



The Influence of Pregnancy Disorders Causing Preterm Delivery on In-Hospital Outcomes in Preterm Infants at Less than 32 Weeks of Gestation

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Received: 16 January 2017

Revised: 5 July 2017

Accepted: 5 September 2017

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Objective: We assessed the influence of small for gestational age (GA) with placental disorders (SGA-P) and histologic chorioamnionitis (HCA) on the in-hospital outcomes of preterm infants.

Methods: Preterm infants with a GA <32 weeks born at Seoul National University Hospital between 2007 and 2014 were included and divided into 4 groups according to the presence of SGA-P and HCA: group 1, SGA-P only; group 2, HCA only; group 3, both SGA-P and HCA; and group 4, no SGA-P or HCA. Multivariate logistic regression was done to compare neonatal outcomes including death, moderate to severe bronchopulmonary dysplasia (BPD) or death, patent ductus arteriosus with treatment, sepsis, necrotizing enterocolitis \geq stage 2b, and intraventricular hemorrhage \geq grade 3.

Results: A total of 572 infants were included. There were 77 patients (13.5%) in group 1, 226 patients (39.5%) in group 2, and 24 patients (4.2%) in group 3. After adjusting for GA, cesarean section, 5 minute Apgar score, multiple pregnancy, premature rupture of membrane before 18 hours prior to delivery, and preeclampsia, group 1 showed higher risks of mortality (adjusted odds ratio [aOR] 3.15, 95% confidence interval [CI] 1.13-8.80), moderate to severe BPD or death (aOR 9.12, 95% CI 3.98-20.90), sepsis (aOR 2.12, CI 1.01-4.46), and pulmonary hypertension (aOR 3.26, 95% CI 1.15-9.22) compared with group 4. There were no significant differences in mortality and in-hospital outcomes between groups 2 and 4 or between groups 3 and 4.

Conclusion: Close monitoring and early intervention are suggested in SGA-P infants.

Key Words: Preterm infants, Placenta disorders, Fetal growth retardation, Chorioamnionitis, Patient outcome assessment

Introduction

Preterm infants have a high mortality and morbidities throughout their lives. Previous reports have suggested that pregnancy disorders causing preterm delivery also affect the neonatal outcomes of preterm infants.¹ Recently, many epidemiologists have been trying to group pregnancy disorders associated with preterm delivery to find common therapeutic interventions. McElrath et al.² and Klebanoff et al.³ classified disorders leading to preterm delivery into 2 groups: disorders with intrauterine inflammation and those associated with primary aberrations of placentation. Histologic chorioamnionitis (HCA) is a representative disorder of intrauterine inflammation, and hypertensive disorders of pregnancy and intrauterine growth restriction (IUGR) are representative disorders of aberrant placentation.

IUGR is defined as in-utero growth retardation, and small for gestational age (SGA) is defined when the birthweight is less than the 10th percentile or 2 standard deviations and based on a cross-sectional evaluation. The term IUGR and SGA are often used interchange-

ably, and only 12% were not SGA among IUGR neonates. However, some neonatologist reported that about 1/3 of SGA cases were not fetal growth restriction.⁴ Among maternal, environmental and fetal causes of IUGR or SGA, placental problems such as placental insufficiency, preeclampsia, and placental abruption leads to a preterm birth. There have been studies that have reported that SGA is a significant risk factor of mortality, bronchopulmonary dysplasia (BPD), or sepsis.⁵ Additionally, others have reported that such associations occurred regardless of whether IUGR was suspected antenatally.⁴

For the association between HCA and neonatal outcomes of preterm infants, some studies have reported that HCA decreases the frequency of respiratory distress syndrome (RDS) in preterm infants.⁶ However, it is still controversial whether HCA increases the risk of BPD or a poor neurodevelopmental outcome.⁷⁻⁹ Such reports have classified their study population according to the presence of HCA only; thus, the control group could contain other significant pregnancy disorders, which could affect neonatal outcomes, and do not represent a 'normal' control group. Additionally, both SGA and HCA are stressful conditions, and mortality and adverse neonatal outcomes can increase due to the combined effects of SGA and HCA; however, there are few reports on the proportion of infants with both SGA and HCA as well as on comparing the combined effects of SGA and HCA on neonatal outcomes.

Thus, this study assessed whether there are any differences in major neonatal morbidities in preterm infants with a gestational age (GA) <32 weeks according to the presence of SGA with placental disorders (SGA-P) and HCA, which are representative disorders for the 2 major types of disorders causing preterm delivery.

