Title

Profile of severely growth restricted births undelivered at 40 weeks in Western Australia

Short title: Profile: very growth restricted births

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Acknowledgements

We would like to acknowledge the Data Linkage Branch (Western Australian Government Department of Health), the custodians of the Midwives' Notification System, Birth and Death Registries, Hospital Morbidity Data Collection and Western Australian Register of Developmental Anomalies for providing data for this project. In particular, we acknowledge Dr Rosi Katich, Senior Coding Consultant, WA Clinical Coding Authority (WA Department of Health) who advised us on the International Classification of Diseases-10-AM classification in relation to the neonatal adverse outcome index. We also acknowledge Dr Samantha Lain, Children's Hospital at Westmead Clinical School, University of Sydney, who developed the neonatal adverse outcome index and provided advice about it.

Abstract

Purpose: To investigate the proportion of severely growth restricted singleton births <3rd percentile (proxy for severe fetal growth restriction; FGR) undelivered at 40 weeks (FGR_40), and compare maternal characteristics and outcomes of FGR_40 births and FGR births at 37-39 weeks' (FGR_37-39) to those not born small-for-gestational-age at term (Not SGA_37+).

Methods: The annual rates of singleton FGR_40 births from 2006-2015 were calculated using data from linked Western Australian population health datasets. Using 2013-2015 data, maternal factors associated with FGR births were investigated using multinomial logistic regression to estimate odds ratios (OR) with 95% confidence intervals (CI) while relative risks (RR) of birth outcomes between each group were calculated using Poisson regression. Neonatal adverse outcomes were identified using a published composite indicator (diagnoses, procedures and other factors).

Results: The rate of singleton FGR_40 births decreased by 23.0% between 2006 and 2015. Factors strongly associated with FGR_40 and FGR_37-39 births compared to not SGA_37+ births included the mother being primiparous (ORs 3.13: 95% CI 2.59–3.79; 1.69, 95% CI 1.47, 1.94 respectively) and ante-natal smoking (ORs 2.55, 95% CI 1.97, 3.32; 4.48, 95% CI 3.74,5.36 respectively). FGR_40 and FGR_37-39 infants were more likely to have a neonatal adverse outcome (RRs 1.70, 95% CI 1.41, 2.06 and 2.46 95% CI 2.18, 2.46 respectively) compared to Not SGA 37+ infants.

Conclusions:

Higher levels of poor perinatal outcomes among FGR births highlight the importance of appropriate management including fetal growth monitoring. Regular population-level monitoring of FGR_40 rates may lead to reduced numbers of poor outcomes.

Key words

Infant, Small for gestational age; Fetal growth restriction; Perinatal mortality; Western Australia;

Abbreviations

CI	Confidence interval
LHT	Linear Hypothesis test
MNS	Midwives Notification System
Not SGA 37+	Birth at 37 or more weeks' gestation without SGA
OR	Odds ratio
RCOG	Royal College of Obstetricians and Gynaecologists
RR	Relative risk
SGA	Small-for-gestational-age
FGR	Fetal growth restriction (<3rd percentile)
FGR_37-39	Severely growth restricted birth delivered at 37-39 weeks' gestation
FGR_40	Severely growth restricted birth undelivered at 40 weeks' gestation

Introduction

Being born small for gestational age (SGA), defined as birthweight for gestation and sex < 10th percentile, is associated with poor outcomes such as perinatal death [1] and neonatal morbidity [2]. These early life outcomes are more likely when SGA is undetected before birth [1,3], in cases of SGA below the 3rd percentile which can be used as a proxy for severe fetal growth restriction (FGR;) [4] and with advancing gestational age [5]. SGA is also associated with later sequelae including neurodevelopmental delay [6], coronary heart disease and type 2 diabetes [7]. However, ante-natal detection of SGA remains problematic, and the majority of SGA cases are detected at birth [8], even when maternal medical and/or obstetric risk factors are present [9]. While the sensitivity to detect FGR in late third trimester ultrasounds at around 35 weeks are higher than to detect SGA, up to a quarter of cases may still be missed by the best performing index tests (estimated fetal weight and abdominal circumference both <1 standard deviation) [10].

SGA births can be divided into two main groups: those who are truly growth restricted, who have an increased risk of poor outcomes [11] and constitutionally small babies (approximately 20% of all SGA births) [12]. Risk factors for fetal growth restriction include those that can be identified at the ante-natal booking appointment (e.g. maternal age of 35 years or more, primiparity, extremes of body mass index, smoking, and chronic diseases), while others manifest during the pregnancy such as pre-eclampsia and ante-partum haemorrhage [13]. On the other hand, being constitutionally small is associated with maternal small stature and ethnicity [14].

A recent comparison of different national guidelines found that although there are some variations, once SGA is identified, delivery is universally recommended by 40 weeks' gestation [12]. In line with these recommendations and the existing evidence on the health

consequences for babies with FGR, the proportion of FGR below the 3rd percentile singleton births of at least 32 weeks gestation that were undelivered at 40 weeks (FGR_40) was adopted as a health system performance indicator of the quality of ante-natal care in Victoria, Australia in 2010 with a goal of <28.6% for each hospital [15]. Since then, the proportion has decreased from nearly 40% [16] to 28% state-wide by 2018 [17]. The importance of this measure has now been recognised with its inclusion as a key performance indicator to improve detection and management of FGR in the recently released 'Safer Baby Bundle', an Australia wide initiative to reduce stillbirth by 20% [18]. To our knowledge, no other Australian jurisdiction has published data about FGR_40 trends, or the associated risk factors and health outcomes. Accordingly, the first objective of this study was to investigate trends in the proportion of FGR births undelivered at 40 weeks' gestation in Western Australia (WA) in the ten-year period from 2006-2015. This period was chosen to observe practice prior to and after the introduction of the performance indicator elsewhere in Australia. Using the most recent years of data (2013-2015) to best reflect current practice, the second objective was to investigate the differences between FGR births undelivered at 40 weeks' gestation and those delivered at 37-39 weeks' gestation (FGR_37-39). To do this we compared the profile of maternal and other characteristics of both groups of severely growth restricted singletons (FGR_40 and FGR_37-39) and their outcomes with those born without SGA.

Methods

Study design and population

This study included all singleton births in WA from 2006 to 2015. For the first objective of the study, the cohort consisted of all births with a gestation of at least 32 weeks (to allow for direct comparison with the Victorian findings [16]) who were born FGR (SGA below the 3rd percentile), between 2006 and 2015. For the second objective, the cohort consisted of births

between 2013 and 2015 with a gestation of at least 37 weeks, divided into three groups: (1) FGR_40 (FGR undelivered at 40 weeks); (2) FGR_37-39 (FGR births at 37-39 weeks); and (3) those born who were not SGA at 37 weeks or later (Not SGA 37+) (Figure 1). Those with SGA, but not FGR (3rd to under 10th percentile) were excluded from the analyses.

