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Association of the dysfunctional placentation endotype of prematurity with bronchopulmonary dysplasia: a systematic review, meta-analysis and meta-regression

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ABSTRACT

Background Antenatal pathological conditions are key in the pathogenesis of bronchopulmonary dysplasia (BPD). Pathophysiological pathways or endotypes leading to prematurity and perinatal lung injury can be clustered into two groups: infection and dysfunctional placentation, which include hypertensive disorders of pregnancy (HDP) and intrauterine growth restriction (IUGR). We conducted a systematic review of observational studies exploring the association between the dysfunctional placentation endotype and BPD.

Methods MEDLINE, Embase and Web of Science databases were searched up to February 2020 for studies reporting data on the diagnosis of HDP, IUGR or small for gestational age (SGA) and BPD risk. BPD was classified as BPD28 (supplemental oxygen on day 28), BPD36 (oxygen at 36 weeks postmenstrual age), severe BPD (≥ 30% oxygen or mechanical ventilation), BPD36/death and BPD-associated pulmonary hypertension.

Results Of 6319 studies screened, 211 (347 963 infants) were included. Meta-analysis showed an association between SGA/IUGR and BPD36 (OR 1.56, 95% CI 1.37 to 1.79), severe BPD (OR 1.82, 95% CI 1.36 to 2.29) and BPD/death (OR 1.91, 95% CI 1.55 to 2.37). Exposure to HDP was not associated with BPD but was associated with decreased odds of BPD/death (OR 0.77, 95% CI 0.64 to 0.94). Both HDP (OR 1.41, 95% CI 1.10 to 1.80) and SGA/IUGR (OR 2.37, 95% CI 1.86 to 3.02) were associated with BPD-associated pulmonary hypertension.

Conclusion When placental vascular dysfunction is accompanied by fetal growth restriction or being born SGA, it is associated with an increased risk of developing BPD and pulmonary hypertension. The placental dysfunction endotype of prematurity is strongly associated with the vascular phenotype of BPD.

Prospero registration number Review protocol was registered in PROSPERO database (ID=CRD42018086877).

Key messages

What is the key question?

► Is the dysfunctional placentation endotype of prematurity, as represented by hypertensive disorders of pregnancy and intrauterine growth restriction, associated with an increased risk of developing bronchopulmonary dysplasia?

What is the bottom line?

► When placental vascular dysfunction is accompanied by fetal growth restriction or being born small for gestational age, it is associated with an increased risk of developing bronchopulmonary dysplasia and bronchopulmonary dysplasia-associated pulmonary hypertension.

Why read on?

► This meta-analysis review combines data from 211 studies (347 963 infants) and provides evidence that the placental dysfunction endotype of prematurity is strongly associated with the vascular phenotype of bronchopulmonary dysplasia.

INTRODUCTION

Very preterm birth is defined by a gestational age (GA) of less than 32 weeks, and extremely preterm birth by a GA of less than 28 weeks.[1 2] This degree of prematurity is the leading cause of neonatal mortality and morbidity due to a combination of organ immaturity and iatrogenic injury.[1 2] Preterm birth is always the result of a pathological process, which may not only contribute to early delivery but may also adversely impact neonatal outcomes.[3–6] The pathogenic pathways leading to very and extremely preterm birth can be clustered into two main groups: (1) intrauterine infection/inflammation and (2) dysfunctional placentation.[3–6] The first group is related to histological chorioamnionitis and placental microbial invasion, whereas the second group is associated with hypertensive disorders of pregnancy (HDP), and the entity identified as fetal indication/intrauterine growth restriction (IUGR).[3–6]

Characterisation of these two groups provides strong rationale for establishing each as a distinct endotype that impacts the risk and outcome of prematurity. The term endotype was coined by Anderson to cluster asthmatic patients not only by their clinical characteristics but also by the pathophysiological features of the disease.[7] The term has subsequently been extended to other conditions in an attempt to identify the subtypes of a disease defined by a unique or distinctive functional or pathophysiological mechanism.[8–10] The use of

endotypes is highly valuable to more fully describe specific biological pathways or biomarkers underlying clinical observations expressing the phenotype, which can enhance clinical care and research.[8–10]

Bronchopulmonary dysplasia (BPD), the chronic lung disease of prematurity, is the most common complication of very and extreme preterm birth.[11–14] Low GA at birth is the greatest single predictor of the risk for BPD. However, BPD is increasingly recognised as the result of an aberrant reparative response to both antenatal and postnatal injury to the developing lung.[11–15] Antenatal stresses, including chorioamnionitis, HDP and IUGR are frequently identified as risk factors for BPD.[11–17] However, it is very difficult to unravel which part of their pathogenic action is due to the alterations that these conditions induce in lung development and which part is due to their role as triggers of prematurity.

Intrauterine and postnatal injury to a developing lung can affect any number, if not all, of the three main lung compartments: (1) airways, (2) alveoli and adjacent lung parenchyma and (3) pulmonary vasculature.[18–21] A growing body of evidence indicates that these compartments are variably affected within each patient, which leads to different clinical phenotypes.[18–21] In particular, the 'vascular phenotype' of BPD is being increasingly recognised and BPD-associated pulmonary hypertension (PH) is a strong contributor to poor survival.[18–24] Our understanding of the risk factors and natural history of BPD-associated PH continues to grow but already the first reports on the condition suggested a strong association with both IUGR and HDP.[25 26]

Refining BPD risk according by endotypes and clinical phenotypes may be valuable for developing personalised medicine approaches that can potentially improve outcomes and lead to better-designed clinical trials. In a recent systematic review, we analysed the association between the paradigmatic example of the infectious/inflammatory endotype of prematurity (ie, chorioamnionitis) and BPD.[16] Meta-analysis showed that exposure to chorioamnionitis was associated with higher risk of BPD. However, GA in the chorioamnionitis-exposed group was ~1.2 weeks lower than in the 'control' group and meta-regression analysis showed that this difference in GA significantly modulated the association between chorioamnionitis and BPD.[16] The aim of this systematic review is to further address these questions by performing a comprehensive analysis to determine the association between the endotype of placental dysfunction, as represented by HDP and IUGR, and the risk of developing BPD and/or BPD-associated PH. In addition, through the use of meta-regression, we aimed to unravel the role of GA in the association between the placental dysfunction endotype and BPD.

