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Risk factors and pregnancy outcomes of term fetal growth restriction

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Objective: To evaluate the maternal risk factors associated with term fetal growth restriction (FGR) and immediate perinatal outcomes in these pregnancies.
Methods: This was a retrospective cohort study conducted at a regional obstetric unit in Hong Kong over a 6-year period. All singleton livebirths delivered at term (≥37 weeks of gestation) were analysed. Those with major congenital abnormalities were excluded. Maternal epidemiological and anthropometric characteristics, presence of antenatal complications (gestational diabetes and medical disorders), and pregnancy outcomes (need for labour induction, mode of delivery, Apgar scores, occurrence of shoulder dystocia, and birth trauma) were compared between those with FGR (defined as birthweight ≤10th percentile for gestation) and those with birthweight appropriate for gestational age. Logistic regression analysis was conducted to identify risk factors associated with FGR.
Results: From 2012 to 2017, 24 010 singleton term livebirths were stratified into FGR (n=2425, 10%), appropriate for gestational age (n=19 162, 80%), and large for gestational age. Those classified as FGR were compared with those appropriate for gestational age pregnancies. A logistic regression model confirmed that the key risk factors for FGR included maternal underweight (adjusted odds ratio [OR]=1.88), hypertensive disorders of pregnancy (adjusted OR=1.78), smoking (adjusted OR=2.02), and antenatal anaemia (adjusted OR=1.20), whereas multiparity, gestational diabetes, and hepatitis B antigen carrier status were apparently protective. Pregnancies with FGR were more likely to undergo induction of labour, but were less likely to have shoulder dystocia, Caesarean section, or postpartum haemorrhage.
Conclusion: Despite the inherent risks associated with FGR at term, the immediate perinatal outcomes of these pregnancies appeared to be comparable to those appropriate for gestational age.

Keywords: Fetal growth retardation; Pregnancy outcome; Risk factors

Introduction

Fetal growth restriction (FGR) is a common obstetric problem that confers a considerable risk of perinatal morbidity and mortality[1]. FGR is often referred as 'small for gestational age' or 'intrauterine growth restriction'[2]. Traditionally, an estimated fetal weight below the 10th percentile raises concerns over suboptimal intrauterine growth, although this distinction between normal and pathologic growth is arbitrary. It has been estimated that over 70% of fetuses below the 10th percentile have a normal perinatal outcome, particularly if the growth restriction occurs late in the pregnancy and the baby is born at term gestation[3,4]. FGR is likely a manifestation of various underlying maternal, placental, fetal, and environmental causes and therefore a heterogeneous condition. There are wide variations in the definition of FGR and in fetal weight standards. Ethnic, cultural, and epidemiological factors could affect fetal growth and hence different populations should develop their own reference values for FGR[5,6]. Within our own local population in Hong Kong, previous studies have reported that there could be secular changes, and that the birth weights in Hong Kong have been increasing in the past decades[6-8]. Antenatal detection of FGR is of particular concern, given that only one-third of such pregnancies are prenatally recognised[9,10]. Low detection rates of FGR can result in an increased risk of adverse perinatal outcomes for these pregnancies. Pregnancies with unrecognised FGR could carry an 8-fold increased risk of stillbirth when compared with normal pregnancies[11]. Antenatal recognition of such risk factors is therefore crucial for appropriate surveillance for fetal well-being[12].

This study aimed to assess the associations between different maternal and pregnancy characteristics with term FGR to determine risk factors for FGR and immediate neonatal outcomes.

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Methods

All singleton livebirths delivered at gestation ≥37 weeks over 6 years from 2012 to 2017 in the United Christian Hospital were retrospectively reviewed. Data were retrieved from the electronic antenatal record system, obstetrics clinical information system, and case records of the women, and neonates. Multiple pregnancies, stillbirths, and cases with known major congenital malformations were excluded. All included pregnancies had an early ultrasonographic scan for dating or Down syndrome screening, or a second-trimester morphology scan to exclude date problems.