Data sources

The data for this study were obtained from population health datasets including those which are routinely linked by the Data Linkage Branch of the Western Australian Department of Health. This includes the Midwives Notification System (MNS), Birth and Death Registers, Hospital Morbidity Data Collection as well as the Western Australian Register of Developmental Anomalies. The Data Linkage Branch uses probabilistic matching techniques [19] and provides data with identifying fields removed for researchers. The MNS contains information about all live births and stillbirths of at least 20 weeks' gestation in WA while the Hospital Morbidity Data Collection has information about all inpatient episodes in public and private hospitals in WA. The Western Australian Register of Developmental Anomalies contains information based on statutory notification of congenital anomalies diagnosed before the age of six years in WA.

Ethics approvals

Ethics approvals were obtained from the Western Australian Department of Health Human Ethics Research Committee (2016/51) and the Western Australian Aboriginal Health Ethics Committee (797).

Data management

Definition of FGR and SGA

Australian sex-specific national singleton birthweight centiles [20], which only take in account sex and gestation, were used to assign the appropriateness of growth for gestation into FGR, SGA and not SGA.

Maternal and other factors

Variables from the MNS were categorised into yes/no as follows: any smoking during pregnancy, primiparous, remote or very remote birth residence [21], and late ante-natal booking appointment (later than 10 weeks' gestation) [22]. Remoteness of residence was assessed using the Accessibility/Remoteness Index of Australia based on the mother's usual residence at the time of the child's birth, and includes five categories that range from none (Perth metropolitan area) through to very remote. Three categories were created for an area-based measure of socio-economic status of the birth residence [23], maternal age at birth (<25, 25-34 and >34 years), body mass index at the ante-natal booking appointment (<18.5, 18.5 <25, 25<30 and ≥30), tertiles of maternal height (<162, 162-167, >167 cm) and inter-pregnancy interval (IPI), based on those below and above the referent group in the IPI literature studies[24,25] (<18 18-23, and >23 months). Socio-economic status tertiles were based on the WA distribution of small area (average population 400) values of the Index of Relative Socio-Economic Disadvantage, generated from data collected in the 2011 Census [23]. This index ranks areas using the attributes of all persons in the area, including measures of education, income, unemployment, family status and housing. Women were classified as having the following medical conditions (pre-existing diabetes, essential hypertension) or pregnancy complications (threatened miscarriage, gestational diabetes or hypertension, pre-eclampsia, any ante-partum haemorrhage) if they were recorded in the MNS or as a principal or additional diagnosis in the Hospital Morbidity Data Collection (available from 1970) in any admission prior to birth (medical conditions) or during pregnancy (pregnancy complications)

(see Table S1 for International Classification of Diseases diagnosis codes). Further, all births to the same mother in the MNS were linked using the unique mother identifier, enabling us to ascertain these conditions and complications in all earlier pregnancies. This also supported the calculation of inter-pregnancy interval (IPI)—which was defined as the difference between the time between a birth and the estimated conception date for the subsequent pregnancy. History of these and adverse outcome variables in previous pregnancies identified in MNS were also created for multiparous women. If the woman was nulliparous at the time of her first recorded birth, it was assumed that we had the complete history of all previous pregnancies.

We created a composite variable, using a cross-classification of region of birth and ethnicity. Firstly, maternal country of birth (obtained from the Birth Register) was grouped into major regions, according to the Standard Australian Classification of Countries Table 1 [26]. In the MNS, maternal ethnic origins were classified into eight groups (Caucasian, Aboriginal and/or Torres Strait Islander (hereafter Aboriginal), Asian, Indian, African, Polynesian, Maori and Other). Finally, maternal region of birth and ethnic origin were combined into a single variable with three levels for Australian born (Caucasian, Aboriginal, Other) and 10 levels for Overseas-born (Oceania not Australia, North-West Europe, Southern and Eastern Europe, North Africa and the Middle East, South-East Asia, North-East Asia, Southern and Central Asia, Americas, and Sub-Saharan Africa). Groups where there were two ethnic groups who made up at least 30% of the region's population each (Oceania other than Australia, Sub-Saharan Africa) were divided into Caucasian/non-Caucasian (Table S2).

Data were available for the majority of the risk factors for having a SGA fetus listed in the Royal College of Obstetricians and Gynaecologists (RCOG) guidelines[13] although maternal and paternal SGA were restricted to 38% of mothers and 28% of fathers who also had records

in the MNS (i.e. born in WA in 1980 or later) (Table S3). As these guidelines recommend that all women with at least one major or three minor risk factor(s) at the booking appointment or later are screened for fetal growth, we created a binary variable to identify these pregnancies.

Birth outcomes

Mode of birth was categorised into spontaneous vaginal, instrumental vaginal, elective and emergency caesarean section. Elective caesarean section was defined as a planned procedure with no onset of labour, attempted induction or ruptured membranes, and emergency caesarean section as a procedure performed at short notice, including those performed because of a complication, ruptured membranes, or onset of labour before the planned time of the elective procedure. Onset of labour was categorised as spontaneous, induced, and prelabour caesarean section. Stillbirths and deaths in the neonatal period and first six months of life were identified using data from the MNS and Death Register. As the overall numbers were small, these were combined into a single 'early loss' variable (stillbirth or death in first six months). A neonatal adverse outcome was identified using a previously published composite indicator [27] (Table 1) which used the Hospital Morbidity Data Collection diagnosis and procedure codes as well as the MNS and Death Register data. Modifications were made to reflect coding changes with assistance of the WA Clinical Coding Authority (Table S4). The other indicators of adverse outcomes were low Apgar (five-minute Apgar score below seven) and any resuscitation at birth (any use of oxygen, bag and mask, intubation, external cardiac massage or drugs).

Statistical Analyses

The annual rate of FGR singleton births undelivered at 40 weeks' gestation was calculated using all FGR singleton births of at least 32 weeks' gestation as the denominator [15] and the

presence of a linear trend by year was assessed using the Cochran-Armitage trend test [28,29].

The following analyses were conducted using SAS version 9.4, (SAS Institute Inc, Cary, NC, USA), and featured a comparison of both FGR_40 and FGR_37-39 births to Not SGA 37+ births. Multinominal logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) of maternal factors associated with the two categories of FGR. Factors associated with FGR in the univariable models were included in a multivariable model. Linear hypothesis testing (LHT), which calculates Wald Chi-square *P* values, was used to detect differences (if any) between the adjusted ORs for FGR_40 and FGR_37-39. In addition, we tested for effect modification by primiparous status, and if present, stratified analyses were performed. The regression models to estimate ORs and 95% CI for the composite indicator of RCOG risk factors were adjusted for factors associated with FGR which were not already included in the index (maternal height and the composite maternal region of birth/ethnicity). Unadjusted relative risks (RR) of birth outcomes comparing FGR_40 and FGR_37-39 births to Not SGA 37+ births were calculated using Poisson regression with robust error variance [30].