METHODS

The methodology for this study was based on our recently published experience on performing meta-analyses to study the associations between chorioamnionitis and BPD,[16] and between IUGR and patent ductus arteriosus.[27] Detailed information on methods is provided as online supplemental material. The study was performed and reported according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) and meta-analysis of observational studies in epidemiology (MOOSE) guidelines.[28] The Population, Exposure, Comparison and Outcome question was: Do preterm infants (P) exposed to HDP or IUGR during pregnancy (E) have a higher risk of developing BPD or BPD-associated PH (O) than preterm infants with no history of exposure (C)?

Sources and search strategy

A comprehensive literature search was undertaken using the PubMed, EMBASE and Web of Science databases. No language limit was applied. The literature search was updated up to February 2020. The search strategy is detailed in online supplemental material.

Study selection

Studies were included if they examined preterm (GA <37 weeks) or very low birth weight (BW) (<1500 g) infants and reported primary data that could be used to measure the association between exposure to HDP or IUGR and the development of BPD or BPD-associated PH. Studies defining IUGR based on BW were also included. Since small for GA (SGA) is not necessarily synonymous with IUGR,[29–32] the group will be referred to as SGA/IUGR.

Data extraction, definitions, and quality assessment

Two reviewers (MP and MA-F) extracted data from relevant studies and three reviewers (EV-M, EvW-K and EV) checked data extraction for accuracy and completeness. Discrepancies were resolved by consulting the primary report. Outcomes considered in meta-analysis were: (1) BPD28, defined as oxygen requirement on postnatal day 28; (2) BPD36, defined as oxygen requirement at the postmenstrual age (PMA) of 36 weeks; (3) BPD36 or death; (4) Severe BPD, defined as need for ≥30% oxygen and/or positive pressure at 36 weeks PMA; (5) BPD-associated PH, defined by any echocardiographic criteria as long as the evaluation was performed at a postnatal age >4 weeks. Using these definition criteria, BPD28 was considered to include all severities of BPD, whereas BPD36 was considered to include a combination of moderate and severe BPD.[16 33] With regard to exposures, any definition of HDP or SGA/IUGR was accepted but we performed subgroup analysis based on the different definitions (Any HDP, pre-eclampsia, pre-eclampsia-hemolysis elevated liver enzymes and low platelets (HELLP) syndrome, BW <P10, BW <P5, BW <P3 or −2SD and IUGR defined by assessment of fetal growth). This subgroup analysis was only performed for the analysis including at least 10 studies. When a study used different BW threshold percentiles to define SGA, data from the lowest percentile were included. When a study did not specify the threshold percentile used, it was grouped together with the studies that used the 10th percentile.

Methodological quality was assessed using the Newcastle-Ottawa Scale (NOS) for cohort or case–control studies.[34] This scale assigns a maximum of nine points (four for selection, two for comparability and three for exposure or outcome). NOS scores ≥7 were considered high-quality studies (low risk of bias), and scores of 5–6 denoted moderate quality (moderate risk of bias).[34]

Statistical analysis

Studies were combined and analysed using Comprehensive Meta-Analysis V.3.0 software (Biostat, Englewood, New Jersey, USA). Summary statistics were calculated with a random-effects model and subgroups were combined with a mixed-effects model.[35] For dichotomous outcomes, the OR with 95% CI was calculated. For continuous outcomes (eg, GA), the mean difference with 95% CI was calculated. Statistical heterogeneity was assessed by Cochran's Q statistic and by the I^2 statistic. Potential sources of heterogeneity were assessed through subgroup analysis and/or random effects (method of moments) univariate meta-regression analysis.[36] For both categorical and continuous covariates, the R^2 analogue, defined as the total between-study variance explained by the moderator, was calculated based on the meta-regression matrix.[36] We used the Egger's regression test and funnel plots to assess publication bias. A probability value of less than 0.05 (0.10 for heterogeneity) was considered statistically significant.

RESULTS

The PRISMA flow diagram of the search process is shown in online supplemental eFigure 1. Of 6319 potentially relevant studies, 211

Table 1 Main meta-analyses

Outcome	Exposure/insult		K	OR	95% CI		P value	Heterogeneity	
					Lower limit	Upper limit		I^2 (%)	P value
All BPD (BPD28)	Hypertensive disorders of pregnancy (HDP)	Any HDP	13	0.927	0.636	1.352	0.695	62.8	0.001
		Pre-eclampsia	14	1.058	0.756	1.482	0.742	59.4	0.002
		Pre-eclampsia/HELLP	6	0.771	0.465	1.279	0.314	64.7	0.015
		HDP overall	33	0.949	0.757	1.188	0.645	61.9	<0.001
	SGA/IUGR	BW <P10	27	0.823	0.618	1.096	0.182	64.7	<0.001
		BW <P3 or −2SD	4	1.234	0.599	2.541	0.569	82.9	0.001
		IUGR	2	1.267	0.532	3.018	0.535	0.0	0.546
		IUGR/SGA overall	33	0.898	0.696	1.158	0.408	66.2	<0.001
Moderate/severe BPD (BPD36)	HDP	Any HDP	27	1.066	0.914	1.243	0.810	68.9	<0.001
		Pre-eclampsia	31	1.093	0.869	1.375	0.448	83.8	<0.001
		Pre-eclampsia/HELLP	3	1.022	0.762	1.372	0.882	75.8	0.017
		HDP overall	61	1.066	0.948	1.198	0.288	79.8	<0.001
	SGA/IUGR	BW <P10	57	1.550	1.308	1.837	<0.001	85.7	<0.001
		BW <P5	2	1.651	0.659	4.138	0.284	0.0	0.674
		BW <P3 or −2SD	23	1.460	1.130	1.884	0.004	87.8	<0.001
		IUGR	9	2.251	1.537	3.297	<0.001	80.0	<0.001
		SGA/IUGR overall	91	1.564	1.369	1.785	<0.001	85.5	<0.001
Severe BPD	HDP	HDP overall*	8	0.940	0.582	1.517	0.799	41.8	0.100
	SGA/IUGR	BW <P10	11	1.491	1.001	2.220	0.049	34.5	0.123
		BW <P3	4	2.277	1.296	4.031	0.005	0.0	0.788
		IUGR	2	2.285	1.220	4.290	0.010	71.6	0.061
		SGA/IUGR overall	17	1.821	1.363	2.288	<0.001	24.5	0.171
BPD or death	HDP	HDP overall*	8	0.771	0.635	0.937	0.009	38.9	0.120
	SGA/IUGR	BW <P10	12	1.792	1.387	2.315	<0.001	90.5	<0.001
		BW <P5	1	2.970	0.899	9.814	0.074	0.0	1.000
		BW <P3 or −2SD	2	2.538	1.323	4.869	0.005	54.1	0.140
		IUGR	3	1.934	1.126	3.323	0.017	87.7	<0.001
		SGA/IUGR overall	18	1.914	1.545	2.373	<0.001	88.7	<0.001
BPD-associated pulmonary hypertension	HDP	Any HDP	11	1.408	1.034	1.917	0.030	38.3	0.094
		Pre-eclampsia	9	1.418	0.944	2.128	0.092	0.0	0.554
		HDP overall	20	1.412	1.104	1.805	0.006	18.3	0.227
	SGA/IUGR	BW <P10	17	2.275	1.771	2.922	<0.001	40.8	0.041
		BW <P3 or −2SD	3	4.418	1.689	11.556	0.002	0.0	0.390
		SGA/IUGR overall	20	2.373	1.862	3.023	<0.001	38.7	0.040