Gestation at delivery was defined as the completed weeks of gestation according to the date of last menstrual period or ultrasonography. Admission to special care neonatal unit was defined as immediate admission until up to 28 days after birth. A body mass index of ≤18.5 kg/m^2 before pregnancy was considered as underweight. Antenatal anaemia was identified when the haemoglobin level dropped <10 g/dL any time during the pregnancy. The diagnosis of gestational diabetes or diabetes mellitus in pregnancy was based on the 75-g oral glucose tolerance test, according to the departmental protocol and the World Health Organization 2013 criteria. Hypertensive disorders in pregnancy were defined as blood pressure of >140/90 mmHg on two occasions at least 4 hours apart, and pre-eclampsia was diagnosed when pregnancy hypertension was associated with proteinuria defined as spot urine protein/creatinine ratio of ≥0.5, or 24-hour urine protein of ≥0.3 g.

Pregnancies with birthweight of ≤10th percentile were defined as FGR and those of ≥90th percentile were defined as large for gestational age. All eligible pregnancies were also re-categorised with available local and Southern Chinese birthweight percentile charts[5,6,8,13,14] published in the past three decades to evaluate whether the incidence of FGR would be different using different cut-off criteria. Maternal epidemiological and pregnancy characteristics, presence of antenatal complications, and immediate perinatal outcomes were then compared between pregnancies with FGR and pregnancies appropriate for gestational age. The management of term FGR was in accordance with standard departmental protocols. Ultrasonography was performed for monitoring serial growth and liquor volume, and umbilical artery Doppler measurements for fetal surveillance, and induction of labour was offered as indicated before 40 weeks.

A logistic regression model using the enter method was used to identify risk factors associated with term FGR, and adjusted odds ratios (ORs) with 95% confidence intervals (CIs) were calculated for all significant factors. A p value of <0.05 was considered statistically significant. Statistical analysis was performed using SPSS (Windows version 23; IBM Corp, Armonk [NY], US).

Results

From 2012 to 2017, 24 010 singleton term livebirths were stratified into FGR (n=2425, 10%), appropriate for gestational age (n=19 162, 80%), and large for gestational age (Table 1). Using other local or Southern Chinese growth charts[5,6,8,13,14] with different cut-offs, the percentages of FGR varied widely from 1.7% to 10.2%, while using a single cut-off of 2.5 kg as the criteria for small for gestational age would only include 2.8% of all pregnancies. The percentiles of our current cohort correlated best with the New Territories cohort of Rogers et al[6] and the recent large Guangzhou cohort[14].

Comparing the FGR and the appropriate for gestational age groups, women with FGR were more likely to be nulliparous (60.8% vs 48.4%, p<0.001), shorter in height (155.8 vs 156.5 cm, p<0.001), have a lower early pregnancy weight (54.9 vs 56.5 kg, p<0.001) and body mass index (22.6 vs 23.1 kg/m^2), and were underweight (5.3% vs 3.3%, p<0.001) [Table 2]. In addition, women with FGR had a higher incidence of antenatal anaemia (9.7% vs 8.1%, p=0.01), smoking during pregnancy (2.0% vs 1.1%, p<0.001), and hypertensive disorders or pre-eclampsia (7.5% vs 4.2%, p<0.001). Furthermore, women with FGR were less likely to be ≥40 years old (5.9% vs 7.0%, p=0.035), have previous miscarriages (35.9% vs 39.8%, p<0.001), previous Caesarean section (12.3% vs

Table 1. Incidence of term fetal growth restriction (FGR) among singleton livebirths (n=24 010) varies in different growth charts

Database	No. (%) of cases
Our cohort	2425 (10)*
Woo et al[5]	1327 (5.5)*
Rogers et al[6]	2163 (9)*
Fok et al1[3]	413 (1.7)*
Fok et al[8]	529 (2.2)†
He et al[14]	2440 (10.2)*
Birthweight of <2.5 kg	670 (2.8)