Sensitivity analyses

Sensitivity analyses were carried out to assess the impact of missing data on parental SGA (which was used to create the composite indicator of RCOG risk factors). We created a second version of the RCOG indictor (not including parental SGA) and compared the output from models using each version.

Results

Objective 1: Rate of FGR births undelivered at 40 weeks.

Between 2006 and 2015, there were 322,552 live births and stillbirths, of which 311,486 were singletons for whom appropriateness of growth for gestational age could be estimated (Figure

1). Among the 307,442 births with a gestation of at least 32 weeks, there were 6,855 singleton births (2.2%) with FGR. Among these births, the rate of births undelivered at 40 weeks' gestation decreased by 23.0% from 40.2% in 2006 to 30.9% in 2015 (*P* trend <0.01) (Figure 2). Concurrently, the rate of singleton FGR births at 37-39 weeks' gestation increased by 19.9%—from 50.8% to 61.0% (*P* trend <0.01)—with little change in the rates of births at 32-36 weeks gestation (a decrease from 9.0% to 8.1%, *P* trend 0.66; results not otherwise shown). The comparable rate for singleton births without SGA decreased by 10.6%, from 36.1% to 32.3% (*P* trend <0.01; results not otherwise shown). Between 2013-2015 (the years of interest for Objective 2), the rates of FGR singleton births undelivered at 40 weeks' gestation decreased from 35.5% to 30.9%.

Objective 2: Factors associated with, and outcomes of, FGR births undelivered at 40 weeks.

Between 2013-2015, there were 92,532 singleton births with a gestation of at least 37 weeks. Of these, 696 were FGR_40 (0.8%), 1,208 FGR_37-39 (1.3%), 84,918 Not SGA 37+ (91.8%), and 5710 had SGA but not FGR (6.2%) and were excluded from the analyses (Figure 1). The complete histories of all previous pregnancies were available for 187 (80.6%) FGR_40, for 455 (82.0%) FGR_37-39 and 42,391 (85.1%) Not SGA 37+ singleton births of multiparous women.

Risk factors for FGR births

In the multinomial multivariable analysis, compared to Not SGA 37+ births, the factors strongly associated with both FGR_40 and FGR_37-39 births were: the mother being primiparous, a smoker during pregnancy, non-Australian born, particularly born in Sub-Saharan African (non-Caucasians), Southern and Central Asia and North Africa and the Middle East, being underweight and less than 162 cm tall (Table 2). For example, relative to women who did not smoke during pregnancy, the odds of having a FGR_40 and FGR_37-39 birth

among those who smoked was 2.6 and 4.5 times higher, respectively, compared with Not SGA 37+ births (LHT *P* <0.01).

Having gestational diabetes was negatively associated with an FGR_40 birth but positively associated with a FGR_37-39 birth (LHT *P* <0.01) (Table 2). The following factors were only positively associated with FGR_37-39 births: having a major congenital anomaly, a mother aged >34 years, experiencing a pregnancy complication (threatened miscarriage, pre-eclampsia, gestational hypertension) and living in the most disadvantaged area (tertile). Further, there was a negative association between having a maternal body mass index of 30 or more and a FGR_37-39 birth. There were no or few cases of pre-existing diabetes and essential hypertension among mothers of FGR births and neither were included in the multivariable models. The univariable ORs for the full list of factors investigated are reported in Table S5.

Smoking during pregnancy was the only factor where there was effect modification by primiparous status and the association appeared stronger in multiparous than primiparous women (FGR_40: OR 3.80, 95% CI 2.50, 5.77 and 1.69, 95% CI 1.17, 2.45, respectively; interaction *P* <0.01; FGR_37-39: OR 4.19, 95% CI 3.19, 5.50 and 3.53, 95% CI 2.71, 4.60, respectively; interaction *P* =0.01) (results not otherwise shown).

Risk factors for FGR births among multiparous women

Women with a previous FGR birth or with an IPI of 24 months or greater had elevated risks of FGR_40 and FGR_37-39 births while there was a marginal association between a neonatal adverse outcome for a previous birth and FGR_37-39 (Table 2).

Compared with mothers who had a non-SGA 37+ birth, mothers who had a FGR_40 or FGR_37-39 birth were more likely to have at least 1 major or 3 minor RCOG risk factors for SGA births (OR 1.42, 95% CI 1.21, 1.65 and 2.34, 95% CI 2.07, 2.65 respectively, LHT *P* <0.01)

(results not otherwise shown), although these risk factors were prevalent in all three groups (43.6%, 51.7% and 63.8% of Not SGA 37+, FGR_40 and FGR_37-39 births respectively) (Table S3). These estimates remained similar when parental SGA history was excluded from the list of risk factors.

Birth outcomes

There was a greater likelihood of induction for both FGR_40 and FGR_37-39 births compared with Not SGA 37+ births. Whereas the onset of labour FGR_40 births was more likely to be spontaneous than FGR_37-39 births. Further, FGR_40 births were considerably less likely to have a prelabour caesarean than other births. Compared with Not SGA 37+ births, both FGR_40 and FGR_37-39 births were more likely to be by emergency caesarean section, but less likely to be by elective caesarean section while FGR_40 births were more likely to be by instrumental vaginal delivery (Table 3). While the estimates for early loss were imprecise, it was more likely among the FGR_40 births and FGR_37-39 births compared with Not SGA 37+ births (Table 3). All indicators of neonatal morbidity (an adverse neonatal outcome, a low five-minute Apgar or any resuscitation) were also more likely among the FGR_40 births and FGR_37-39 births compared with Not SGA 37+ births, while FGR_40 births had lower levels of adverse neonatal outcomes than FGR_37-39 births (Table 3).

Discussion

Principal findings

From 2006-2015 in WA, the rate of FGR birth undelivered at 40 weeks' gestation declined by about 23%, while the comparable rate among births without SGA decreased by around 11%. Our findings, based on population-based data, confirm previously known risk factors for SGA [13] as well as those associated with having a small but healthy baby [14]. Mothers of FGR births were more likely to have smoked during pregnancy and be primiparous, with FGR_37-

39 mothers the most likely to have smoked, but FGR_40 mothers the most likely to be primiparous. In addition, we found that even after adjusting for maternal height and body mass index, non-Australian born mothers were more likely to have a FGR birth than Australian-born Caucasian women, with the strength of association varying by region of birth. Importantly, among the FGR births, we found evidence of a risk gradient with the prevalence of having at least one major or three minor RCOG risks factors being highest among FGR births delivered at 37-39 weeks' gestation and lowest among terms births without SGA. Similarly, while all the FGR births were at higher risk of having a neonatal adverse outcome or being stillborn or dying in the first six months of life, the risk was highest in those born at 37-39 weeks' gestation, although the estimates for mortality were imprecise. FGR_40 births were the least likely to have some form of intervention to precipitate birth (induction or prelabour caesarean section) indicating problems were not foreseen but, by contrast, they appear to have had the highest level of labour or delivery complications for mother or fetus (highest risk of instrumental vaginal delivery or emergency caesarean section).

