Original Article

Increased incidence of chronic lung disease and respiratory sequelae in growth restricted versus appropriately grown preterms

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ABSTRACT

Background: Fetal growth restriction (FGR) affects 5–10% term gestational age pregnancies. When accompanied by prematurity, FGR infants have significantly greater risk of perinatal morbidity and/or mortality compared to non-growth restricted preterm infants. **Aim:** Current study aimed to ascertain the incidence FGR among premature infants and its association with respiratory morbidity. **Methods:** Institution database for preterm infants of 23–31^{+6} weeks of gestation was accessed. FGR infants were compared with gestation/sex matched appropriately grown infants. **Results:** During the period 2016–2018, 973 infants between 23 and 31^{+6} weeks gestation were admitted amongst whom, 206 (27%) were FGR. Between 28 and 31^{+6} weeks gestation, approximately 1/3rd were FGR. Gestation and birth weight of the FGR and appropriately grown cohorts were 30.2±0.2 versus 30.1±0.2 weeks (p=0.8) and 1132±43 versus 1499±54 g (p<0.0001), respectively. While antenatal steroids, surfactant, mechanical ventilation, sepsis, and ductal therapy were comparable, respiratory outcomes were significantly worse in the FGR cohort (duration of respiratory support: 37±10 vs. 23±5 days [p=0.016], home oxygen: 24 [11.6%] vs. 8 [3.8%]; [p=0.005] and chronic lung disease [CLD]: 53 [25.7%] vs. 28 [13.6%], [p=0.002], respectively). The odds ratio (95% confidence intervals) for developing CLD and for home oxygen when born FGR were 2.2 (1.3–3.6) and 3.2 (1.4–7.4), respectively. **Conclusions:** In spite of comparable postnatal variables, FGR infants had significantly greater respiratory morbidity.

Key words: Chronic lung disease, Fetal growth restriction, Incidence, Morbidity, Prematurity

Fetal growth restriction (FGR) affects 5–10% term gestational age (GA) pregnancies worldwide [1]. Relatively low prevalence of FGR in published birth cohorts, heterogeneity in definitions of FGR alongside the heterogeneity of causes of FGR has meant that the true incidences of preterm-FGR birth are not well appreciated and have limited number of clinical studies till date [2-4]. Small for GA (SGA) is a commonly used surrogate definition of FGR [3-5]. Nonetheless, combined with prematurity, these cohorts may be at a higher risk of perinatal morbidity, mortality, and respiratory sequelae compared to those appropriate for GA (AGA) [6-8]. Chronic lung disease (CLD) is the most common respiratory sequelae of prematurity. The previous literature linking FGR and CLD is characterized by two limitations: some of the studies defined CLD as oxygen requirement at 28 days or primarily assessed SGA infants (which is a distinct cohort from FGR infants). Some of the previous studies used SGA terminology to depict links with CLD [7,9,10]. A recent study on infants <28 weeks GA noted that at 27 weeks GA, 25% of infants without FGR developed CLD compared to 90% with severe FGR. No accompanying antenatal Doppler data were mentioned in this study. The study designated FGR exclusively on weight centiles [6]. While FGR may be an important demographic, contributing to the increased incidence of CLD, a range of other contributory variables may confound the association. Male sex, patent ductus arteriosus (PDA), infection, and mechanical ventilation are conventional risk factors for developing CLD. Earlier descriptions of CLD attributed it primarily to neonatal exposures (occurrence and management of neonatal diseases). These included mechanical ventilation, high levels of supplemental oxygen and PDA. However, CLD may not always be preceded by such exposures [11], indicating that exposures and events in the *pre-natal* period may offer a new adjunctive perspective. The objectives of this study were to (a) ascertain the incidence of FGR amongst preterm infants born at a tertiary center and (b) compare their respiratory morbidity indices with AGA infants. FGR was defined as birth weight was <10th centile for GA and sex and abnormal (absent/reverse) antenatal Doppler [12].

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METHODS

After institution's ethics approval, database for all preterm infants born between 23 and 31^{+6} weeks GA admitted during the 3-year

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period (2016–2018) was accessed. The study was performed at a tertiary center with 64 neonatal cots (half of them providing ventilator support), caring for infants>23 weeks GA and those needing surgery. In infants born <32 weeks GA, the Australian and New Zealand Neonatal Network (ANZNN) defines CLD as lung disease with ongoing requirement for supplemental oxygen therapy or ventilation support (high-flow oxygen, continuous positive airway pressure, or mechanical ventilation) at 36 weeks' post-menstrual age. This definition was used for this study. All neonatal units in the country submit annual data to the registry (ANZNN); the registry was the primary source of the current data while remaining variables were sourced from medical records. We excluded infants with congenital heart disease or chromosomal anomalies from the current analysis. For this retrospective study, we enlisted all infants who fulfilled the inclusion criteria for FGR. All inclusions in this study underwent antenatal Doppler recordings. We compared the FGR cohort with an equal number of consecutively born GA and sex-matched AGA infants (97 infants of same sex with comparable GA were available in the database). GA for the infants was calculated by early gestation ultrasound. Respiratory sequelae parameters included CLD (as defined above), duration of respiratory support and discharge on home oxygen. The two groups were compared using the student "t-test" for nonparametric continuous variables and Chi-square or Fisher's exact test as appropriate for categorical variables.