* FGR defined as birthweight of ≤10th percentile

† FGR defined as two standard deviations below the mean birthweight (around the 3rd percentile)

Table 2. Maternal characteristics between fetal growth restriction (FGR) and appropriate for gestational age groups

Parameter	FGR (n=2425)*	Appropriate for gestational age (n=19 162)*	Mean difference (95% confidence interval)	Odds ratio (95% confidence interval)	P value
Maternal age, years	32±5.36	31.9±5.1	-0.07 (-0.15 to 0.28)		0.53
Gestation at delivery, weeks	39±1.12	39±1.13	0.004 (-0.04 to 0.05)		0.86
Maternal age ≥35 years	572 (23.6)	4701 (24.5)		0.95 (0.86-1.05)	0.16
Maternal age ≥40 years	143 (5.9)	1354 (7)		0.82 (0.69-0.98)	0.035
Parity				0.60 (0.55-0.66)	<0.001
Nulliparous	1475 (60.8)	9288 (48.4)			
Multiparous	950 (39.2)	9874 (51.6)			
Maternal height, cm	155.8±5.52	156.5±5.46	-0.64 (-0.87 to -0.41)		<0.001
Early pregnancy weight, kg	54.9±8.61	56.5±8.38	-1.55 (-1.91 to -1.20)		<0.001
Body mass index (BMI), kg/cm^2	22.61±3.34	23.1±3.21	-0.45 (-0.58 to -0.31)		<0.001
Underweight (BMI of <18.5 kg/cm^2)	128 (5.27)	627 (3.27)		1.86 (1.53-2.26)	<0.001
Previous miscarriages	871 (35.9)	7627 (39.8)		0.16 (0.07-0.25)	<0.001
Previous Caesarean section	299 (12.3)	3462 (18)		0.64 (0.56-0.72)	<0.001
Post-term delivery (≥41 weeks)	259 (10.7)	2337 (12.2)		0.86 (0.75-0.98)	0.86
Antenatal anaemia (haemoglobin of <10 g/dL)	235 (9.69)	1560 (8.14)		1.21 (1.05-1.40)	0.01
Smoking during pregnancy	50 (2)	220 (1.1)		1.81 (1.33-2.41)	<0.001
Gestational diabetes / diabetes mellitus in pregnancy	220 (9)	2161 (11.2)		0.78 (0.68-0.91)	0.001
Hypertensive disorders / pre-eclampsia	183 (7.54)	798 (4.16)		1.87 (1.59-2.22)	<0.001
Hepatitis B Antigen carrier	144 (5.9)	1557 (8.1)		0.71 (0.60-0.85)	0.001
Other medical disorders (cardiac, thyroid, neurological, autoimmune, renal diseases)	303	2207		1.09 (0.96-1.25)	0.84

* Data are presented as mean ± standard deviation or No. (%) of subjects

18.0%, p<0.001), gestational diabetes (9.0% vs 11.2%, p<0.001), or positive carrier status of hepatitis B (5.9% vs 8.1%, p<0.001).

In the logistic regression analysis, risk factors for FGR identified from univariate analysis that remained significant were hypertensive disorders in pregnancy (adjusted OR=1.78, 95% CI=1.51-2.12), maternal underweight (adjusted OR=1.88, 95% CI=1.54-2.30), smoking in pregnancy (adjusted OR=2.02, 95% CI=1.47-2.77), and antenatal anaemia (adjusted OR=1.20, 95% CI=1.04-1.39) [Table 3]. In addition, protective factors associated with a lower risk of FGR included multiparity (adjusted OR=0.64, 95% CI=0.58-0.69), hepatitis B antigen carrier status (adjusted OR=0.75, 95% CI=0.63-0.89), and gestational diabetes (adjusted OR=0.82, 95% CI=0.71-0.95) [Table 3]. Maternal age >40 years, previous miscarriages, and previous Caesarean section were not significant risk factors in the logistic regression analysis.

