very much higher than that reported for Australia in general and for Aboriginal and Torres Strait Islander people specifically (1.06; [26]). Deliberate action reflecting male preference and sex-selection during assisted reproduction [27] are unlikely to be responsible for the sex ratio imbalance seen in this Indigenous cohort. Natural causes of sex ratio imbalances could also be at play. In a comprehensive study of the sex ratio of Finnish babies born between 1865-2003 Helle et al. found that both environmental temperature and wars did increase male to female sex ratio but that famine and economic stress were not factors [28]. At this time, it is unclear however why there are more males born in this cohort since this study is reporting on a relatively small number of births (170 babies where the sex is known) but it may be that those environmental factors that distort the male to female sex ratio are operating within this Australian Indigenous community.

It is well described that rates of preterm birth are significantly higher in male infants [29,30]. The incidence was exceptionally high in our cohort; 20/23 preterm and 5/6 SGA infants were male. Thus these infants are already at high risk of neonatal death. Indeed, 30% of all male infants were admitted to NICU while only 22% of female babies were. Helle et al. however found no association between annual birth sex ratio and annual sex biased infant mortality [28]. We await data for much larger numbers in this cohort to make firm conclusions.

Conclusion

Analysis of the birth outcomes from the first 227 women in the Gomeroi gaaynggal cohort demonstrates that infants born from this cohort are at significantly greater risk of chronic disease development later in life, because they are born preterm or SGA. The very high rate of preterm male infants suggests that they are particularly vulnerable. Since this preliminary study has shown that there is a high prevalence of adverse maternal factors that adversely influence pregnancy outcome,
focus should be directed towards the introduction of programs that directly target maternal health during and prior to pregnancy such as weight reduction, early monitoring of plasma glucose levels and of albumin/creatinine ratios.

References
1. Barker DJ, Gluckman PD, Godfrey KM, Harding JE, Owens JA, et al. (1993) Fetal nutrition and cardiovascular disease in adult life. Lancet 341: 938-941.
2. Barker DJ (2012) Sir Richard Doll Lecture. Developmental origins of chronic disease. Public Health 126: 185-189.
3. Hilder L, Zhichao Z, Parker M, Jahan S, Chambers GM (2014) Australia's mothers and babies 2012. Perinatal statistics series 30: 69.
4. Hoy WE, Rees M, Kile E, Mathews JD, McCredie DA, et al. (1998) Low birthweight and renal disease in Australian aborigines. Lancet 352: 1826-1827.
5. Hoy WE, White AV, Tipiloura B, Singh GR, Sharma S, et al. (2014) The influence of birth weight, past post streptococcal glomerulonephritis and current body mass index on levels of albuminuria in young adults: the multi-determinant model of renal disease in a remote Australian Aboriginal population with high rates of renal disease and renal failure. Nephrol Dial Transplant 0: 1-7.
6. Hoy WE, Nicol JL (2010) Birthweight and natural deaths in a remote Australian Aboriginal community. Med J Aust 192: 14-19.
7. Kandasamy Y, Smith R, Wright IM, Lumbers ER (2014) Reduced nephron endowment in the neonates of Indigenous Australian peoples. J Dev Orig Health Dis 5: 31-35.
8. Luyckx VA, Bertram JF, Brenner BM, Fall C, Hoy WE, et al. (2013) Effect of fetal and child health development and long-term risk of hypertension and kidney disease. Lancet 382: 273-283.
9. Tamworth Regional Council. Tamworth Regional Council: SEIFA and disadvantage Tamworth: Tamworth Regional Council 2015.
10. Australian Bureau of Statistics. SEIFA by Local Government Area 2015.
11. Moscovis SM, Hall ST, Burns CJ, Scott RJ, Blackwell CC (2014) The male excess in sudden infant deaths. Innate Immun 20: 24-29.
12. Gardosi J, Mongelli M, Wilcox M, Chang A (1995) An adjustable fetal weight standard. Ultrasound Obstet Gynecol 6: 168-174.
13. Kildea S, Stapleton H, Murphy R, Kosiak M, Gibbons K (2013) The maternal and neonatal outcomes for an urban Indigenous population compared with their non-Indigenous counterparts and a trend analysis over four triennia. BMC Pregnancy and Childbirth 13: 167.
14. Muglia LJ, Katz M (2010) The enigma of spontaneous preterm birth. N Engl J Med 362: 529-535.
15. Pringle KG, Rae K, Weatherall L, Hall S, Burns C, et al. (2015) Effects of maternal inflammation and exposure to cigarette smoke on birth weight and delivery of preterm babies in a cohort of Indigenous Australian women. Front Immunol 6: 89.
16. Passey ME, Sanson-Fisher RW. Provision of antenatal smoking cessation support: a survey with pregnant Aboriginal and Torres Strait Islander Women. Nicotine Tob Res 17: 746-749.
17. Thrift AP, Callaway LK (2014) The effect of obesity on pregnancy outcomes among Australian Indigenous and non-Indigenous women. Med J Aust 201: 592-595.
18. Chamberlain C, Banks E, Joshy G, Olfert D, Oats JJ, et al. (2014) Prevalence of gestational diabetes mellitus among Indigenous women and comparison with non-Indigenous Australian women: 1990-2009. Aust N Z J Obstet Gynaecol 54: 433-440.
19. Ishak M, Petocz P (2003) Gestational diabetes among Aboriginal Australians: prevalence, time trend, and comparisons with non-Aboriginal Australians. Ethn Dis 13: 55-60.
20. Stone CA, McLachlan KA, Halliday JL, Wein P, Tippett C (2002) Gestational diabetes in Victoria in 1996: incidence, risk factors and outcomes. Med J Aust 177: 486-491.
21. Anna V, van der Ploeg HP, Cheung NW, Huxley RR, Bauman AE (2008) Sociodemographic correlates of the increasing trend in prevalence of gestational diabetes mellitus in a large population of women between 1995 and 2005. Diabetes Care 31: 2286-2293.
22. Yu Z, Han S, Zhu J, Sun X, Ji C, et al. (2013) Pre-pregnancy body mass index in relation to infant birth weight and offspring overweight/obesity: a systematic review and meta-analysis. PLoS One 8: e61627.
23. Yue DK, Molynieux LM, Ross GP, Constantinou MI, Child AG, et al. (1996) Why does ethnicity affect prevalence of gestational diabetes? The underwater volcano theory. Diabet Med 13: 748-752.
24. Kim C, Newton KM, Knopp RH (2002) Gestational diabetes mellitus among Australian Indigenous and non-Aboriginal Australians: 1990-2009. Aust N Z J Obstet Gynaecol 42: 592-595.
25. Chalmers L, Kaskel FJ, Bamgboya O (2006) The role of obesity and its bioclinical correlates in the progression of chronic kidney disease. Adv Chronic Kidney Dis 13: 352-364.
26. Australian Bureau of Statistics. Estimates and projections, Aboriginal and Torres Strait Islander Australians.
27. Report on the international workshop on skewed sex ratios at birth: addressing the issue and the way forward. United Nations Population Fund, 2011.
28. Helle S, Helama S, Lertola K (2009) Evolutionary ecology of human birth sex ratio under the compound influence of climate change, famine, economic crises and wars. J Anim Ecol 78: 1226-1233.
29. Zeillinger J, Saurel-Cubizolles MJ, De Mouzon J, Rivera L, Ancel PY, et al. (2002) Fetal sex and preterm birth: are males at greater risk? Hum Reprod 17: 2762-2768.
30. Vatten LJ, Skjærven R (2004) Offspring sex and pregnancy outcome by length of gestation. Early Hum Dev 76: 47-54.