Mixed effects analysis. A random effects model is used to combine studies within each subgroup. A fixed effect model is used to combine subgroups and yield the overall effect.
*Studies were not divided into subgroups because K<10 . OR >1 indicates association with increased risk of the outcome and OR <1 indicates association with decreased risk of the outcome.
BPD28, BPD defined as oxygen requirement on postnatal day 28; BPD36, BPD defined as oxygen requirement at the postmenstrual age of 36 weeks; BPD, bronchopulmonary dysplasia; BW, birth weight; IUGR, intrauterine growth restriction (defined on the basis of fetal growth assessment); K, number of studies; P3, third percentile; P5, 5th percentile; P10, 10th percentile; SGA, small for gestational age.

met inclusion criteria. These studies included 347 963 preterm infants. Characteristics of the studies are summarised in online supplemental table 1. In 76 studies, the exposure (HDP or SGA/IUGR) was the independent variable and the outcome (BPD) was the dependent variable. In 135 studies, the outcome was the independent variable and the exposure the dependent variable. Fifty-seven studies reported data on BPD28, 129 studies on BPD36, 19 studies on severe BPD, 23 studies on BPD/death and 27 on BPD-associated PH. The NOS score of each study is depicted in online supplemental table 1. All studies received at least six points indicating a low to moderate risk of bias.

The main results of the meta-analysis are summarised in table 1 and figure 1. The raw count data are depicted in online supplemental tables 4 to 13. Meta-analysis did not find a significant association between exposure to either HDP (figure 1, online supplemental figure S2) or SGA/IUGR (figure 1, online supplemental figure S3) and risk of developing BPD28. Exposure to HDP was also not associated with the risk of developing BPD36 (figure 1, online supplemental figrue S4). In contrast, exposure to SGA/IUGR was significantly associated with an increased risk of BPD36 (figure 1, online supplemental figure S5 and S6). When subdividing by definition of SGA/IUGR, the association with BPD36 remained significant for SGA

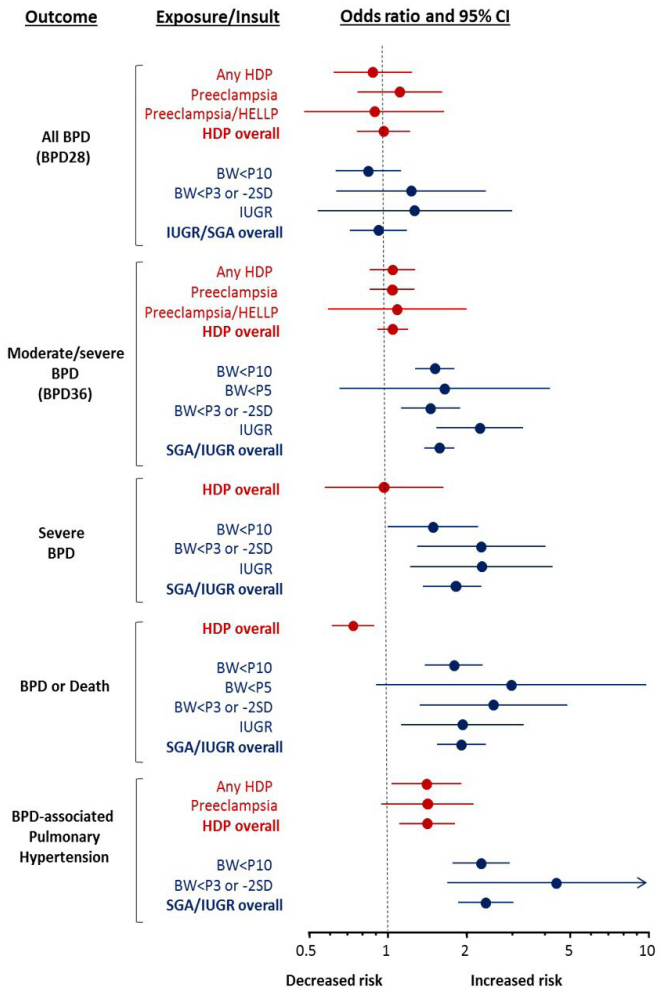

Figure 1 Summary of meta-analyses on the association between the dysfunctional placentation endotype ofprematurity and bronchopulmonary dysplasia (BPD). BPD28: BPD defined as oxygen requirement onpostnatal day 28; BPD36: defined as oxygen requirement at the postmenstrual age of 36 weeks; (defined on the basis of fetal growth assessment); BW, birthweight; HDP, hypertensive disorders of pregnancy; IUGR, intrauterine growthrestriction; P3, 3rd percentile; P10, 10th percentile; SGA, small for gestational age.

defined as BW <P10, as BW <P3 or −2SD or for IUGR, as defined by assessment of fetal growth (figure 1, online supplemental figure S5 and S6). Meta-regression analysis did not show significant differences in the association between SGA/IUGR and BPD36 depending on the criteria used to define SGA/IUGR (p=0.672).

For the outcome of severe BPD, meta-analysis showed a significant association with exposure to SGA/IUGR but did not demonstrate a significant association with exposure to HDP (figure 1, online supplemental figure S7 and S8). HDP was associated with a lower risk of developing the combined outcome BPD36 or death while SGA/IUGR was associated with a higher risk of developing this outcome (figure 1, online supplemental figure S9 and S10). Finally, both HDP and SGA/IUGR were significantly associated with an increased risk of developing BPD-associated PH (figure 1, online supplemental figure S11 and S12).