Regarding pregnancy outcomes, compared with pregnancies appropriate for gestational age, pregnancies with FGR were more likely to have induction of labour (24.0% vs 15.8%, OR=1.68, p<0.001) or normal vaginal delivery (72.6% vs 69.9%, OR=0.81, p<0.001) instead of Caesarean section (17.4% vs 20.6%), but more likely to require instrumental delivery (40.0% vs 29.7%, OR=1.62, p=0.015) or Caesarean section (17.0% vs 5.7%, OR=3.37, p<0.001) for fetal distress (Table 4). Pregnancies with FGR resulted in less blood loss at delivery (187 vs 234 mL, p<0.001) and lower incidence of postpartum haemorrhage (3.5% vs 8.8%, OR=0.38, p<0.001). None of the cases with FGR were complicated by shoulder dystocia. Pregnancies with FGR resulted in a higher rate of admission to special

Table 3. Logistic regression analysis on risk factors for fetal growth restriction

Variable	B	Standard error	Wald	Adjusted odds ratio (95% confidence interval)	p Value
Hypertensive disorders	0.581	0.086	45.6	1.78 (1.51-2.12)	<0.001
Underweight	0.634	0.101	39.0	1.88 (1.54 -2.30)	<0.001
Smoking in pregnancy	0.703	0.162	18.8	2.02 (1.47-2.77)	<0.001
Antenatal anaemia	0.186	0.074	6.29	1.20 (1.04-1.39)	0.012
Multiparity	-0.450	0.045	99.0	0.64 (0.58-0.69)	<0.001
Hepatitis B carrier status	-0.287	0.090	10.1	0.75 (0.63-0.89)	0.001
Gestational diabetes	-0.203	0.076	7.22	0.82 (0.71-0.95)	0.007
Maternal age >40 years	-0.046	0.093	0.24	0.95 (0.79-1.15)	0.62
Previous miscarriages	-0.047	0.051	0.84	0.95 (0.86-1.05)	0.36
Previous Caesarean section	-0.125	0.079	2.49	0.88 (0.76-1.03)	0.12

Table 4. Maternal and immediate neonatal outcomes between fetal growth restriction (FGR) and appropriate for gestational age groups

Variable	FGR (n=2425)*	Appropriate for gestational age ((n=19 162)*	Mean difference (95% confidence interval)	Odds ratio (95% confidence interval)	P Value
Birthweight, g	2600±210	3196±278	-596 (-607 to -584)		<0.001
Induction of labour	582 (24)	3027 (15.8)		1.68 (1.52-1.86)	<0.001
Mode of delivery				0.81 (0.73-0.91)†	0.001
Normal vaginal	1761 (72.6)	13391 (69.9)			
Instrumental	241 (10)	1816 (9.5)			
Caesarean section	423 (17.4)	3955 (20.6)			
Instrumental delivery for fetal distress	98 (40)	538 (29.7)		1.62 (1.23-2.13)	0.015
Caesarean section for fetal distress	72 (17)	227 (5.74)		3.37 (2.52-4.48)	<0.001
Blood loss at delivery, mL	187±152	234±181	-47 (-57 to -36)		<0.001
Postpartum haemorrhage	86 (3.54)	1682 (8.78)		0.38 (0.30-0.48)	0.001
Apgar score of ≤7 at 5 mins	6 (0.25)	21 (0.11)		2.26 (0.91-5.60)	0.07
Shoulder dystocia	0	58 (0.3)			-
Birth trauma	2 (0.08)	12 (0.06)		1.31 (0.29-5.89)	0.71
Admission to special care neonatal unit	1310 (54)	7250 (37.8)		1.93 (1.77-2.10)	0.001
Neonatal death	1 (0.04)	2 (0.01)		3.95 (0.35-43.6)	0.30

* Data are presented as mean ± standard deviation or No. (%) of subjects

† Caesarean section versus vaginal delivery

care neonatal unit (54.0% vs 37.8%, OR=1.93, p<0.001). One baby in the FGR group died from persistent pulmonary hypertension, and two babies in the appropriate for gestational age group died: one from a massive subgaleal haemorrhage after vacuum extraction and another being born and succumbed to unknown causes before arrival to hospital.