Strengths of the study

The strength of this study is the use of total population birth data, free from the issues of selection and non-participation biases and reflects practices state-wide, including in hospitals less likely to be involved in research. The study was also supplemented with multiple data sources which enabled the tracking of women and babies who were transferred across the health system, often for higher level care. The use of hospital discharge data enabled both the identification of additional cases of maternal medical conditions and pregnancy complications and the application of a validated neonatal morbidity index to more common outcomes than early mortality. Similarly, combining the MNS maternal ethnicity and Birth

Register maternal country of birth data allowed more nuanced analyses than using the individual data items.

Limitations of the data

Routinely collected data sources typically do not have detailed information on all key factors of interest. In our study, there was no information about whether FGR was suspected, or the conduct and results of relevant screening, e.g. PAPP-A levels, uterine Doppler velocimetry assessments or third trimester ultrasounds. This is an important limitation as failure to receive an indicated third trimester ultrasound or having one with falsely reassuring findings were some of the main factors associated with having a FGR_40 birth in a recent Victorian study [31]. We also did not have data about the indications for induction or caesarean sections or cause of death. Additionally, there has been some modification of clinical protocols over the time-periods of interest and uncertainty about how they influenced practice. Care was provided in both the private and public sector and the births occurred at over 60 different sites so it is likely there would have been variations by time and place. There are limitations with the classification of maternal chronic conditions and pregnancy complications in the MNS, with low sensitivity noted [32], but these were supplemented with the Hospital Morbidity Data Collection diagnosis codes which increased their prevalence. Nevertheless, while the overall prevalence of maternal pre-existing diabetes and essential hypertension remained low (0.8% and 1.1% respectively), they are in line with the reported prevalence in the National Health Survey 2014-2015 [33] for women under 35 years (the age of about 80% of study mothers). While we had data in the MNS from 1980 and the Hospital Morbidity Data Collection from 1970 for women resident in WA, we did not have data from other women. Thus, we may have underestimated chronic conditions and history of pregnancy complications, especially in women born outside WA. In particular, we only had information

about parental SGA for the small sample (>40%) of parents born in WA since 1980. Despite this concern with completeness, responses are likely to be more accurate than self-reported information on the historical medical history.

Interpretation

The rate of FGR births undelivered at 40 weeks' gestation fell from 40.2% in 2006 to 30.9% in 2015. This parallels the trend seen in Victoria, which annually publishes rates at individual hospitals and where the target of <28.6% [15] was surpassed in the 2017-2018 report [17]. However, it is not clear how much of the reduction has been due to careful monitoring to better identify and manage FGR pregnancies in WA or whether it reflects the general trend for earlier births given the comparable rate in non-FGR births was only slightly (1.4 percentage points) higher in 2015. The reasons for this trend towards earlier term births, which is an Australia wide trend [34], are unclear. Among term births without SGA in WA over this time period, there were small increases in the rates of medically initiated births and emergency caesarean section but no change in elective caesarean section rates or in the proportion of births that occurred in the private sector, a factor that may be associated with earlier births and more intervention [35]. We note that half of the reduction in FGR_40 occurred since 2013, which coincides with the release of both the RCOG guidelines [13] and a similar quality indicator (proportion of births at 40 weeks or later with a birthweight of <2750g) by both the Australasian Council on Health Care Standards [36] and the Australian Institute of Health and Welfare [37]—implicating better management of FGR as the primary driver of FGR_40 reductions.[18].

We did not find any specific factors that were only associated with FGR_40 which highlights the difficulty in ante-natal screening for SGA. However, the differences between the FGR groups provide some insight into factors that are associated with detection or non-detection

of FGR. Although we do not have direct evidence of early detection of FGR, we have the indirect evidence of higher levels of intervention (induction or prelabour caesarean section) among the FGR_37-39 group. While the presence of major congenital anomalies, maternal underweight, smoking, pregnancy complications or residence in a low socio-economic status area may be associated with detection, primiparity may be associated with non-detection. Although primiparity is classed as a minor risk factor for SGA in the RCOG guidelines [13] it is listed as having the highest point estimate of all minor risk factors, apart from low fruit intake pre-pregnancy (for which we do not have data). This and our finding suggest that further clinical protocols consider recommending SGA screening among primiparous women with only one other minor risk factor.

It is notable that nearly half of the mothers with an FGR_40 birth were born outside Australia which raises the key issue of how to distinguish between pathological fetal growth restriction and being small for physiological reasons such as maternal ethnicity and anthropometric measures. We chose to define FGR and SGA based on national birthweight centiles [20] developed from all singleton births in Australia from 1998-2007, which did not take into account maternal characteristics such as height, parity or ethnicity. The use of customised birthweight centiles may have resulted in fewer births to mothers born in Sub-Saharan Africa, Southern and Central Asia and North Africa and the Middle East being classified as FGR, but opinion remains divided about the optimal growth centiles [38,39] with equal numbers of national guidelines for management of SGA pregnancies recommending the use of population centiles (Canada, France and US) and customised centiles (Ireland, New Zealand and United Kingdom) [12]. However, an assumption cannot be made that all the FGR_40 births to women born outside Australia were small but healthy. Higher risks of stillbirth among certain ethnic groups have previously been reported, including in Australia [40-43], UK,[44,45], Sweden [46]

and elsewhere [43], specifically among Southern Asian [40-42], Middle Eastern [46], and Sub Saharan African [43], African [40], Black [45] or Afro-Caribbean women [44]. Importantly, there is evidence that the relative stillbirth rate among South Asian and East African women compared to Australian/New Zealand born women increases rapidly from 39 weeks [41] and that emergency caesarean section rates are higher among Southern Asian [47,44] and Afro-Caribbean women [44].

While the risk of FGR_40 birth was higher among non-Australian born mothers, any association among Aboriginal mothers was only found at the univariable level which may reflect the higher prevalence of other risk factors (such as smoking and underweight) in this group. In an unexpected finding, the risk of FGR_40 birth was higher among smokers who were multiparous than those who were primiparous—perhaps reflecting less opportunity to detect FGR due to less regular ante-natal care among multiparous women or that practitioners were less likely to intervene if the first birth was uneventful.