Neither visual inspection of funnel plots (online supplemental figure S13) nor Egger's test suggested publication or selection bias for any of the associations analysed.

To investigate the potential sources of heterogeneity, we conducted additional meta-analyses exploring the differences in baseline and clinical characteristics (GA, sex, exposure to antenatal corticosteroids, rate of respiratory distress syndrome (RDS)) between the groups exposed and non-exposed to HDP or SGA/IUGR. We also performed meta-regression and subgroup analysis. These latest analyses were limited to BPD36, the outcome with the largest number of studies.

Infants exposed to HDP had a significantly higher GA than the unexposed (table 2). Meta-regression showed that the difference in GA between the HDP-exposed and -unexposed groups significantly correlated with the effect size of the association between HDP and BPD36 (figure 2A, online supplemental table 2). The difference in GA was associated with 95% (R^2 analogue=0.95) of the variance in the association between HDP and BPD36 across studies (figure 2A, online supplemental table 2). To further assess the effect of GA on the association between HDP and BPD36, we carried out a meta-analysis of studies where the difference in mean GA was non-significant (p>0.05). In this subgroup of studies, HDP was significantly associated with risk of developing BPD36 (table 3).

The group of SGA/IUGR infants also showed a significantly higher GA (table 2). Meta-regression showed that the difference in GA between the SGA/IUGR-exposed and unexposed groups significantly correlated with the effect size of the association between SGA/IUGR and BPD36 (figure 2B, online supplemental table 2). However, this

Table 2 Meta-analyses of other covariates

Exposure/Insult	Meta-analysis (effect size)	K	Effect size	95% CI		P value	Heterogeneity	
				Lower limit	Upper limit		I^2 (%)	P value
Hypertensive disorders of pregnancy (HDP)	GA (MD in weeks)	33	0.613	0.399	0.826	<0.001	97.0	<0.001
	Male sex (OR)	27	0.755	0.714	0.798	<0.001	7.4	0.354
	Antenatal corticosteroids (OR)	21	1.124	0.974	1.297	0.109	85.0	<0.001
	IUGR/SGA (OR)	21	5.618	4.765	6.623	<0.001	80.0	<0.001
	RDS (OR)	20	1.164	0.907	1.494	0.234	80.6	<0.001
SGA/IUGR	GA (MD in weeks)	48	0.358	0.106	0.564	0.001	97.0	<0.001
	Male sex (OR)	27	0.921	0.818	1.037	0.173	68.668	<0.001
	Antenatal corticosteroids (OR)	20	1.123	0.908	1.388	0.286	80.4	<0.001
	HDP (OR)	22	4.858	3.365	7.013	<0.001	97.6	<0.001
	RDS (OR)	23	0.842	0.724	0.979	0.026	81.9	<0.001

GA, gestational age; HDP, hypertensive disorders of pregnancy; IUGR, intrauterine growth restriction (defined on the basis of fetal growth assessment); K, number of studies; MD, mean difference; RDS, respiratory distress syndrome; SGA, small for gestational age.

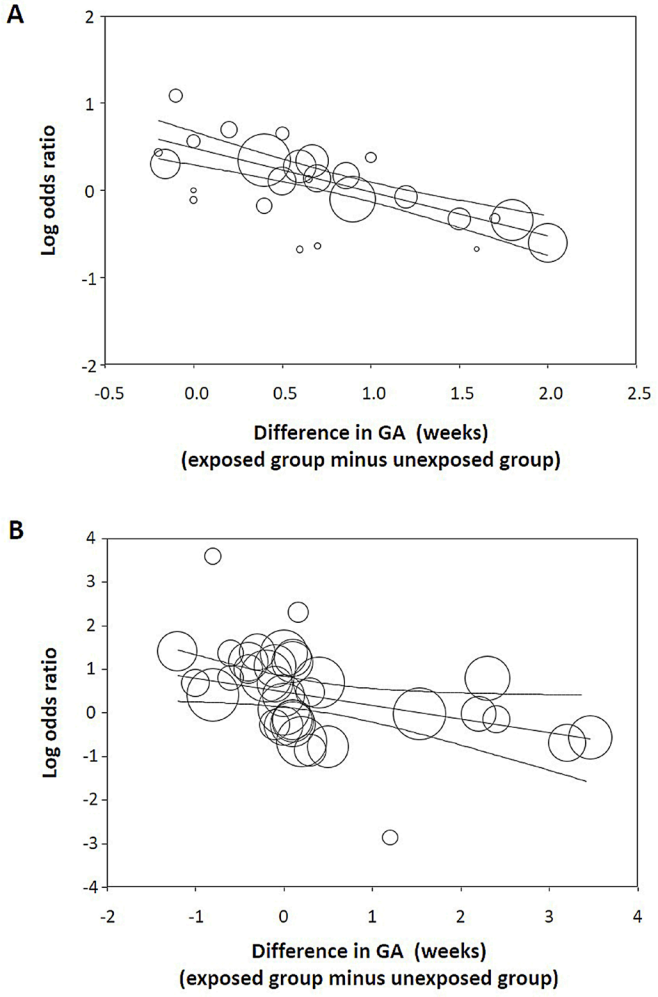

Figure 2 Meta-regression plot showing the correlation between the association of the dysfunctional placentation endotype of prematurity with moderate/severe bronchopulmonary dysplasia (BPD) and the difference in gestational age (GA) between exposed and non-exposed groups. (A) Univariate regression model correlating the difference in GA between hypertensive disorders of pregnancy (HDP)-exposed and HDP-unexposed infants. A total of 24 studies were included (coefficient, −0.50; 95% CI −0.65 to −0.35; p<0.001; R^2 analogue, 0.95). Each week that HDP-exposed infants were born later than control infants resulted in a decrease in BPD36 log OR of 0.50 (the equivalent of going from an OR of 1.00 to an OR of 0.61). (B) Univariate regression model correlating the difference in GA between small for GA (SGA)/intrauterine growth restriction (IUGR)-exposed and SGA/IUGR-unexposed infants. A total of 35 studies were included (coefficient, −0.31; 95% CI −0.57 to −0.05; p=0.002; R^2 analogue, 0.08). Log OR=lognOR.

difference in GA was only associated with 8% (R^2 analogue=0.08) of the variance in the association between HDP and BPD36 across studies (figure 2B, online supplemental table 2). In the subgroup of studies in which the GA was significantly (p<0.05) higher in the SGA/IUGR group, meta-analysis did not show any significant association between SGA/IUGR and BPD36 (table 3).

