

BMJ Open Fetal Doppler velocimetry and bronchopulmonary dysplasia risk among growth-restricted preterm infants: an observational study

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ABSTRACT

Objective To investigate whether fetal growth restriction (FGR) diagnosis, based on pathological prenatal fetal Doppler velocimetry, is associated with bronchopulmonary dysplasia (BPD) independently of being small for gestational age (SGA) per se at birth among very preterm infants.

Design Prospective, observational study. FGR was defined as failing fetal growth in utero and fetal Doppler velocimetry abnormalities.

Setting Policlinico Universitario Agostino Gemelli, Roma, Italy.

Patients Preterm newborns with gestational age ≤ 30 weeks and birth weight (BW) ≤ 1250 g.

Main outcome measures Bronchopulmonary dysplasia.

Results In the study period, 178 newborns were eligible for the study. Thirty-nine infants (22%) were considered fetal growth-restricted infants. Among the 154 survived babies at 36 weeks postmenstrual age, 12 out of 36 (33%) of the FGR group developed BPD versus 8 out of 118 (7%) of the NO-FGR group ($p < 0.001$). BPD rate was sixfold higher among the SGA-FGR infants compared with the SGA-NO-FGR infants. In a multivariable model, FGR was significantly associated with BPD risk (OR 5.1, CI 1.4 to 18.8, $p = 0.01$), independently from BW z-score that still remains a strong risk factor (OR 0.5, CI 0.3 to 0.9, $p = 0.01$).

Conclusion Among SGA preterm infants, BPD risk dramatically increases when placenta dysfunction is the surrounding cause of low BW. Antenatal fetal Doppler surveillance could be a useful tool for studying placenta wellness and predicting BPD risk among preterm babies. Further research is needed to better understand how FGR affects lung development.

INTRODUCTION

Bronchopulmonary dysplasia (BPD) is one of the most concerning complications of very preterm birth as it leads to frequent hospitalisations, persistent abnormal lung function and neurodevelopmental impairment.^{1 2} Recently, fetal growth restriction (FGR) has been suggested as an additional risk factor

Strengths and limitations of this study

- This is one of the first studies defining fetal growth restriction as the coexistence of failing of fetal growth and abnormal fetal Doppler velocimetry rather than just a low birth weight (BW).
- We reported that small for gestational age preterm infants have the highest bronchopulmonary dysplasia (BPD) risk when placenta dysfunction is the surrounding cause of low BW.
- The small sample size of BPD infants could limit the power of our estimates.
- Different Doppler patterns were not considered in the analyses, as well as the exact duration of time the fetus was exposed to abnormal Doppler flows.

for BPD both in human and animal studies.^{3–6} The presence of uteroplacental insufficiency leads to physiological, metabolic and haemodynamic adaptations that can affect development of the FGR fetus. FGR is a common condition of preterm births but there is a lack of standard definitions in literature. In several published works, FGR infants were considered those small for gestational age (SGA), but a significant proportion of smallness is due to constitutional causes. FGR is probably the result of underlying placental pathology and occurs when the growth restriction is pathological, indicating that the fetus has failed to achieve its full growth potential.⁷ An adverse environment before birth could interfere with development and lead to fetal epigenetic changes that increase vulnerability of the lungs after birth. Up to now, several studies have suggested an association between placental disorders affecting fetal wellness and BPD.^{8–11} Aim of this study was to evaluate whether FGR diagnosis, based on pathological prenatal fetal Doppler velocimetry, is

associated with BPD independently of being SGA per se in a cohort of preterm infants.

MATERIALS AND METHODS

The study included newborns with gestational age (GA) ≤ 30 weeks and birth weight (BW) ≤ 1250 g consecutively admitted to our neonatal intensive care unit (NICU) in the period from January 2009 to June 2013. Data about prenatal and neonatal characteristics were prospectively collected in the obstetric medical record and Neonatal Unit database, respectively.