A positive finding from this study was the low levels of maternal chronic conditions and pregnancy complications among the mothers of FGR_40 births. This and the lower levels of RCOG risk factors and neonatal morbidity compared to FGR_37-39 births suggests that at least some with the most severe degree and/or highest risk of fetal growth restriction may have been appropriately identified and managed, resulting in birth prior to 40 weeks. For example, it appears that pregnancies complicated with gestational diabetes are being carefully monitored, so are rarely left undelivered at 40 weeks if there are any concerns about fetal growth, leading to a negative association with FGR_40 births but positive association with FGR_37-39 births. The challenge remains on how to identify those with relatively mild and late onset growth restriction who risk being undelivered with an aging placenta.

Conclusions

The higher levels of neonatal morbidity and early life mortality among FGR births undelivered at 40 weeks' gestation (compared to births without SGA) highlights the importance of management of these births, albeit the difficulties in their identification. While there has been a drop in rates in WA, experience in Victoria suggests that reporting at smaller geographical and health service levels allows for comparison between providers of peer maternity services [15,17] and leads to further reductions. Reporting may also detect over-zealous management leading to unnecessary early delivery of constitutionally small babies [48], which also have adverse consequences [49]. Therefore, the introduction of regular monitoring WA is recommended.

Author contributions

HD Bailey: Project development, Data management and analysis, Manuscript writing

AA Adane, BM Farrant, SW White, P Hardelid: Critical revision of the manuscript

CCJ Shepherd: Project development, Critical revision of the manuscript

All authors reviewed and approved the final version.

Figure legends

Figure 1: Study flow chart for investigation of severely growth restricted births undelivered at 40 in Western Australia, 2006-2015

Figure 2: Proportion of severely growth restricted singletons undelivered at 40 weeks' gestation in Western Australia (2006-2015)

Compliance with Ethical Standards

Funding

This research was supported by funding from an Australian National Health and Medical Research Council (NHMRC) Project Grant (GNT1127265) which funded AAA, HDB, BMF and

CCJS. Research at UCL Great Ormond Street Institute of Child Health is supported by the NIHR Great Ormond Street Hospital Biomedical Research Centre (PH).

Conflict of interest

All authors declare no competing interests.

Ethical Approval

All procedures performed were in accordance with the ethical standards of Western Australian Department of Health Human Ethics Research Committee and the Western Australian Aboriginal Health Ethics Committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent

Consent for the study was obtained from the data custodians. As the study was based on routinely collected anonymised population health data, individual consent from the participants was not obtained.

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Table 1: Components of the NSW composite neonatal adverse outcome indicator[a] used as indicator for neonatal morbidity

Conditions
Gestation <32 weeks
Very low birthweight
Death in the neonatal period or before discharge home
Respiratory Distress Syndrome
Seizure
Intraventricular haemorrhage, grades 2 - 4
Cerebral infarction
Periventricular leukomalacia
Specified birth trauma
Hypoxic ischemic encephalopathy
Necrotising enterocolitis
Broncho-pulmonary dysplasia, pneumonia and specified respiratory conditions
Specified sepsis/septicaemia
Procedures
Resuscitation
Ventilatory support
Central venous or arterial line, blood or blood products transfusion, intravenous fluids
Intercostal catheter for Pneumothorax
Specified surgical procedures

[a]From Lain SJ, Algert CS, Nassar N, Bowen JR, Roberts CL. Incidence of severe adverse neonatal outcomes: use of a composite indicator in a population cohort. *Matern Child Health J.* 2012;16(3):600-608. lease see paper for more details.

Table 2. Maternal and other factors associated with having a severely growth restricted singleton birth of 37 or more weeks' gestation in WA (2013-15).

	Not SGA 37+[a]		FGR_40				FGR_37-39				
					OR (95% CI)				OR (95% CI)		
	n	%	n	%	Unadjusted	Adjusted[b]	n	%	Unadjusted	Adjusted[b]	LHT P value[c]
	n= 84,918		n = 696				n=1,208				
Maternal age (years)											
<25	13,759	*16.2*	159	*22.8*	1.41 (1.18, 1.70)	0.94 (0.75, 1.18)	278	*23*	1.56 (1.36, 1.80)	0.91 (0.76, 1.09)	0.22
25-34	53,399	*62.9*	437	*62.8*	1.00 (Reference)	1.00 (Reference)	690	*57.1*	1.00 (Reference)	1.00 (Reference)	
>34	17,760	*20.9*	100	*14.4*	0.69 (0.55, 0.86)	0.95 (0.74, 1.22)	240	*19.9*	1.05 (0.90, 1.21)	1.31 (1.10, 1.55)	0.04
Booking appointment BMI											
<18.5	2,339	*2.8*	40	*5.7*	1.90 (1.37, 2.64)	1.73 (1.21, 2.46)	120	*9.9*	2.13 (1.87, 3.58)	2.86 (2.28, 3.58)	<0.01
18.5 <25	39,179	*46.1*	353	*50.7*	1.00 (Reference)	1.00 (Reference)	591	*48.9*	1.00 (Reference)	1.00 (Reference)	
25<30	22,681	*26.7*	142	*20.4*	0.70 (0.57, 0.85)	0.74 (0.60, 0.92)	269	*22.3*	0.79 (0.68, 0.91)	0.68 (0.58, 0.80)	0.90
≥30	16,584	*19.5*	107	*15.4*	0.72 (0.58, 0.89)	0.91 (0.72, 1.16)	145	*12*	0.58 (0.48,0.70)	0.41 (0.33, 0.50)	<0.01
Missing values[d]	4,135	*4.9*	54	*7.8*			83	*6.9*			
Maternal height (cm)											
<162	24,846	*29.3*	345	*49.6*	1.84 (1.55, 2.18)	1.88 (1.54, 2.29)	641	*53.1*	2.13 (1.87, 2.43)	2.09 (1.79, 2.44)	0.28
162-167	29,107	*34.3*	220	*31.6*	1.00 (Reference)	1.00 (Reference)	352	*29.1*	1.00 (Reference)		
>167	30,396	*35.8*	125	*18*	0.54 (0.44, 0.68)	0.59 (0.46, 0.76)	209	*17.3*	0.57 (0.48, 0.68)	0.57 (0.47, 0.70)	0.54
SES area birth residence tertiles											
Lowest	26,830	*31.6*	262	*37.6*	1.52 (1.25, 1.85)	1.09 (0.87, 1.36)	538	*44.5*	2.04 (1.75, 2.37)	1.41 (1.18, 1.67)	0.02
Middle	27,234	*32.1*	220	*31.6*	1.25 (1.02, 1.54)	1.09 (0.87, 1.36)	316	*27.2*	1.18 (1.00, 1.39)	1.06 (0.89, 1.27)	0.20
Highest	24,993	*29.4*	161	*23.1*	1.00 (Reference)	1.00 (Reference)	246	*20.4*	1.00 (Reference)	1.00 (Reference)	
Missing values[d]	5,861	*6.9*	53	*7.6*			108	*8.9*			
Primiparous	35,100	*41.3*	462	*66.4*	2.83 (2.41, 3.31)	3.13 (2.59, 3.79)	653	*54.1*	1.67 (1.49, 1.87)	1.69 (1.47,1.94)	<0.01
Ante-natal booking appointment >10 weeks GA	35,337	*41.6*	303	*43.5*	1.09 (0.94, 1.28)	1.06 (0.90, 1.26)	563	*46.6*	1.22 (1.08, 1.37)	1.19 (1.05, 1.36)	0.29
Missing values[d]	4,674	*5.5*	41	*5.9*			57	*4.7*			