The GA of the entire cohort was also analysed as potential source of heterogeneity. The GA (mean or median) of each cohort did not correlate with the effect size of the association between HDP and BPD36 or SGA/IUGR and BPD36 (online supplemental table 2). In addition, when we conducted a subgroup analysis in which we separated studies that only included extreme preterm infants (GA <28 weeks), we observed that this criterion of subgrouping significantly affected the association between SGA/IUGR and BPD36 but not the association between HDP and BPD36 (table 3).

Additional meta-analyses showed that exposure to HDP was negatively associated with male sex of the newborn but did not find any significant association between HDP or SGA/IUGR and risk of receiving antenatal corticosteroids (table 2). Meta-regression did not show any significant correlation between risk of male sex, antenatal corticosteroids or RDS in the HDP-exposed infants and the effect size of the association between HDP and BPD36 (online supplemental table2). SGA/IUGR was negatively associated with the risk of developing RDS (table 2). Meta regression did not show any significant correlation between risk of male sex, antenatal corticosteroids or RDS in the SGA/IUGR-exposed infants and the effect size of the association between SGA/IUGR and BPD36 (online supplemental table2). As expected, meta-analyses showed a strong association between HDP and SGA/IUGR (table 2). This association was observed for all definitions of HDP and for all definitions of SGA/IUGR (online supplemental table 3).

Another potential sources of heterogeneity were the geographical location (continent) of the studies and the period of time in which they were conducted. The positive association between SGA/IUGR and BPD36 remained present in studies from America and Europe but was not observed in studies from Asia (table 3). The median year in which the study was conducted was not significantly associated with the effect size of the association between HDP or SGA/IUGR and BPD36 (online supplemental table 2).

Due to the homogeneous good quality of the studies (online supplemental table 1), we did not perform a sensitivity analysis based on the NOS scores. However, in order to investigate the role of the study design on the results of the meta-analysis, we conducted subgroup analyses in which studies were grouped depending on three criteria: (1) prospective versus retrospective; (2) cohort versus case–control and (3) exposure versus outcome as independent variable (table 3). Meta-regression did not show any significant differences among these subgroups (table 3).

DISCUSSION

This is the first meta-analysis that comprehensively addresses how two conditions related to the endotype of placental dysfunction are associated with the risk of BPD. Our data suggest that when placental vascular dysfunction is accompanied by fetal growth restriction or being born SGA, the condition is associated with an increased risk of developing moderate/severe BPD, severe BPD, BPD or death, and BPD-associated PH. The analysis also shows that preterm infants with a history of intrauterine exposure to HDP or growth restriction tended to be older at birth than their respective controls. Meta-regression analysis showed that this higher GA significantly affected the association of BPD with HDP and IUGR.

Several mechanisms have been proposed to explain the association between placental dysfunction and BPD. The main etiopathogenic hypotheses are based on the interference of chronic hypoxia and/or an imbalance between proangiogenic and antiangiogenic factors with alveolar and pulmonary vascular development.[13 14 24 37–41] Poor placentation in early stages of pregnancy that is associated with vascular underperfusion may develop into different clinical presentations: (1) maternal (HDP), (2) fetal (IUGR) or (3) both.[42 43] Different placental lesions, whether from maternal or fetal origin, are associated with the corresponding clinical presentation.[42–45] However, the correlation of these pathological conditions with a specific profile of angiogenic factors is controversial. Preliminary studies showed that HDP and IUGR of placental origin have similar proangiogenic

Table 3 Subgroup analyses

Meta-analysis	Criteria for subgrouping	K	OR	95% CI		P value	Heterogeneity		Meta-regression	
				Lower limit	Upper limit		I^2 (%)	P value	P value	R^2 analogue
HDP and BPD36	America	21	0.877	0.683	1.124	0.300	54.0	0.002	0.088*	0.0
	Asia	15	0.974	0.765	1.241	0.832	79.0	<0.001		
	Europe	17	1.182	0.947	1.474	0.139	71.5	<0.001		
	GA significantly higher in HDP group	13	0.890	0.723	1.097	0.276	81.2	<0.001	<0.001	0.53
	GA no significantly different	11	1.440	1.281	1.618	<0.001	63.0	0.006		
	Inclusion GA <28 weeks	9	1.223	0.943	1.585	0.129	63.0	0.006	0.201	0.22
	Inclusion GA >28 weeks	45	0.972	0.848	1.113	0.678	71.1	<0.001		
	Cohort	50	1.034	0.906	1.180	0.618	82.3	<0.001	0.233	0.0
	Case-control	11	1.301	0.964	1.775	0.085	34.1	0.126		
	Prospective	36	1.130	0.975	1.310	0.105	60.5	<0.001	0.300	0.0
	Retrospective	25	1.007	0.824	1.230	0.946	88.3	<0.001		
	Independent variable: Exposure	25	1.123	0.941	1341	0.197	87.4	<0.001	0.404	0.0
	Independent variable: Outcome	36	1.010	0.852	1.198	0.907	63.1	<0.001		
SGA/IUGR and BPD36	America	31	1.651	1.318	2.068	<0.001	89.6	<0.001	0.077*	0.0
	Asia	12	1.000	0.662	1.510	0.999	82.9	<0.001		
	Europe	46	1.655	1.373	1.997	<0.001	79.6	<0.001		
	GA significantly higher in SGA/IUGR group	7	0.964	0.628	1.482	0.869	88.2	<0.001	0.052	0.0
	GA no significantly different	26	1.590	1.219	2.074	0.001	69.9	<0.001		
	Inclusion GA <28 weeks	10	2.244	1.568	3.213	<0.001	95.2	<0.001	0.034	0.00
	Inclusion GA >28 weeks	81	1.477	1.280	1.703	<0.001	81.1	<0.001		
	Cohort	76	1.535	1.331	1.770	<0.001	87.9	<0.001	0.122	0.0
	Case-control	15	2.050	1.419	2.960	<0.001	50.4	0.013		
	Prospective	57	1.674	1.411	1.986	<0.001	87.0	<0.001	0.281	0.0
	Retrospective	34	1.479	1.197	1.828	<0.001	83.7	<0.001		
	Independent variable: exposure	34	1.884	1.539	2.306	<0.001	87.9	<0.001	0.060	0.0
	Independent variable: outcome	57	1.397	1.168	1.671	<0.001	85.0	<0.001		