FGR diagnosis was based on the coexistence of failing fetal growth in utero, defined as the reduction of the estimated fetal weight of at least 1 SD in two ultrasound scans within 2 weeks and fetal Doppler velocimetry abnormalities, defined as the presence of one of the following conditions:¹¹

- ▶ umbilical artery pulsatility index (PI) greater than the 95th centile,
- ▶ absent or reversed end diastolic flow velocities on at least 50% of the Doppler waveforms from the umbilical artery on at least one occasion during pregnancy,
- ▶ cerebral redistribution, defined as occurring when both the umbilical artery PI is greater than the 95th centile and the middle cerebral artery PI is less than the 5th centile for GA.

The Doppler studies were performed by two certified perinatologists (PR and IM). The last Doppler assessment was done between 48 hours and 5 days before delivery.

The exclusion criteria were:

- ▶ no fetal Doppler velocimetry information available,
- ▶ major congenital malformation,
- ▶ hydrops fetalis,
- ▶ prolonged preterm rupture of membranes (pPROM) that occurred more than 3 weeks before the delivery,
- ▶ suspected twin-to-twin transfusion.

The BW was recorded and the BW z-score was calculated for each infant. According to the most common definition, SGA infants were those with a BW < 10 th percentiles (z-score < -1.28) for GA on Bertino growth curves for Italian babies, independently from their fetal Doppler velocimetry.¹² GA was estimated by the first trimester ultrasound. Maternal pre-eclampsia was diagnosed in previously normotensive woman with onset of hypertension and proteinuria after 20 weeks of gestation according to the American Congress of Obstetricians and Gynaecologists criteria.¹³ Histological chorioamnionitis was diagnosed when the chorion–amnion contained a polymorphonuclear leucocytic infiltrate accompanied by oedema and congestion of the vessels.¹⁴ Placental histology was performed by a single pathologist who was unaware of the patient's history and evolution. Two main causes of delivery were identified:¹⁵ an 'indicated' preterm delivery (for a placenta dysfunction disorder such as FGR, maternal pre-eclampsia, pregnancy-related hypertension) and a 'spontaneous' preterm delivery (triggered by an

inflammatory condition such as pPROM, cervical insufficiency and preterm labour). Antenatal corticosteroids were considered to have been administered if at least two betamethasone doses were given 24 hours apart and the delivery took place not less than 24 hours and no more than 7 days after the last dose.

BPD, the primary outcome, was defined as oxygen dependency at 36 weeks of postmenstrual age (PMA).¹⁶ Secondary outcomes included the incidence of respiratory distress syndrome (RDS) and its severity (need of ≥ 2 doses of surfactant), persistent pulmonary hypertension of the newborn (PPHN) requiring inhaled nitric oxide (iNO) therapy according to our local protocols, sepsis (defined as the presence of clinical signs of infection with a positive blood culture for bacteria or fungi), pneumonia (defined as clinical sign of infection and a positive bronchoalveolar lavage fluid culture for bacteria or fungi), severe intracranial haemorrhage (IVH) (grade 3 or 4 according to Papile's classification), haemodynamically significant patent ductus arteriosus (Hs-PDA) (ductal diameter > 1.6 mm, growing or pulsatile ductus flow from left to right, reversal of flow in the descending aorta, increased left atrium to aortic ratio > 1.3), duration of mechanical ventilation and duration of oxygen therapy.

Clinical strategies were unchanged throughout the study period. American Heart Association Guidelines for neonatal resuscitation were applied in the delivery room.¹⁷ All the babies received caffeine at the admission in NICU. If intubation was needed (at birth or after non-invasive ventilation support failure), elective high-frequency oscillatory ventilation was performed with Draeger Babylog 8000 plus (Draeger, Lubeck, Germany)¹⁸ providing gentle ventilation and early extubation. We used Curosurf (Chiesi Farmaceutici) at a dose of 200 mg/kg as RDS treatment and iNO therapy for PPHN. Continuous positive airway pressure was always applied after extubation. All the newborns received ibuprofen therapy in case of Hs-PDA. Surgery was performed if an Hs-PDA persisted after two courses of ibuprofen or if it was contraindicated.¹⁹