Discussion

Before local charts are available, growth charts based on Western populations developed more than 50 years earlier were often referred to[15]. The first widely adopted local growth chart was published in 1986 based on 15 000 singleton births from two teaching hospital units[5], and subsequently, a number of similar datasets were published.

When we applied the cut-offs of previous local studies that used the 10th percentile to our dataset, the incidence of FGR varied from 1.7% to 10.2%. Similarly, when we compared our data with a previous cohort that used minus two standard deviations as the cut-off, the incidence of FGR was only 2.2%. The under-estimation of FGR with older growth charts could be explained by the trend of increasing birthweight in Hong Kong babies. Comparing a cohort of 10 339 babies from 1998 to 2001[8] with a cohort of 8445 babies from 1982 to 1986[13], the mean birthweight was significantly greater at each gestation after 34 weeks in the newer cohort, compared with the older cohort. However, in another study comparing birthweights of 10 512 deliveries between 1985 and 86 with those of 7857 deliveries between 1995 and 1996, the mean birthweights in the two periods were comparable, suggesting that birthweight has reached a plateau despite continuous improvements in socioeconomic status in Hong Kong[6]. Despite the conflicting findings, such studies showed the importance of having up-to-date data to produce standard growth charts relevant to a specific population.

To determine whether a single international standard for fetal growth can be applied to all populations, a retrospective study of 506 658 neonates from Guangzhou from 2009 to 2011 aimed to compare the birthweight reference with the global reference and the reference used in China[14]. The birthweight in the Guangzhou cohort was higher than the references used in both China and global models at advanced gestational ages. Recently, the World Health Organization conducted a multi-national prospective observational longitudinal study of fetal growth involving ten countries (two in South-East Asia), and showed wide variations in fetal growth standards across different parts of the world[16]. The authors concluded that the growth charts cannot be generalised owing to limited sample sizes for different populations[16], and the need for population-specific growth charts is highlighted. In addition, the smoothed birthweight percentiles from 37 weeks to 41 weeks of the Guangzhou study matched closely with our cohort. This could be explained by the fact that the Guangzhou study was also conducted within the past 10 years, and the ethnicity and socioeconomic characteristics are also similar to our cohort.

In our study, maternal underweight, hypertensive disorder, smoking, and anaemia were risk factors for FGR. Using the World Health Organization definition of maternal underweight (body mass index of <18.5 kg/m^2), a retrospective cohort study of 29 303 Chinese women reported that 9% of the cohort was underweight[17], which was higher than the 5.27% in our cohort. It remains controversial whether maternal underweight leads to FGR owing to nutritional deficiencies, and conversely, whether increasing pre-pregnancy weight or gestational weight gain is associated with better neonatal outcome[18]. Hypertensive disorders and pre-eclampsia have been reported to be associated with FGR. The pathogenesis of dysfunctional placental implantation in pre-eclampsia is hypothesised to lead to decreased uteroplacental flow and placental ischaemia, decreasing oxygen and nutritional supply to the fetus[18,19]. In our study, the incidence of hypertensive disorders or pre-eclampsia was 4.5%, which was comparable to the 5.2% reported in a large retrospective study of 112 386 Chinese women[20]. Further studies are needed to determine whether variations in the incidence of hypertensive disorders are associated with variations in birthweights in different populations.

In our study, smoking was a risk factor for FGR. In a retrospective cohort study of 13 661 non-malformed singleton deliveries in Spain[21], smoking during pregnancy was a risk factor for FGR, with an adjusted odds ratio of 1.9, which was comparable to the 2.0 in our logistic regression analysis. The effect of smoking on FGR is dose-dependent and is therefore modifiable. In a previous study of 18 816 pregnant women from our centre, the incidence of smoking in early pregnancy was 1.7%, of which 53.5% continued to smoke throughout pregnancy and 26.9%, 13.8%, and 5.8% quit smoking in the first, second, and third trimester, respectively[22]. According to the Royal College of Obstetricians and Gynaecologists guideline[1], women who stop smoking by 15 weeks of gestation can lower the risk to that of non-smokers. Therefore, it is vital to advocate the importance of smoking cessation in antenatal management.