Subgroups were compared using univariate, random effects (method of moments) meta-regression analysis. The R^2 analogue, defined as the total between-study variance explained by the moderator, was calculated based on the meta-regression matrix.
*Reference group: Asia.
GA, gestational age; HDP, hypertensive disorders of pregnancy; IUGR, intrauterine growth restriction (defined on the basis of fetal growth assessment); K, number of studies; SGA, small for gestational age.

and antiangiogenic profiles.[46] In contrast, later studies on placental pathology showed that lesions of maternal vascular underperfusion are more frequently associated with decreased cord blood angiogenic factors, as well as increased risk of both BPD and BPD-associated PH, than placental vascular lesions from fetal origin.[39 45 47]

Regardless of the origin of the placental lesions, the data from our analysis suggest that the increased risk of BPD may be predominantly associated with placental vascular dysfunction that is sufficiently severe to impair fetal growth. The relevance of the presence of growth restriction was particularly evidenced in the analysis of the combined outcome of BPD36 or death. Thus, HDP exposure had a 'protective' effect on this outcome while SGA/IUGR was associated with a higher risk of BPD/death. Interestingly, BPD-associated PH was the only condition associated with both SGA/IUGR and HDP. As mentioned in the introduction, the presence of PH is the most relevant feature of the 'vascular phenotype' of BPD. The data from this meta-analysis confirm the association between this vascular phenotype and the placental dysfunction endotype reinforcing the hypothesis that antenatal mechanisms that promote an anti-angiogenic fetal environment contribute to high risk for BPD and PH.[13 24 39–41]

A constant in our analyses was the presence of high statistical heterogeneity. We attempted to discern the sources of this heterogeneity through subgroup analysis and meta-regression. Since very and extremely preterm birth is by definition a pathological condition, a major problem when analysing the association between triggers and complications of prematurity is the absence of a healthy 'control' group. If a preterm infant is born to a mother with pre-eclampsia, the infant will be less likely to have chorioamnionitis and vice versa.[48] In fact, the studies included in our meta-analysis are comparing infants exposed to the placental dysfunction endotype with infants most likely belonging to the infectious/inflammatory endotype. Accordingly, the present results are in part a mirror image of the findings of our previous meta-analysis on the association between chorioamnionitis and BPD.[16] Herein, GA was significantly higher in the HDP and SGA/IUGR groups than in their respective control groups, while chorioamnionitis-exposed infants were born significantly earlier than non-exposed infants.[16] In all three cases (chorioamnionitis, HDP and SGA/IUGR), meta-regression showed a significant correlation between the difference in GA and the risk of developing BPD. However, this should not be interpreted as a call to adjust for GA. Although widely used, conditioning on GA in studies of prenatal exposures and their association to postnatal outcomes may not reduce but actually lead to bias through overadjustment and selection bias.[48]

The GA was also a relevant moderator in a previous meta-analysis on the association between HDP and BPD conducted by Razak *et al*.[17] They included only nine studies and did not find a significant association between HDP and risk of BPD36. However, the association was present in the subgroup analysis that included the three studies involving infants below 29 weeks' gestation.[17] Our data do not confirm those findings. Subgroup analysis of studies that only included extremely preterm newborns (GA <28 weeks) did not show a significant association between HDP and BPD but confirmed the association between SGA/IUGR and BPD. Interestingly, the studies that exclusively included infants with GA <28 weeks showed a significantly higher association between SGA/IUGR and BPD36 than the studies that also included infants above 28 weeks of gestation (table 3). Nevertheless, meta-regression did not demonstrate the presence of linear correlation between the mean GA of the infants included in the studies and the effect size of the associations between BPD and HDP or SGA/IUGR (online supplemental table 2). In another meta-analysis, including 15 studies, Bi *et al* found an association between HDP and BPD[49] that we could not confirm in our meta-analysis with a larger number of studies.

Besides the difference in GA, infants with a history of prenatal exposure to HDP or growth restriction differed from the 'control' group in other important characteristics that may have affected the association with BPD. Exposure to HDP was associated with female sex (table 2). Interestingly, mortality and several complications of prematurity, including BPD, are reported to occur at higher rates in preterm boys than girls.[50 51] Nevertheless, meta-regression did not demonstrate that sex differences affected the associations that we analysed (table 3). We also found that growth restriction, but not exposure to HDP, was associated with a decreased risk of RDS. These data would support that placental insufficiency may accelerate pulmonary maturation through chronic intrauterine stress.[52] However, this lower rate of acute respiratory morbidity in children with IUGR is followed by a higher incidence of BPD and BPD-associated PH.

Heterogeneity in the definitions of both exposures and outcomes is one of the main limitations of meta-analyses of observational studies. The controversy regarding how to best define BPD has occupied neonatologists for decades and still seems far from resolved.[11–14] Most of the studies included in this meta-analysis used the criterion of the need for oxygen or respiratory support at 36 weeks of PMA (ie, BPD36). This means that the categories of moderate and severe BPD were grouped, which does not allow differentiating those children who are sicker and at greater risk of respiratory sequelae. In addition, the current BPD definitions do not differentiate between the possible causes of respiratory support requirements (ie, the BPD phenotype). Moreover, the classical definitions of BPD do not take into consideration those children with severe respiratory problems who die before reaching 36 weeks of PMA as required for making the formal diagnosis of BPD and its severity. Finally, regarding BPD-associated PH, controversies persist regarding which echocardiography-derived measurements are best for assessing the condition and when is the optimal time for screening.[53]

Similarly, despite the publication of periodically updated consensus documents on the classification and diagnostic criteria for HDP,[54] marked heterogeneity remains among obstetricians regarding the application of these criteria. In addition, an emerging concept is that pre-eclampsia may have several subtypes, the final clinical manifestation being the result of the maternal response to either abnormal placental function or abnormal placentation.[53] Regarding IUGR, in the absence of placental pathology examination, it is uncertain whether placental vascular malperfusion was the aetiology for the growth restriction in all of the infants. In addition, the majority of the studies in this report are actually defining SGA, even though the terms SGA and IUGR are not synonymous.[29–32] SGA is a statistical definition based on BW, with the 10th percentile as the most commonly used threshold, and also encompasses constitutionally small but healthy infants at lower risk of complications. On the other hand, growth restricted infants who have a BW above the 10th percentile may be falsely classified as normally grown.[29–32 55]