Statistical analyses

A descriptive analysis was conducted to report prenatal and neonatal characteristics of the studied neonates. Values were expressed as mean and SD for continuous variables or absolute frequency and percentages for categorical variables. Comparison of continuous variables between groups was evaluated by the t test, and comparison of categorical variables was appraised by the Z test for the difference between two proportions or the Fisher test as appropriate. A p value < 0.05 was considered significant. In order to evaluate the association between the BPD risk and each explanatory variable, a univariable analysis was performed using a logistic regression model by including one variable at a time. 'Prenatal and early-birth history'-related independent variables found to be significant in the univariable analyses (p value equal or lower than 0.05) were included in the multivariable model. A likelihood ratio test was used to compare the goodness of fit

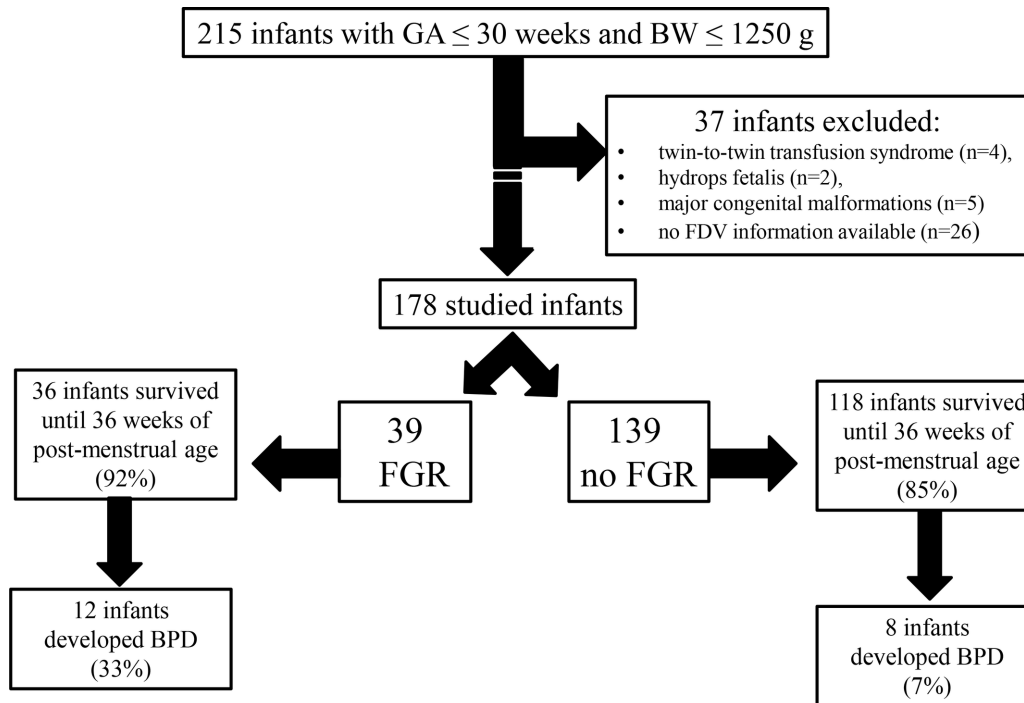


Figure 1 Flow diagram of the study participants. BPD, bronchopulmonary dysplasia; BW, birth weight; FDV, fetal Doppler velocimetry; FGR, fetal growth restriction; GA, gestational age.

of the models and for selection of the most appropriate model.²⁰ Statistical analyses were done with Stata version 2013 software (*Stata Statistical Software: Release 13*, College Station, Texas, USA).

Ethical approval

The study protocol was approved by the Ethics Committee of the Policlinico Universitario A. Gemelli-Università Cattolica del S. Cuore.