Smoker during pregnancy	7,588	*8.9*	131	*18.8*	2.37 (1.96, 2.87)	2.55 (1.97, 3.32)	328	*27.2*	3.80 (3.34, 4.32)	4.48 (3.74, 5.36)	<0.01
Threatened miscarriage	7458	8.8	73	*10.5*	1.22 (0.96, 1.56)	1.19 (0.90, 1.58)	248	*20.5*	2.68 (2.33, 3.09)	2.78 (2.36, 3.28)	<0.01
Gestational diabetes	11,573	*13.6*	64	*9.2*	0.64 (0.50, 0.83)	0.56 (0.42, 0.75)	239	*19.8*	1.56 (1.36, 1.80)	1.45 (1.23, 1.71)	<0.01
Gestational hypertension	3,167	3.7	21	*3.0*	0.81 (0.52, 1.25)	0.87 (0.55, 1.37)	76	*6.3*	1.72 (1.36, 2.17)	1.45 (1.10, 1.90)	0.06
Pre-eclampsia	2,051	2.4	18	*2.6*	1.08 (0.67, 1.72)	1.04 (0.63, 1.73)	54	*4.5*	1.89 (1.43, 2.49)	1.83 (1.34, 2.50)	0.06
Major congenital anomaly	3,156	*3.7*	26	3.7	1.01 (0.68, 1.49)	0.93 (0.59, 1.48)	101	*8.4*	2.36 (1.92, 2.91)	2.30 (1.82, 2.92)	<0.01
Remote or very remote birth residence	5,380	*6.3*	61	*8.8*	1.42 (1.09, 1.85)	1.30 (0.92, 1.83)	111	*9.2*	1.52 (1.25, 1.85)	1.04 (0.80, 1.36)	0.32
Missing[d]	3,890	*4.6*	30	*4.3*			66	*5.5*			
Maternal region of birth and ethnic origins											
Australian-born											
Caucasian	45,584	53.7	280	40.2	1.00 (Reference)	1.00 (Reference)	476	39.4	1.00 (Reference)	1.00 (Reference)	
Aboriginal	3,629	*4.3*	59	*8.5*	2.65 (2.00, 3.51)	1.24 (0.82, 1.88)	135	11.2	3.56 (2.93, 4.33)	1.59 (1.21, 2.09)	0.16
Other	2,408	*2.8*	21	*3*	1.42 (0.91, 2.22)	1.16 (0.70, 1.90)	33	2.7	1.31 (0.92, 1.87)	1.01 (0.67, 1.53)	0.87
Born outside Australia[e]	33,133	*39*	334	*48.0*	1.64 (1.40, 1.93)	1.37 (1.13, 1.65)	552	45.7	1.60 (1.41, 1.81)	1.31 (1.13, 1.52)	0.64
Oceania (not Australia) Caucasian	2,477	*2.9*	16	*2.3*	1.05 (0.63, 1.74)	0.86 (0.47, 1.59)	23	1.9	0.89 (0.58, 1.35)	0.83 (0.51, 1.35)	0.91
Oceania (not Australia) non-Caucasian	1,788	*2.1*	13	*1.9*	1.18 (0.68, 2.07)	1.26 (0.68, 2.34)	27	2.2	1.45 (0.98, 2.14)	1.62 (1.06, 2.49)	0.35
North-West Europe	7,786	*9.2*	35	*5*	0.73 (0.52, 1.04)	0.70 (0.47, 1.03)	65	5.4	0.80 (0.62, 1.04)	0.76 (0.56, 1.03)	0.46
Southern & Eastern Europe	1,471	*1.7*	<12[f]	*<1.7*[f]	1.22 (0.67, 2.23)	1.26 (0.66, 2.39)	24	2	1.56 (1.03, 1.36)	1.59 (1.02, 2.48)	0.39
North Africa & Middle East	1,754	*2.1*	22	*3.2*	2.04 (1.32, 3.16)	2.33 (1.46, 3.72)	34	2.8	1.86 (1.31, 2.64)	2.06 (1.40, 3.02)	0.89
South-East Asia	5,263	*6.2*	56	*8*	1.73 (1.30, 2.31)	1.13 (0.80, 1.60)	101	8.4	1.84 (1.48, 2.28)	1.15 (0.89, 1.48)	0.60
North-East Asia	2,811	*3.3*	31	*4.5*	1.80 (1.24, 2.61)	1.31 (0.86, 1.98)	40	3.3	1.36 (0.99, 1.89)	0.85 (0.59, 1.24)	0.19
Southern & Central Asia	4,592	*5.4*	90	*12.9*	3.19 (2.51, 4.05)	2.31 (1.73, 3.07)	178	14.7	3.71 (3.12, 4.42)	2.63 (2.12, 3.26)	0.19
Americas	1,470	*1.7*	13	*1.9*	1.44 (0.82, 2.52)	1.12 (0.57, 2.19)	<12[f]	<1[f]	0.72 (0.39, 1.31)	0.69 (0.35, 1.34)	0.37
Sub-Saharan Africa Caucasian	1,592	*1.9*	<12[f]	*<1.7*[f]	1.02 (0.54, 1.93)	1.05 (0.52, 2.14)	<12[f]	<1[f]	0.54 (0.28, 1.05)	0.64 (0.32, 1.31)	0.39
Sub-Saharan Africa non-Caucasian	2,129	*2.5*	37	*5.3*	2.83 (2.00, 4.00)	3.08 (2.11, 4.49)	40	3.3	1.80 (1.30, 2.49)	1.98 (1.39, 2.82)	0.14