Methods

1. Study design

A retrospective study was done for 704 infants who were born and admitted to the neonatal intensive care unit of Seoul National University Children's hospital between 2007 and 2014. Clinical and demographic data were collected from the reviewed medical records of the enrolled patients. Thirty-seven infants who had major congenital anomalies, 47 twin to

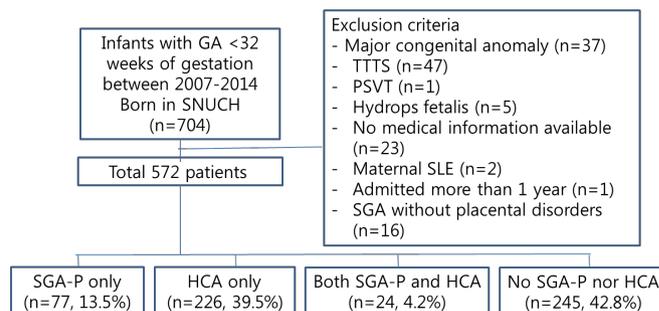


Fig. 1. Flow chart of the study population. A total of 572 patients with <32 weeks of gestation born between 2007 and 2014 were included in the analysis. 77 patients (13.5%) were in group 1, 226 patients (39.5%) were in group 2, and 24 patients (4.2%) were in group 3. GA, gestational age; SNUCH, Seoul National University Children's Hospital; TTTS, twin to twin transfusion syndrome; PSVT, paroxysmal supraventricular tachycardia; SLE, systemic lupus erythematosus; SGA-P; small for gestational age with placental disorders; HCA, histologic chorioamnionitis.

twin transfusion syndrome patients, 1 paroxysmal supraventricular tachycardia, 5 fetal hydrops and 2 maternal systemic lupus erythematosus were excluded. Twenty-three patients with inadequate medical records and 1 patient admitted for more than 1 year were also excluded. Sixteen SGA patients without placental disorders (such as SGA due to maternal malnutrition or no specific cause) were excluded. Finally, a total of 572 preterm infants were included in the analysis (Fig. 1).

We categorized the entire study population into four groups according to the presence of SGA-P or HCA. Group 1 consisted of patients with SGA-P only, group 2 with HCA only, group 3 with both SGA-P and HCA, and group 4 with no SGA-P or HCA.

Then, we compared the baseline demographic characteristics including the GA at birth, birthweight, gender, cesarean section, multiple pregnancy, antenatal steroid use started before 12 hours from birth, preeclampsia, premature rupture of membrane (PROM) before 18 hours from birth, maternal gestational diabetes, cord pH, and Apgar score at 1 and 5 minutes between the two groups. We also examined the difference in the mortality and in-hospital outcomes such as surfactant use, patent ductus arteriosus (PDA) requiring treatment, inhaled nitric oxide treatment before 14 postnatal days, pulmonary hypertension, bronchopulmonary dysplasia (BPD), sepsis, necrotizing enterocolitis (NEC) \geq stage 2b, intraventricular hemorrhage (IVH) \geq grade 3, retinopathy of prematurity (ROP) requiring

surgery or vascular endothelial growth factor (VEGF) treatment, discharge with respiratory support, and the duration of hospital stay between the two groups.

2. Definitions

Preeclampsia was defined as any maternal diagnoses of preeclampsia, eclampsia or hemolysis, elevated liver enzymes, and low platelet count syndrome. SGA was defined according to the definitions published by Olsen et al.¹⁰ SGA-P was defined when causes of SGA were as follows: preeclampsia, absent or reversed umbilical artery end-diastolic flow, fetal growth restriction with fetal distress due to placental insufficiency, and placenta abruptio. HCA was defined according to the definition of Salafia et al.¹¹: the presence of acute inflammation and infiltration of polymorphonuclear leukocytes in the amnion, chorionic decidua, umbilical cord, or the chorionic plate reported by pathologists in our hospital. Sepsis was defined as the presence of clinical symptoms and signs with proven causative organisms documented from blood cultures. If the organisms were identified within 7 postnatal days, it was defined as early sepsis. If the organisms were identified after 8 or more postnatal days, it was defined as late sepsis. Pulmonary hypertension was defined according to the echocardiographic findings previously published.¹² Discharge with respiratory support was defined as discharge with oxygen supply or home ventilator support.

3. Statistical analysis

All continuous variables are expressed as the median (interquartile range), and all categorical variables are expressed as numbers and proportions. For the univariate analysis, continuous variables were compared with the Kruskal-Wallis test, and categorical variables were compared with the chi-square test or Fisher's exact test. To assess the independent association between the presence of SGA-P or HCA and neonatal outcomes including mortality, moderate to severe BPD or death, severe BPD or death, PDA with treatment, sepsis, IVH \geq grade 3 of Papile's classification,¹³ NEC \geq stage 2 of Bell's criteria,¹⁴ ROP requiring surgery or VEGF treatment, and pulmonary hypertension, binary logistic regression analysis was done adjusting for GA, cesarean section, 5 minute Apgar score, multiple pregnancy, PROM, and preeclampsia. We also performed multiple linear regression analysis to assess whether there is any

difference in the duration of hospital stay when compared with group 4. The statistical analysis was done with IBM SPSS Statistics version 20 (IBM Corp., Armonk, NY, USA) and R version 3.3.2. (The R Foundation, Vienna, Austria). *P* values less than 0.05 were considered statistically significant.