RESULTS

In the study period, 215 newborns with GA \leq 30 weeks and BW \leq 1250 g were admitted to our NICU. Thirty-seven newborns were excluded because of twin-to-twin transfusion syndrome (n=4), hydrops fetalis (n=2), major congenital malformations (n=5) and no fetal Doppler velocimetry information available (n=26). Consequently, 178 newborns were eligible for the study (figure 1). All the mothers of the studied infants underwent to a prenatal surveillance programme for pregnancy at risk of preterm birth that included a fetal Doppler examination.

Thirty-nine infants (22%) were considered FGR infants as they had a failing fetal growth and an abnormal fetal Doppler velocimetry. As shown in table 1, FGR infants were significantly more mature than NO-FGR infants and their BW was significantly lower with consequent BW z-score significantly lower than in NO-FGR group. FGR infants received antenatal corticosteroids more frequently than the others did (97% vs 83%). Histological chorioamnionitis was significantly more frequent in NO-FGR placentas. Maternal pre-eclampsia was more frequent in the FGR group than in the other group, but the difference

was not statistically significant. We did not observe any difference between the groups regarding incidence and severity of RDS, incidence of PPHN, PDA pharmacological treatment and ligation. Duration of O₂-therapy was significantly longer in the FGR infants compared with the NO-FGR infants. There were no differences between the two groups in terms of survival. Only one death after 36 weeks PMA occurred in the FGR group. Among the survived babies at 36 weeks of PMA, 12 out of 36 (33%) of the FGR group developed BPD versus 8 out of 118 (7%) of the NO-FGR group and the difference was statistically significant. We did not observe any case of periventricular leukomalacia in the study population. The incidence of severe forms of IVH (grade 3–4) was significantly higher in the NO-FGR group compared with the FGR group. The cause of delivery significantly differed between the groups: ‘indicated preterm delivery’ was more represented in the FGR group whereas ‘spontaneous preterm delivery’ was more common in the NO-FGR group. In 32 cases, the delivery was neither indicated nor spontaneous.

In order to understand the role of FGR in developing BPD, we made a univariable analysis between BPD and NO-BPD infants considering prenatal and neonatal factors. Of the 178 studied newborns, we analysed only the 154 babies survived until 36 weeks PMA (table 2). Significant risk factors for BPD were: BW, Apgar score at 5 min, length of ventilation, severity of acute respiratory failure at birth, PPHN, pneumonia and sepsis. GA was lower in BPD infants, but this difference was not statistically significant. Neither histological chorioamnionitis nor maternal pre-eclampsia was associated with an increased BPD risk. Moreover, the ‘indicated’ preterm delivery was related

Table 1 Prenatal and neonatal characteristics of the studied neonates

	FGR (n=39)	NO-FGR (n=139)	p Value
Gestational age (weeks)	27.5±1.1	26.7±1.7	0.008
Birth weight (g)	720±198	927±242	<0.001
Caesarean section	37 (95)	110 (79)	0.03
Indicated preterm birth	35 (90)	30 (22)	<0.001
Spontaneous preterm birth	1 (3)	80 (58)	<0.001
Male sex	19 (49)	72 (52)	0.73
Apgar score at 5 min	7.8±1	7.4±1.5	0.14
Antenatal corticosteroids	38 (97)	115 (83)	0.02
Histological chorioamnionitis	2 (5)	34 (31)	0.006
Pre-eclampsia	6 (15)	9 (6)	0.08
Birth weight z-score	-1.22±0.8	0.31±1.04	<0.001
Small for gestational age	15 (38)	9 (6)	<0.001
Respiratory distress syndrome	32 (82)	101 (75)	0.23
Need of 2 or more doses of surfactant	10 (26)	36 (26)	0.97
Persistent pulmonary hypertension of the newborn	5 (12)	13 (9)	0.53
Length of ventilation (hours)	305±393	226±347	0.22
Length of O ₂ -therapy (hours)	907±989	556±837	0.02
Pneumonia	17 (44)	41 (29)	0.10
Sepsis	14 (36)	51 (37)	0.93
Patent ductus arteriosus—pharmacological treatment	12 (31)	65 (47)	0.09
Patent ductus arteriosus—surgical closure	4 (10)	18 (13)	0.65
Survival	35 (90)	118 (85)	0.44
Bronchopulmonary dysplasia*	12 (33)	8 (7)	<0.001
Severe intraventricular haemorrhage	1 (3)	21 (15)	0.03

Data expressed as mean ± SD or n (%).