Multiparous women with details of previous pregnancies Any history of	n= 42,391		n= 187				n= 455				
Threatened miscarriage	10,687	25.2	59	*31.6*	1.41 (1.03, 1.92)	0.93 (0.63, 1.39)[f]	161	*35.4*	1.67 (1.38, 2.03)	1.11 (0.87, 1.41)[g]	0.47
Previous FGR birth	1,277	3	40	21.4	8.75 (6.14, 12.47)	5.69 (3.59, 9.01)[f]	137	30.1	13.85 (11.25, 17.05)	7.32 (5.59, 9.59)[g]	0.34
Gestational hypertension	2,807	6.6	17	*9.1*	1.41 (0.86, 2.33)	1.66 (0.84, 3.28)[f]	41	*9.0*	1.40 (1.01, 1.92)	1.21 (0.74, 1.99)[g]	0.46
Ante-partum haemorrhage	2,649	*6.3*	12	*6.4*	1.03 (0.57, 1.85)	0.97 (0.49, 1.93)[f]	36	*7.9*	1.29 (0.92, 1.82)	1.11 (0.74, 1.65)[g]	0.74
Previous infant with a neonatal adverse outcome[h]	4,823	11.5	21	11.4	0.98 (0.62, 1.55)	0.79 (0.46, 1.35)	86	19.3	0.54 (0.32, 0.89)	1.28 (0.96, 1.71)[g]	0.12
Interpregnancy interval (months)[i]											
<18	16,029	*37.8*	50	*26.7*	1.13 (0.66, 1.92)	0.95 (0.54, 1.65)	133	29.2	1.02 (0.75, 1.40)	1.06 (0.75, 1.50)	0.49
18-23	6,892	*16.3*	19	*10.2*	1.00 (Reference)	1.00 (Reference)	56	12.3	1.00 (Reference)	1.00 (Reference)	
>23	19,470	*45.9*	118	*63.1*	2.20 (1.35, 3.57)	1.70 (1.03, 2.83)	266	58.5	1.68 (1.26, 2.25)	1.54 (1.12, 2.13)	0.45

BMI: Body Mass Index, CI: Confidence Interval, GA: gestational age, LHT: Linear Hypothesis Test, OR: Odds Ratio, SES: Socio-economic status, SGA: Small for gestational age (birth weight <10th centile for sex and gestation), FGR: Severely growth restricted (birth weight <3rd centile for sex and gestation), FGR_40: Births undelivered at 40 weeks with FGR, Not SGA 37+: Births at 37 or later weeks' gestation not SGA, FGR_37-39: Births between 37-39 weeks' gestation with FGR.

[a] The reference group for the multinomial analyses was the Not SGA 37+ group.

[b] Unless otherwise stated, mutually adjusted for primiparous, smoker during pregnancy, threatened miscarriage, gestational diabetes, pre-eclampsia, gestational hypertension, major birth defect, ante-natal booking appointment >10 weeks GA, remote or very remote birth residence, (all Yes/No), maternal age group (3 level), BMI group (4 level), maternal height (3 level), SES area birth residence tertiles (3 levels), maternal region of birth and ethnic origins (14 levels).

[c] Linear Hypothesis Test: Wald Chi square *P* value testing whether the adjusted ORs for FGR_40 compared to Not SGA 37+ FGR_37-39 compared to Not SGA 37+ are different.

[d] Missing values only shown if ≥5%.

[e] Using 4 level maternal region of birth and ethnic origins variable (3 levels for Australian born, 1 level for all overseas born).

[f] Exact numbers and percentages not shown for small cells to maintain confidentiality.

[g] Mutually adjusted for smoker during pregnancy, threatened miscarriage, gestational diabetes, pre-eclampsia, gestational hypertension, major birth defect, ante-natal booking appointment >10 weeks GA , remote or very remote birth residence, Any history of threatened miscarriage, gestational hypertension, FGR birth or birth with neonatal adverse outcome in previous pregnancy (all Yes/No), maternal age group (3 level), BMI group (4 level), maternal height (3 level), SES area birth residence tertiles (3 levels), maternal region of birth and ethnic origins (4 levels).

[h]See Supplementary Table 4 for components of the NSW composite neonatal adverse outcome indicator used as indicator for neonatal morbidity.
[i] Mutually adjusted for smoker during pregnancy, threatened miscarriage, gestational diabetes, major birth defect, any history of previous FGR birth (all Yes/No), BMI group (4 level), maternal region of birth and ethnic origins (4 levels).

Table 3. Outcomes of severely growth restricted singleton births in WA (2013-15)

	Not SGA 37+		FGR_40		1. FGR_40 compared to Not SGA 37+	FGR_37-39		2. FGR_37-39 compared to Not SGA 37+	3. FGR_40 compared to FGR_37-39
	n	*%*	*%*		Relative Risk (95% CI) [a]	n	*%*	Relative Risk (95% CI) [a]	Relative Risk (95% CI) [a]
	n= 84,918		n = 696			n=1,208			
Onset of labour									
Spontaneous	42,214	*49.7*	394	56.9	1.14 (1.07, 1.22)	479	*39.9*	0.80 (0.74, 0.86)	1.43 (1.30, 1.57)
Induced	25,113	*29.6*	261	*37.7*	1.27 (1.15, 1.40)	494	*41.1*	1.38 (1.29, 1.48)	0.92 (0.82, 1.03)
Prelabour caesarean section	17,570	*20.7*	39	*5.6*	0.27 (0.20, 0.37)	235	*19.6*	0.94 (0.84, 1.06)	0.29 (0.21, 0.40)
Method of delivery									
Spontaneous vaginal	43,322	*51.0*	338	*48.7*	0.95 (0.88, 1.03)	590	*48.8*	0.96 (0.90, 1.01)	1.00 (0.91, 1.10)
Instrumental vaginal	13,126	*15.5*	139	*20.0*	1.30 (1.12, 1.50)	183	*15.1*	0.98 (0.86,1.12)	1.32 (1.08, 1.61)
Elective caesarean section	15,871	*18.7*	21	*3.0*	0.16 (0.11, 0.25)	170	*14.1*	0.75 (0.65, 0.87)	0.22 (0.14, 0.34)
Emergency caesarean Section	12,580	*14.8*	196	*28.2*	1.91 (1.69, 2.15)	265	*21.9*	1.48 (1.33, 1.65)	1.29 (1.10, 1.51)
Stillbirth or death in 1st 6 months of life	122	*0.1*	<10[b]	*<1.4*	7.00 (3.28, 14.94)	18	*1.5*	10.37 (6.34, 16.96)	0.68 (0.28, 1.61)
Restricted to live births	n=84,859		n=692			n=1,201			
Neonatal adverse outcome[c]	6,763	*8.0*	94	*13.6*	1.70 (1.41, 2.06)	235	*19.6*	2.46 (2.18,2.76)	0.69 (0.56, 0.87)
5 Minute Apgar score <7	548	*0.6*	16	*2.3*	2.07 (1.27, 3.38)	39	*3.2*	2.91 (2.12, 3.98)	0.71 (0.40, 1.27)

Any resuscitation at birth	10,641	*12.5*	128	*18.5*	1.48 (1.26, 1.73)	237	*19.5*	1.57 (1.40, 1.77)	0.94 (0.77, 1.14)

CI: Confidence Interval, SGA: Small for gestational age (birth weight <10th centile for sex and gestation), FGR: Severely growth restricted (birth weight <3rd centile for sex and gestation), FGR_40: Births undelivered at 40 weeks' gestation with FGR, Not SGA 37+: Births at 37 or later weeks' gestation not SGA, FGR_37-39: Births between 37-39 weeks' gestation with FGR.