Results

A total of 572 patients were included in the final analysis. Seventy-seven patients (13.5%) were in group 1, 226 patients (39.5%) in group 2, 24 patients (4.2%) in group 3, and 245 patients (42.8%) in group 4 (Fig. 1). The proportion of the group 2 decreased and the proportion of the group 1 increased as the GA increased ($P=0.045$, Fig. 2). In group 1, causes of SGA were as follows: preeclampsia in 12 infants (15.6%), absent or reversed umbilical artery end-diastolic flow in 26 infants (33.8%), both preeclampsia and absent or reversed umbilical artery end-diastolic flow in 27 infants (35.1%), fetal growth restriction with fetal distress due to placental insufficiency in 11 infants (14.3%), and placental abruptio in 1 infants (1.3%). In group 3, causes of SGA were preeclampsia in 4 infants (16.7%), absent

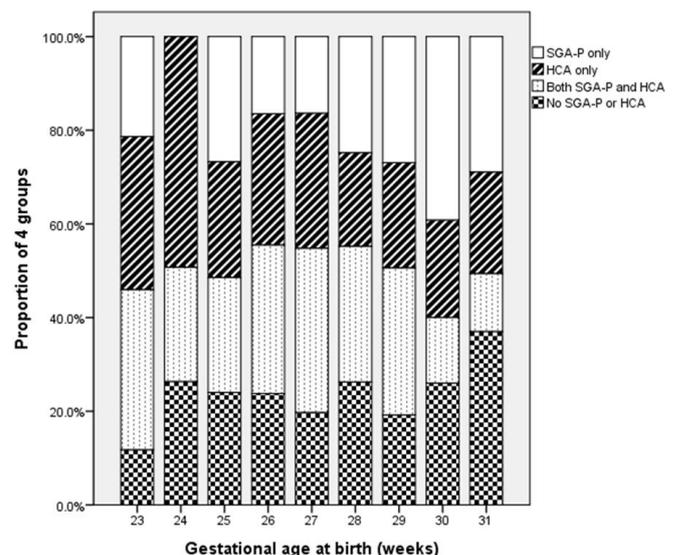


Fig. 2. The proportion of 4 groups according to the gestational age at birth. The percentage of histologic chorioamnionitis group was decreased and the percentage of small for gestational age with placental disorders was increased as the gestational age gets older ($P=0.045$). SGA-P, small for gestational age with placental disorders; HCA, histologic chorioamnionitis.

or reversed umbilical artery end-diastolic flow in 6 infants (25.0%), both preeclampsia and absent or reversed umbilical artery end-diastolic flow in 11 infants (45.8%), and fetal growth restriction with fetal distress due to placental insufficiency in 3 infants (12.5%).

1. Baseline and demographic characteristics

There were significant differences in the GA, birthweight, multiple pregnancy, cesarean section, cord pH, and the 1 and 5 minute Apgar scores between the four groups. When compared with group 4, group 2 was younger, and the birthweights of groups 1, 2, and 3 were lower. The proportion of infants delivered from mothers with preeclampsia was higher in group 1 and 3, and lower in group 2 when compared with group 4. Cord pH and 5 minute Apgar score were lower in groups 1 and 3 when compared with group 4 (Table 1).

2. Mortality and in-hospital outcomes

In the univariable analysis, there were significant differences in the mortality, moderate to severe BPD at 36 weeks of corrected age, and pulmonary hypertension between the 4 groups. When compared with group 4, the mortality was higher in groups 1 and 3 (Table 2). The proportion of infants with moderate to severe BPD was higher in group 1 when compared

with group 4.

After the multivariable analysis adjusting for GA, cesarean section, 5 minute Apgar score, multiple pregnancy, PROM before 18 hours prior to delivery, and preeclampsia, group 1 showed higher risks for death, moderate to severe BPD or death, sepsis, and pulmonary hypertension when compared with group 4 (Table 3). When compared with group 4, there were no significant differences of neonatal outcomes in group 2 and 3.

After multiple linear regression analysis adjusting for GA, cesarean section, 5 minute Apgar score, multiple pregnancy, PROM before 18 hours prior to delivery, and preeclampsia, there was no significant difference in the duration of hospital stay when compared with group 4 (group 1: β 10.39, 95% CI -1.89-27.53, P -value=0.151; group 2: β -2.71, 95% CI -9.97-3.06, P -value=0.405; group 3: β -0.46, 95% CI -20.18-13.99, P -value=0.957).