*Data are referred to the survived babies at 36 weeks postmenstrual age.

FGR, fetal growth restriction.

to an increased BPD rate, whereas the ‘spontaneous’ delivery did not show any further BPD risk.

SGA infants were at higher risk for BPD and this risk increased in FGR-SGA infants: BPD developed in 1/7 (14%) of SGA-NO-FGR infants compared with 11/12 (92%) of SGA-FGR infants (table 3). Accordingly, the severe forms of BPD were more represented in the SGA-FGR group.

We examined a logistic model in order to define the role of FGR in developing BPD, regardless of being SGA and other potential confounder factors. Table 4 presents the adjusted ORs and 95% CI of the independent variables included in the final multivariable model. FGR was significantly associated with BPD risk (OR 5.1, CI 1.4 to 18.8, p=0.01), independently from BW z-score that still remains a strong risk factor (OR 0.5, CI 0.3 to 0.9, p=0.01).

DISCUSSION

Nowadays BPD is considered as a multifactorial disease resulting from arrest of lung development and other

processes injuring the lungs before and on birth.^{21 22} FGR has been indicated as a risk factor for BPD in newborns with an extremely low GA.^{3 4} Our data confirm that SGA infants are at high risk of developing BPD, regardless of GA and other factors involved in BPD development such as severity of RDS at birth, PPHN, mechanical ventilation and post-natal infectious insults. Moreover, the same data show that SGA infants are more likely to develop BPD when placenta dysfunction is the external cause of low BW. This confirms our hypothesis according to which in a cohort of preterm infants, the presence of uteroplacental insufficiency, based on fetal Doppler velocimetry abnormalities, is more associated with BPD risk than low BW per se. We may assume that placental insufficiency triggers a process affecting epigenetic fetal programme and this could explain both low BW and the worst respiratory outcome. This speculation is in agreement with the most recent literature showing that the concomitance of low BW and an adverse fetal environment leads to a high BPD risk. Recently, two large prospective population-based cohort studies have investigated this

Table 2 Univariate analyses between BPD and NO-BPD infants

	BPD (n=20) 13%	NO-BPD (n=134) 87%	OR	CI	p Value
Gestational age (weeks)	26.6±1.9	27.2±1.4	0.76	0.56 to 1.03	0.08
Birth weight (100 g)	662±306	946±209	0.54	0.41 to 0.71	<0.0001
Caesarean section	17 (85)	117 (87)	0.82	0.22 to 3.11	0.77
Indicated preterm birth	13 (65)	45 (34)	3.67	1.37 to 9.85	0.01
Spontaneous preterm birth	5 (25)	61 (45)	0.40	0.14 to 1.16	0.09
Male sex	13 (65)	65 (48)	1.97	0.74 to 5.24	0.17
Fetal growth restriction	12 (60)	24 (18)	6.87	2.53 to 18.64	<0.0001
Small for gestational age	12 (60)	7 (5)	27.21	8.41 to 88.07	<0.0001
Antenatal corticosteroids	18 (90)	120 (90)	1.05	0.22 to 5.01	0.95
Birth weight z-score, 1 unit	-1.08±1.56	0.12±1.01	0.38	0.23 to 0.62	<0.0001
Histological chorioamnionitis	2 (10)	27 (20)	0.40	0.08 to 1.91	0.25
Pre-eclampsia	1 (5)	12 (9)	0.54	0.06 to 4.35	0.56
Apgar score at 5 min	6.9±1.2	7.8±1.2	0.63	0.45 to 0.88	0.007
Respiratory distress syndrome	15 (75)	94 (70)	1.27	0.43 to 3.75	0.66
Need of two or more doses of surfactant	9 (45)	25 (19)	3.56	1.33 to 9.53	0.01
PPHN	6 (30)	7 (5)	7.77	2.29 to 26.39	0.001
Ventilation length (24 hours)	801±678	155±198	1.1	1.06 to 1.15	<0.0001
Pneumonia	15 (75)	31 (23)	9.97	3.35 to 29.61	<0.0001
Patent ductus arteriosus pharmacological treatment	10 (50)	55 (41)	1.43	0.56 to 3.68	0.45
Patent ductus arteriosus surgical closure	6 (30)	14 (10)	0.40	0.08 to 1.91	0.25
Sepsis	12 (60)	42 (31)	3.29	1.25 to 8.63	0.02