CONCLUSIONS

In addition to inducing very and extremely preterm birth, the placental dysfunction and the infectious/inflammatory endotypes can each disrupt normal fetal growth and development and are strongly associated with BPD. As neither of these two endotypes is desirable, further research is necessary to prevent preterm birth and develop novel interventions in both settings. Altogether, the data from the present and our previous meta-analysis[16] suggest that the infectious/inflammatory endotype has a greater overall impact on BPD risk as it is the most frequent endotype in the lower and more vulnerable GA. However, when the endotype of placental dysfunction is accompanied by fetal growth restriction or being born SGA, it is strongly associated with higher rates of BPD even though newborns are more mature. Moreover, BPD associated with placental vascular dysfunction may have a greater component of vascular disease manifested as PH. In other words, the placental dysfunction endotype of prematurity is associated with increased risk of developing the vascular phenotype of BPD. However, neither endotypes of prematurity nor BPD phenotypes are discrete and there are cases in which the placenta may combine lesions of infection/inflammation and vascular dysfunction.[44] Nevertheless, it is necessary to recognise BPD as a heterogeneous condition and therefore prevention and treatment strategies should be targeted to the particular endotype and phenotype of each infant.

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REFERENCES

1 Blencowe H, Cousens S, Chou D, *et al*. Born too soon: the global epidemiology of 15 million preterm births. *Reprod Health* 2013;10 Suppl 1:S2.
2 Raju TNK, Buist AS, Blaisdell CJ, *et al*. Adults born preterm: a review of general health and system-specific outcomes. *Acta Paediatr* 2017;106:1409–37.
3 McElrath TF, Hecht JL, Dammann O, *et al*. Pregnancy disorders that lead to delivery before the 28th week of gestation: an epidemiologic approach to classification. *Am J Epidemiol* 2008;168:980–9.
4 Gagliardi L. Pregnancy complications and neonatal outcomes: problems and perspectives. *Acta Paediatr* 2014;103:682–3.
5 Gagliardi L, Rusconi F, Da Frè M, *et al*. Pregnancy disorders leading to very preterm birth influence neonatal outcomes: results of the population-based action cohort study. *Pediatr Res* 2013;73:794–801.
6 Gagliardi L, Rusconi F, Bellù R, *et al*. Association of maternal hypertension and chorioamnionitis with preterm outcomes. *Pediatrics* 2014;134:e154–61.
7 Anderson GP. Endotyping asthma: new insights into key pathogenic mechanisms in a complex, heterogeneous disease. *Lancet* 2008;372:1107–19.
8 Wenzel S. Severe asthma: from characteristics to phenotypes to endotypes. *Clin Exp Allergy* 2012;42:650–8.
9 Campo P, Rodríguez F, Sánchez-García S, *et al*. Phenotypes and endotypes of uncontrolled severe asthma: new treatments. *J Investig Allergol Clin Immunol* 2013;23:76–88.
10 Koczulla AR, Vogelmeier CF, Garn H, *et al*. New concepts in asthma: clinical phenotypes and pathophysiological mechanisms. *Drug Discov Today* 2017;22:388–96.
11 Abman SH, Collaco JM, Shepherd EG, *et al*. Interdisciplinary care of children with severe bronchopulmonary dysplasia. *J Pediatr* 2017;181:12–28.
12 Higgins RD, Jobe AH, Koso-Thomas M, *et al*. Bronchopulmonary dysplasia: Executive summary of a workshop. *J Pediatr* 2018;197:300–8.
13 Taglauer E, Abman SH, Keller RL. Recent advances in antenatal factors predisposing to bronchopulmonary dysplasia. *Semin Perinatol* 2018;42:413–24.
14 Thébaud B, Goss KN, Laughon M, *et al*. Bronchopulmonary dysplasia. *Nat Rev Dis Primers* 2019;5:78.
15 Manuck TA, Levy PT, Gyamfi-Bannerman C, *et al*. Prenatal and perinatal determinants of lung health and disease in early life: a national heart, lung, and blood Institute workshop report. *JAMA Pediatr* 2016;170:e154577-e:170.
16 Villamor-Martinez E, Álvarez-Fuente M, Ghazi AMT, *et al*. Association of chorioamnionitis with bronchopulmonary dysplasia among preterm infants: a systematic review, meta-analysis, and metaregression. *JAMA Netw Open* 2019;2:e1914611-e.
17 Razak A, Florendo-Chin A, Banfield L, *et al*. Pregnancy-Induced hypertension and neonatal outcomes: a systematic review and meta-analysis. *J Perinatol* 2018;38:46–53.
18 Wu KY, Jensen EA, White AM, *et al*. Characterization of disease phenotype in very preterm infants with severe bronchopulmonary dysplasia. *Am J Respir Crit Care Med* 2020;201:1398–406.
19 Collaco JM, McGrath-Morrow SA. Respiratory phenotypes for preterm infants, children, and adults: bronchopulmonary dysplasia and more. *Ann Am Thorac Soc* 2018;15:530–8.
20 Logan JW, Lynch SK, Curtiss J, *et al*. Clinical phenotypes and management concepts for severe, established bronchopulmonary dysplasia. *Paediatr Respir Rev* 2019;31:58–63.
21 Mandell E, Hysinger EB, McGrath-Morrow SA. Disease phenotyping of infants with severe bronchopulmonary dysplasia. *Am J Respir Crit Care Med* 2020;201:1327–9.
22 Mourani PM, Abman SH. Pulmonary hypertension and vascular abnormalities in bronchopulmonary dysplasia. *Clin Perinatol* 2015;42:839–55.
23 Al-Ghanem G, Shah P, Thomas S, *et al*. Bronchopulmonary dysplasia and pulmonary hypertension: a meta-analysis. *J Perinatol* 2017;37:414–9.
24 Arjaans S, Wagner BD, Mourani PM, *et al*. Early angiogenic proteins associated with high risk for bronchopulmonary dysplasia and pulmonary hypertension in preterm infants. *Am J Physiol Lung Cell Mol Physiol* 2020;318:L644–54.