[a] Unadjusted Relative Risk

[b] Exact numbers and percentages not shown for small cells to maintain confidentiality.

[c] See eTable 4 for components of the NSW composite neonatal adverse outcome indicator used as indicator for neonatal morbidity

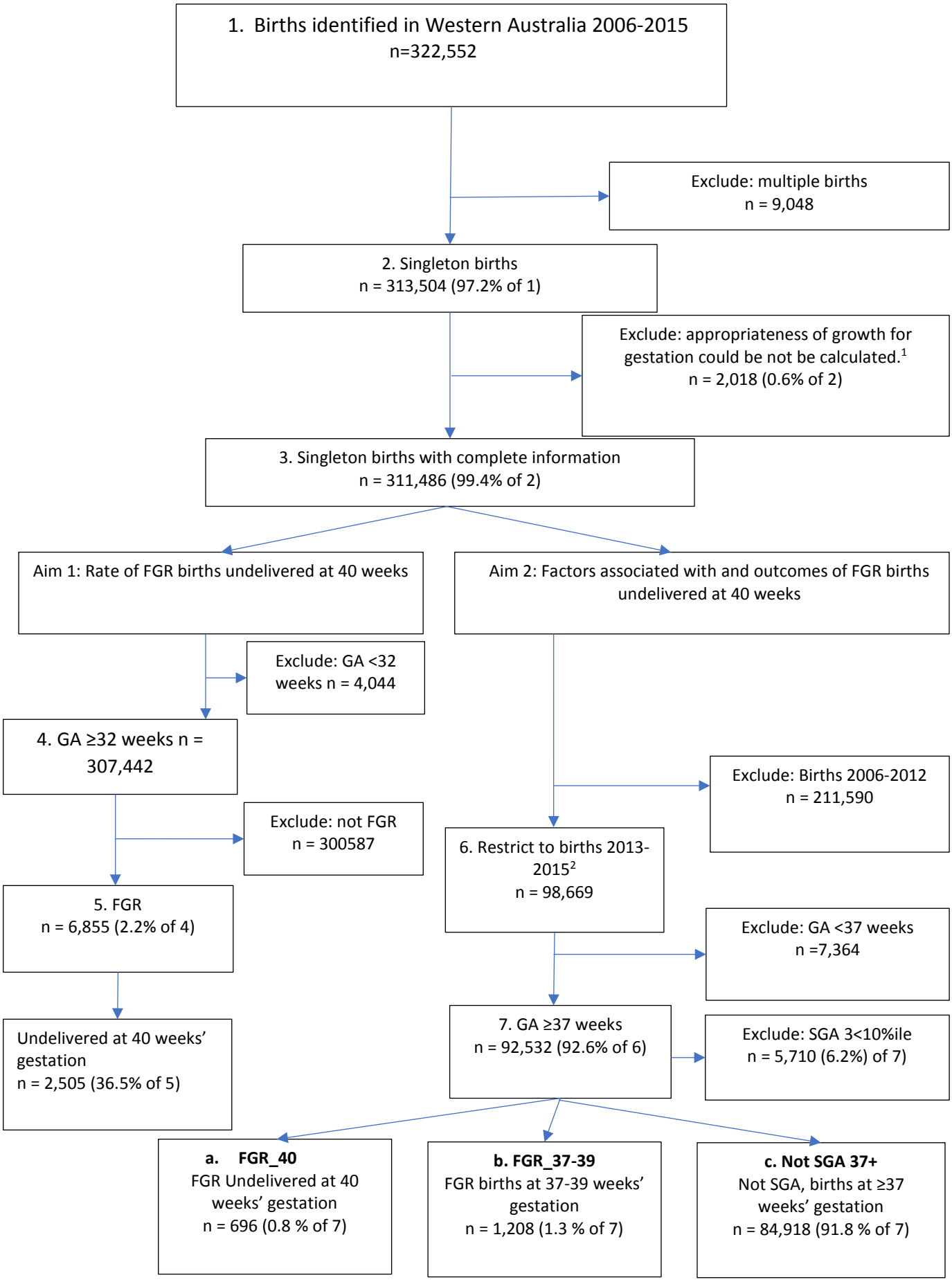


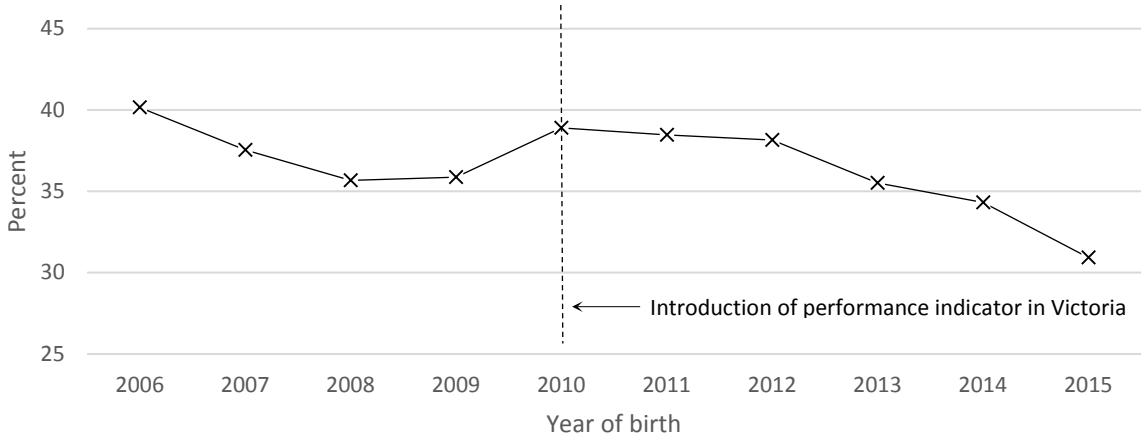
Figure 1: Study flow chart for investigation of severely growth restricted births undelivered at 40 in Western Australia 2006-2015

GA: gestational age, SGA: Small for gestational age (birth weight <10th centile for sex and gestation), FGR: Severely growth restricted (birth weight <3rd centile for sex and gestation), FGR_40: Births undelivered at 40 weeks with FGR, Not SGA 37+: Births at 37 or later weeks' gestation not SGA, FGR_37-39: Births between 37-39 weeks' gestation with FGR.

[1] Missing values for gestation or birthweight, or 3rd percentile not available for gestation (>43 weeks)

[2] These analyses were restricted to the most recent years of data to better reflect most current practice.

Figure 2: Proportion of severely growth restricted (<3rdpercentile) singletons undelivered at 40 weeks' gestation[1] in Western Australia (2006-2015)



[1]The denominator was all singleton births (live and stillborn) with severe growth restriction (<3rdpercentile) at 32 or more weeks' gestation.