Data expressed as mean ± SD or n (%).
BPD, bronchopulmonary dysplasia.

Table 3 BPD incidence according to birth weight and FGR

	Survived at 36 weeks	BPD*	Severe BPD†
AGA—NO-FGR n. 130	111	7 (6)	5 (4)
AGA—FGR n. 24	24	1 (4)	1 (4)
SGA—NO-FGR n. 9	7	1 (14)	1 (14)
SGA—FGR n. 15	12	11 (92)	4 (33)

Data expressed as n (%).

*Need of O₂-therapy with or without positive-pressure ventilation at 36 weeks of postmenstrual age; data are referred to the survived babies at 36 weeks of postmenstrual age.

†Need of O₂-therapy≥30% and/or positive-pressure ventilation at 36 weeks of postmenstrual age; data are referred to the survived babies at 36 weeks of postmenstrual age.

AGA, appropriate for gestational age; BPD, bronchopulmonary dysplasia; FGR, fetal growth restriction; NO-BPD, babies without bronchopulmonary dysplasia; NO-FGR, babies without fetal growth restriction; SGA, small for gestational age.

issue: one showed that the risk of moderate to severe BPD is high in pregnancies with fetal disorders but not in those with maternal disorders only⁸ and the other one showed an increased risk of death and BPD associated with disorder of placentation as compared with presumed infection/inflammation, especially when vascular disorders were associated with a low BW.⁹ Accordingly, in our study, we observed an increased rate of BPD among babies born from a vascular disorder-associated preterm delivery, but mostly we found a significantly higher BPD risk among FGR-SGA infants. Placental insufficiency leads to chronic fetal hypoxia; fetuses adapt to chronic hypoxia via redistribution of

Table 4 Risk factors for bronchopulmonary dysplasia: multivariable analysis

Variable*	OR	95% CI	p Value
Fetal growth restriction	5.10	1.39 to 18.8	0.01
Birth weight z-score	0.50	0.28 to 0.88	0.01
Apgar score at 5 min	0.52	0.34 to 0.80	0.003

*Final model after likelihood ratio test.

cardiac output. Reduced perfusion of splanchnic organs during development causes relative hypoxia/ischaemia that can lead to various disorders in postnatal life.¹⁰ Placenta acts as the director of the whole fetal development and its pathology has already been associated with lung and vascular disease in the offspring: Mestan *et al* have shown that maternal placental vascular underperfusion is associated with the development of BPD among preterm infants.¹¹ Fetal Doppler examination enables clinicians to identify placental underperfusion and the resulting adverse fetal environment. Experimental sheep FGR models have highlighted impaired lung function and structure as well as endothelial dysfunction in growth-restricted offspring suggesting that placental insufficiency may impair both pulmonary angiogenesis and alveolarisation.^{23 24} A recent experimental study has shown that intrauterine growth-restricted lambs did not differ from control lambs in terms of lung function, structure, inflammation and response to ventilation after 1 week of placental dysfunction.²⁵ The authors did not examine the endothelial function and its role in the respiratory outcomes. Moreover, placental insufficiency was either too short in duration or too late in gestation to induce structural changes in the lung. It is possible that the time of onset and the duration of placental insufficiency are essential in lung development. Interestingly, in our cohort population, FGR AGA infants did not show any further BPD risk compared with NO-FGR AGA infants, probably because their exposure to an abnormal intrauterine environment was not long enough to cause neither low BW nor lung susceptibility.