25 Bhat R, Salas AA, Foster C, *et al*. Prospective analysis of pulmonary hypertension in extremely low birth weight infants. *Pediatrics* 2012;129:e682–9.
26 Check J, Gotteiner N, Liu X, *et al*. Fetal growth restriction and pulmonary hypertension in premature infants with bronchopulmonary dysplasia. *J Perinatol* 2013;33:553–7.
27 Villamor-Martinez E, Kilani MA, Degraeuwe PL, *et al*. Intrauterine growth restriction and patent ductus arteriosus in very and extremely preterm infants: a systematic review and meta-analysis. *Front Endocrinol* 2019;10:58.
28 Moher D, Liberati A, Tetzlaff J, *et al*. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* 2009;339:b2535.
29 Figueras F, Gardosi J. Intrauterine growth restriction: new concepts in antenatal surveillance, diagnosis, and management. *Am J Obstet Gynecol* 2011;204:288–300.
30 Gordijn SJ, Beune IM, Thilaganathan B, *et al*. Consensus definition of fetal growth restriction: a Delphi procedure. *Ultrasound Obstet Gynecol* 2016;48:333–9.
31 Beune IM, Bloomfield FH, Ganzevoort W, *et al*. Consensus based definition of growth restriction in the newborn. *J Pediatr* 2018;196:e1:71–6.
32 Monier I, Ancel P-Y, Ego A, *et al*. Fetal and neonatal outcomes of preterm infants born before 32 weeks of gestation according to antenatal vs postnatal assessments of restricted growth. *Am J Obstet Gynecol* 2017;216:516.e1–516.e10.
33 Jobe AH, Bancalari E. Bronchopulmonary dysplasia. *Am J Respir Crit Care Med* 2001;163:1723–9.
34 et alWells GA, Shea B, O'Connell D. The Newcastle-Ottawa scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses. Available: http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm
35 Borenstein M, Hedges LV, Higgins J. Subgroup analyses. *Introduction to Meta-analysis* 2009:149–86.
36 Borenstein M, Hedges LV, Higgins J. Meta-Regression. In: *Introduction to meta-analysis*, 2009: 187–203.
37 Ambalavanan N, Nicola T, Hagood J, *et al*. Transforming growth factor-beta signaling mediates hypoxia-induced pulmonary arterial remodeling and inhibition of alveolar development in newborn mouse lung. *Am J Physiol Lung Cell Mol Physiol* 2008;295:L86–95.
38 Bose C, Van Marter LJ, Laughon M, *et al*. Fetal growth restriction and chronic lung disease among infants born before the 28th week of gestation. *Pediatrics* 2009;124:e450–8.
39 Rozance PJ, Seedorf GJ, Brown A, *et al*. Intrauterine growth restriction decreases pulmonary alveolar and vessel growth and causes pulmonary artery endothelial cell dysfunction in vitro in fetal sheep. *Am J Physiol Lung Cell Mol Physiol* 2011;301:L860–71.
40 Mestan KK, Gotteiner N, Porta N, *et al*. Cord blood biomarkers of placental maternal vascular underperfusion predict bronchopulmonary dysplasia-associated pulmonary hypertension. *J Pediatr* 2017;185:33–41.
41 Dodson RB, Powers KN, Gien J, *et al*. Intrauterine growth restriction decreases NF-κB signaling in fetal pulmonary artery endothelial cells of fetal sheep. *Am J Physiol Lung Cell Mol Physiol* 2018;315:L348–59.
42 Kovo M, Schreiber L, Ben-Haroush A, *et al*. Placental vascular lesion differences in pregnancy-induced hypertension and normotensive fetal growth restriction. *Am J Obstet Gynecol* 2010;202:e1-. e5:561–561.e5.
43 Kovo M, Schreiber L, Ben-Haroush A, *et al*. The placental component in early-onset and late-onset preeclampsia in relation to fetal growth restriction. *Prenat Diagn* 2012;32:632–7.
44 Mir IN, Chalak LF, Brown LS, *et al*. Impact of multiple placental pathologies on neonatal death, bronchopulmonary dysplasia, and neurodevelopmental impairment in preterm infants. *Pediatr Res* 2020;87:885–91.
45 Mestan KK, Check J, Minturn L, *et al*. Placental pathologic changes of maternal vascular underperfusion in bronchopulmonary dysplasia and pulmonary hypertension. *Placenta* 2014;35:570–4.
46 Alahakoon TI, Zhang W, Trudinger BJ, *et al*. Discordant clinical presentations of preeclampsia and intrauterine fetal growth restriction with similar pro- and anti-angiogenic profiles. *J Matern Fetal Neonatal Med* 2014;27:1854–9.
47 Kunjunju AM, Gopagondanahalli KR, Chan Y, *et al*. Bronchopulmonary dysplasia-associated pulmonary hypertension: clues from placental pathology. *J Perinatol* 2017;37:1310–4.
48 Williams TC, Bach CC, Matthiesen NB, *et al*. Directed acyclic graphs: a tool for causal studies in paediatrics. *Pediatr Res* 2018;84:487–93.
49 Bi G-L, Chen F-L, Huang W-M. The association between hypertensive disorders in pregnancy and bronchopulmonary dysplasia: a systematic review. *World J Pediatr* 2013;9:300–6.
50 Lorente-Pozo S, Parra-Llorca A, Torres B, *et al*. Influence of sex on gestational complications, fetal-to-neonatal transition, and postnatal adaptation. *Front Pediatr* 2018;6:63.
51 Garfinkle J, Yoon EW, Alvaro R, *et al*. Trends in sex-specific differences in outcomes in extreme preterms: progress or natural barriers? *Arch Dis Child Fetal Neonatal Ed* 2020;105:158–63.
52 Torrance HL, Voorbij HAM, Wijnberger LD, *et al*. Lung maturation in small for gestational age fetuses from pregnancies complicated by placental insufficiency or maternal hypertension. *Early Hum Dev* 2008;84:465–9.
53 Levy PT, Jain A, Nawaytou H, *et al*. Risk assessment and monitoring of chronic pulmonary hypertension in premature infants. *J Pediatr* 2020;217:e4:199–209.
54 Tranquilli AL, Dekker G, Magee L, *et al*. The classification, diagnosis and management of the hypertensive disorders of pregnancy: a revised statement from the ISSHP. *Pregnancy Hypertens* 2014;4:97–104.
55 Rosenberg A. The IUGR newborn. *Semin Perinatol* 2008;32:219–24.