RESULTS

During the study period, 973 infants (GA: 23–31^{+6} weeks) were admitted to the neonatal intensive care unit (NICU). Of these, 206 (27%) were growth restricted. The percentage of FGR births increased with increasing GA. Between 28 and 31^{+6} weeks GA, approximately one-third infants were born FGR. Overall, 183/206 (89%) FGR infants were born between 28 and 31^{+6} weeks GA (Fig. 1).

Table 1 compares cohort characteristics including risk factors for the development of CLD. The incidence of pregnancy induced hypertension and delivery by pre-labor cesarean section was significantly higher in the FGR group; (74 [36%] vs. 19 [9.2%], p<0.0001 and 186 [90.3%] vs. 123 [61%], p<0.0001), respectively. While postnatal risk factors for CLD were comparable, respiratory outcomes were significantly worse in the FGR cohort (Table 1). Among FGR infants who developed CLD, 35 were on CPAP while 18 were on high flow (among AGA infants, 10 were on CPAP while 18 were on high flow, p=0.01). CLD was significantly higher among the moderately preterm FGR infants (GA=28–31^{+6} weeks, 89% of the cohort) (35/175 [20%] vs. 12/176 [6.8%], p=0.0002). Among <28 weeks GA infants, CLD still trended higher amongst FGR infants (18/22 [82%] vs. 16/23 [69.5%], p=0.49). More than half (12/22 [55%]) FGR infants were extremely premature (GA ≤25 weeks). Overall, the odds ratio (95% confidence intervals [CI]) for developing CLD and for home oxygen was 2.2 (1.3–3.6) and 3.2 (1.4–7.4), respectively, in a born FGR.

DISCUSSION

Our study found that compared to available data on term pregnancies, the incidence of FGR is much higher in preterm deliveries. The significantly higher incidence of CLD in the FGR cohort was noted in the presence of comparable postnatal risk factors (and their management). Our data support that while postnatal variables associated with respiratory sequelae are important, impaired growth during fetal life can affect pulmonary parenchymal and vascular growth and development. In essence, *in utero* experiences (most significantly utero-placental insufficiency) may predispose to CLD.

Zeitlin *et al*. assessed 7766 preterm infants (22–31^{+6} GA) to ascertain the prevalence amongst very preterm infants using national and European intrauterine references. The cohort was defined by birth weight <10^{th} centile (without antenatal Doppler information data). Nonetheless, the prevalence was noted to be 32% with country-specific references and 34% with common European references [13]. Approximately 40% of the cohort were delivered by pre-labor cesarean section and 15% pregnancies were complicated by pregnancy-induced hypertension. SGA was significantly associated with CLD (odds ratio: 6.4, 95% CI: 4.5–9.2) [13]. Much of this data mirrors findings of our study though we included infants with birth weight <10^{th} centile for gestation/sex and abnormal antenatal Doppler's.

Pre-natal exposures and events may predispose to CLD. Comparison of two historical cohorts of SGA and AGA infants (24 and 26^{+6} weeks) noted a higher CLD risk (65% vs. 32%) for AGA [14]. The association persisted after adjustment for a variety of neonatal characteristics also associated with CLD risk. In a recent study, FGR was the only maternal or antenatal characteristic that was highly predictive of CLD [6]. The association between FGR and poor respiratory outcomes may be mediated by alterations in surfactant synthesis and effects of hypoxia on the fetal lung,

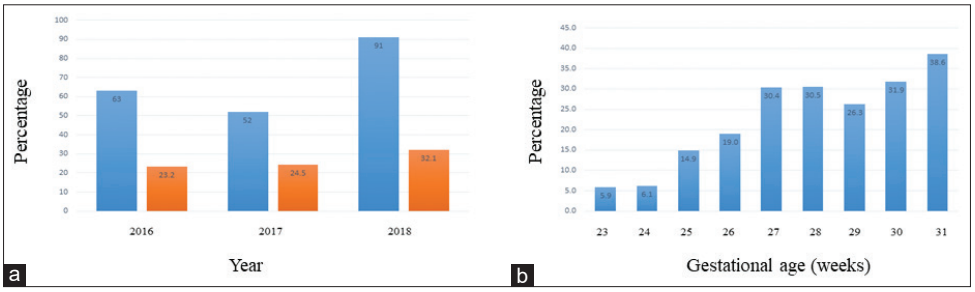

Figure 1: (a) Absolute numbers and percentage of fetal growth restriction (FGR) infants (23–31^{+6} weeks) during study period. (b) Gestation wise incidence (percentage) of FGR