Soudée *et al* showed that antenatal growth-restricted infants are at higher risk of BPD, regardless of their GA at birth.²⁶ Interestingly, in our population BPD and NO-BPD infants have similar GA, confirming that placental insufficiency could influence lung development more than immaturity alone.

The association between BPD and pre-eclampsia is controversial.^{27–29} Our data do not show any association between BPD and pre-eclampsia when considered independently from FGR.

The role of antenatal inflammation in developing BPD remains unclear.³⁰ In our cohort, BPD risk does not seem to be increased by histological chorioamnionitis or by an inflammatory condition triggering delivery regardless of placenta histology.

The Apgar score at 5 min was strongly related to BPD risk, as already suggested by previous observational studies.^{31 32} A higher need of resuscitation at birth could be the consequence of an adverse fetal environment that could affect lung development; moreover, lung injuries caused by invasive ventilation in the delivery room are a well-known occurrence.³³

As previously reported,³⁴ FGR infants did not differ from the others in terms of RDS. Nevertheless, the significantly higher exposure of our FGR infants to antenatal steroids may have played a protective role against RDS development.

We found a lower IVH rate in the FGR group probably because they had a higher GA and they received prenatal steroids more often than the other newborns, although the influence of FGR on brain injury is still unclear.^{35 36}

Our study has some limitations. The small sample size of BPD infants could limit the power to detect differences between groups and might have affected the accuracy of our estimates. Moreover, the statistical power of the study does not allow us to reach some conclusions on several non-significant associations that we observe in our cohort (such as BPD and histological chorioamnionitis or FGR and RDS). Doppler differences in relation to the small sample of the study group are not considered as well as how long exactly was the fetus exposed to abnormal Doppler flows.

In conclusion, SGA preterm infants show the highest BPD risk when placenta dysfunction is the external cause of low BW. We suggest umbilical artery Doppler velocimetry as a tool for identifying high-BPD risk preterm infants, as we strongly believe that characterising fetal environment will be mandatory in future neonatal medicine. Nevertheless, clinicians should be aware that this tool carries with it a risk of false positive results. Further research is needed to investigate thoroughly the link between placenta dysfunction and lung disease.

Contributors All the authors included on the paper fulfil the criteria of authorship as stated by the ICMJE recommendations. Each author listed on the manuscript has seen and approved the submission of this version of the manuscript and takes full responsibility for the manuscript. There is not anyone else who fulfils the criteria that has been excluded as an author. AL gave substantial contributions to the conception and design of the work and to the interpretation of data. She wrote the first draft of the work and approved the final revised version of it. PR gave substantial contributions to the conception and design of the work and to the interpretation of data. He revisited the work critically and approved the final revised version of it. RP gave substantial contributions to the design of the work; she was responsible for the analysis of data and collaborated to their interpretation. She revisited the work critically and approved the final submitted version of it. FC gave substantial contributions to the design of the work, to the analysis and interpretation of data; he revisited it critically and approved the final version to be published. MT CT, CA, CR and AP were responsible for the acquisition of neonatal data; they revisited the work critically and approved final version to be published. AG was responsible for the acquisition of neonatal data; he revisited the work critically and approved final version to be published. IM gave substantial contributions to the design of the work and was responsible for the acquisition of prenatal data; she revisited the work critically and approved final version to be published. SB was responsible for the acquisition of prenatal data; she revisited the work critically and approved final version to be published. GFZ gave substantial contributions to the design of the work and to the acquisition of data about placental histopathology. He revisited the work critically and approved the final revised version of it. CR gave substantial contributions to the design of the work. He revisited the work critically and approved the final revised version of it. GV gave substantial contributions to the conception and design of the work and to the interpretation of data. He revisited the work critically and approved the final revised version of it. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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