Anaemia is a common antenatal problem. In a systemic review involving 341 832 mother-child dyads, moderate to severe anaemia was associated with increased risk for small for gestational age (birthweight ≤10th percentile)[23] babies, with the haemoglobin cut-off being 90 g/L or 80 g/L. In a randomised controlled trial of 1164 Hong Kong women, there were fewer small for gestational age babies born in the group with 60 mg iron supplement daily (OR=0.46) than in the placebo group[24]. However, a recent study suggested that giving too much iron to non-anaemic women can lead to haemoconcentration, which is associated with maternal hypertension, pre-eclampsia, or gestational diabetes[25]. Therefore, there is no consensus on giving prophylactic iron supplement in pregnancy, particularly in those with borderline anaemia.

In our study, multiparity, gestational diabetes, and hepatitis B infection were protective factors against FGR. No consensus could be drawn from previous studies on whether parity was a risk factor for FGR. Subsequent pregnancies are likely to have better weight gain owing to better trophoblast invasion and hence increased placental blood flow and nutrient supply to fetuses[14]. However, multiparity was associated with confounders such as increasing age and increasing risk of gestational diabetes, so it is difficult to deduce the true association between parity and FGR. A retrospective cohort study of 19 614 women in Hong Kong confirmed that multiparity was a risk factor for macrosomia (adjusted OR=1.50), as was diabetic complication in pregnancy (adjusted OR=3.90)[26]. This was consistent with our finding of gestational diabetes being a protective factor for FGR.

Hepatitis B infection is common in the Asian populations. The hepatitis B carrier status is negatively associated with pre-eclampsia[27]. In a meta-analysis of 11 566 Asian patients, chronic hepatitis B infection is associated with 23% decreased risk of pre-eclampsia and increased risks of gestational diabetes[28]. This is compatible with our finding of hepatitis B carrier status being a protective factor for FGR as pre-eclampsia is a risk factor for FGR.

In our study, those with term FGR were more likely to have induction of labour (OR=1.68) before due date to lower the risk of intrauterine death and other perinatal morbidities. In a retrospective cohort study of 2378 neonates small for gestational age, early term induction increased the risks of Caesarean delivery and neonatal metabolic and respiratory complications with no neonatal benefit[29]. A randomised trial comparing induction of labour with expectant monitoring for term FGR, the DIGITAT study, reported no important differences in adverse outcomes between both[30]. Therefore, it remains controversial whether a term fetus with FGR should be induced. In our study, smaller fetuses were less likely to encounter shoulder dystocia but were at higher risk of intrapartum hypoxia and acidosis, so that instrumental delivery and Caesarean section for fetal distress were more common than for fetuses appropriate for gestational age. Less blood loss and postpartum haemorrhage was predictable as FGR is inversely associated with risk factors for postpartum haemorrhage.

One limitation of our study was its retrospective nature. Regarding the management of term FGR, we were unable to verify the proportion of cases that were detected antenatally or that had additional fetal surveillance, which would have affected pregnancy management or outcome. Although we were unable to demonstrate significant perinatal morbidity associated with term FGR apart from the higher admission rate to special care neonatal unit, we were not able to analyse neonatal length of stay or incidence of other minor perinatal problems such as neonatal jaundice or weight-gain patterns.

Conclusion

Risk factors associated with term FGR include maternal underweight, hypertensive disorder, smoking, and antenatal anaemia. In contrast, multiparity, gestational diabetes, and hepatitis B carrier status were protective factors, which themselves are associated with adverse outcomes in pregnancy.

Declaration

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