Table 1: Comparison of characteristics between FGR and AGA cohorts

Variable	FGR (n=206)	AGA (n=206)	p-value
Gestational age (weeks)	30.2±0.2	30.1±0.2	0.8
Birth weight (g)	1132 ±43	1499±54	<0.0001
Gender (male) n (%)	102 (49.5)	97 (47)	0.7
5 min Apgar, median (range)	9 (4,10)	8 (2,10)	0.27
Base excess, Median (IQR) (mmol/L)^	−2.4 (−5, −0.8)	−3 (−5.3, −0.2)	0.9
Mechanical ventilation n (%)	70 (34)	64 (31)	0.6
Any infection n (%)	19 (9.2)	18 (8.7)	0.9
Air leaks n (%)	5 (2.4)	7 (3.3)	0.8
Intraventricular hemorrhage n (%)	39 (19)	37 (18)	0.9
Antenatal steroids n (%)	192 (93)	185 (90)	0.4
Postnatal steroids n (%)	11 (5.3)	4 (2)	0.1
Surfactant n (%)	58 (28.1)	46 (22.3)	0.2
PDA n (%)	33 (16)	32 (15.5)	0.9
Length of stay* (days)	66±6	55±4	0.004
Duration of respiratory support (days)*	37±10	23±5	0.016
Home oxygen n (%)	24 (11.6)	8 (3.8)	0.005
Chronic lung disease n (%)*	53 (25.7)	28 (13.6)	0.002
Death n (%)	9 (4.3)	7 (3.3)	0.8

***For those survived, IQR: Interquartile range, ^Cord gas or within 1 h. FGR: Fetal growth restriction, PDA: Patent ductus arteriosus**

interfering with alveolar, and pulmonary artery development [15]. Abnormal angiogenesis (imbalance between angiogenic/anti-angiogenic factors) as a link between pre-eclampsia and CLD is noted as well [16,17]. Using high-resolution vascular ultrasound, thicker and stiffer pulmonary arteries in FGR infants were noted, compared to preterm AGA infants [18]. FGR infants show a dampened clinical and echocardiographic improvement in response to surfactant, compared to AGA cohorts [19]. This again may reflect the influence of an *in utero* adaptive state.

While CLD pathophysiology is multifactorial, the study on preterm FGR infants (28–32 weeks GA) demonstrated significantly thicker and stiffer pulmonary arterial vasculature compared to GA, gender, and age-matched AGA control infants. Other experimental data indicated impaired vasculogenesis as a contributory factor in the higher prevalence of CLD in preterm FGR infants [16-18]. Persistent effects of FGR on lung structure and function (both alveolar parenchymal and vascular) indicated that reduced fetal growth may be a marker for abnormal intrauterine lung development; clinically reflecting higher prevalence of respiratory morbidities and supporting fetal mechanisms of later onset pulmonary vascular disease. Factors controlling somatic growth during fetal life may also influence vulnerability to lung injury. In summary, fetal growth seems to influence morbidity attributable to CLD as an independent risk factor [6,7].

Nutrition practices are key factors in reducing morbidities. The general unit practice is to administer parenteral nutrition for infants <1500 g birth weight. For FGR infants, we start feeds at a slower pace and grade up a bit slower than for preterm AGA infants. Greater emphasis is placed on preferential feeding with expressed breast milk rather than formula feeds. In case of twin deliveries and discordant growth, expressed breast milk is preferentially given to the smaller of the twins. Pasteurized donor breast milk is available for infants weighing <1000 g irrespective of GA.

In this light, we noted that while the management in our cohorts of preterm FGR and AGA infants was similar (antenatal steroids, surfactant, and ventilation), as was the incidence of variables which contribute to CLD (PDA, infection), the respiratory outcomes were significantly worse in the FGR cohort. This indicates the clinical relevance of the events before birth. From the postnatal management perspective, it remains to be explored whether FGR centered individualized strategies (such as avoiding mechanical ventilation, and minimally invasive surfactant therapy) have the potential to alter respiratory outcomes.

The medical, social, and logistic impact of FGR and lung disease extends beyond the stay in the NICU or infancy. Changes in lung architecture during fetal life and the consequent functional impact persist well into childhood [20,21]. Lung function measurements at ~10 months of age in FGR infants (in comparison to equally premature AGA infants) noted increased airway resistance in the former, after adjustment for confounders, including CLD. Another large-scale study identified an association between FGR and the risk of childhood asthma [22].

The strength of this study is a relatively large cohort of >200 infants. We compared the FGR infants with AGA infants, and common risk factors for respiratory morbidity were comparable between the two cohorts. Based on our data, we recommend a study involving a much larger cohort on a network or country basis to elucidate the true burden of disease on a community level. This data to the growing literature about the exposures in fetal life are important determinants of health and disease. Whether antenatal interventions to alter the cardiopulmonary and biochemical milieu will influence this significantly higher respiratory morbidity, remains to be studied prospectively.

CONCLUSIONS

Infants with FGR have significantly higher rates of chronic lung disease compared to AGA infants.

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