Discussion

In our study, SGA-P was a major risk factor of mortality and adverse in-hospital outcomes in preterm infants. However, HCA was not a significant risk factor of mortality or any neonatal morbidities, and in infants with both SGA-P and HCA,

Table 1. Baseline Demographic Characteristics of the 4 Groups According to the Presence of SGA-P and HCA

	SGA-P only (n=77)	HCA only (n=226)	Both SGA-P and HCA (n=24)	No SGA-P nor HCA (n=245)	P-value
Gestational age	29 ⁺² (27 ⁺⁴ , 30 ⁺³)	28 ⁺⁰ (26 ⁺⁰ , 30 ⁺²)*	27 ⁺⁶ (26 ⁺¹ , 29 ⁺⁶)	29 ⁺⁰ (27 ⁺⁰ , 30 ⁺⁶)	0.002
Birth weight (g)	710 (540, 890)*	1,085 (845, 1,370)*	640 (538, 795)*	1,220 (920, 1,490)	<0.001
Male	36 (46.8)	111 (49.1)	11 (45.8)	143 (58.4)	0.118
Multiple pregnancy	23 (29.9)*	112 (49.6)*	5 (20.8)*	167 (68.2)	<0.001
Cesarean section	70 (90.9)*	99 (43.8)*	21 (87.5)*	144 (58.8)	<0.001
Antenatal steroid use before 12 hours after birth	62 (80.5)	175 (77.4)	17 (70.8)	188 (76.7)	0.784
Preeclampsia	39 (50.6)*	7 (3.1)*	15 (62.5)*	26 (10.6)	<0.001
PROM>18 hours	12 (15.6)*	148 (65.5)	6 (25.0)*	141 (57.6)	<0.001
GDM	4 (5.2)	12 (5.3)	1 (4.2)	11 (4.5)	0.960
Cord pH	7.24 (7.18, 7.29)*	7.32 (7.28, 7.35)	7.23 (7.15, 7.27)*	7.32 (7.27, 7.35)	<0.001
1 minute Apgar score	3 (2, 5)*	5 (2, 6)	3 (1, 5)	5 (2, 6)	0.002
5 minute Apgar score	6 (5, 7)*	7 (5, 8)	6 (3, 7)*	7 (5, 8)	0.003

Values are presented as median (interquartile range) or number (%).

Abbreviations: SGA-P, small for gestational age with placental disorders; HCA, histologic chorioamnionitis; PROM, premature rupture of membranes; GDM, gestational diabetes mellitus.

* P <0.05 versus no SGA-P nor HCA.

there were no significant differences in mortality and major neonatal outcomes when compared with the no SGA-P or HCA group.

Many pregnancy disorders such as spontaneous preterm

Table 2. In-hospital Outcomes of the 4 Groups According to the Presence of SGA-P and HCA

	SGA-P only (n=77)	HCA only (n=226)	Both SGA-P and HCA (n=24)	No SGA-P nor HCA (n=245)	P-value
Mortality	14 (18.2)*	19 (8.4)	6 (25.0)*	18 (7.3)	0.004
Surfactant use	43 (55.8)	100 (44.2)	16 (66.7)	111 (45.3)	0.069
PDA treatment	41 (53.2)	126 (55.8)	16 (66.7)	120 (49.0)	0.253
Pharmacological	38 (49.4)	110 (48.7)	14 (58.3)	106 (43.3)	0.387
Surgical	7 (9.1)	49 (21.7)	6 (25.0)	46 (18.8)	0.066
Moderate or severe BPD at 36 weeks	30 (45.5)*	72 (34.4)	6 (30.0)	58 (25.1)	0.011
Severe BPD at 36 weeks	13 (19.7)	27 (12.9)	4 (20.0)	29 (12.6)	0.348
Sepsis	23 (29.9)	60 (26.5)	6 (25.0)	44 (18.0)	0.067
Early sepsis	6 (7.8)	16 (7.1)	1 (4.2)	8 (3.3)	0.172
Late sepsis	20 (26.0)	51 (22.6)	6 (25.0)	41 (16.7)	0.196
NEC \geq stage 2b	9 (11.7)	15 (6.6)	1 (4.2)	15 (6.1)	0.392
IVH \geq grade 3	4 (5.2)	19 (8.4)	4 (16.7)	16 (6.5)	0.244
ROP with surgery or VEGF	9 (13.2)	39 (18.5)	4 (20.0)	31 (13.3)	0.394
iNO use <14 days from birth	6 (7.8)	17 (7.5)	1 (4.2)	15 (6.1)	0.885
Pulmonary hypertension	11 (14.3)	14 (6.2)	4 (16.7)	17 (6.9)	0.046
Duration of hospital stay	60 (43, 94)	64 (39, 88)	65 (41, 106)	54 (35, 79)	0.209
Discharge with respiratory support	18 (23.4)	59 (26.1)	6 (25.0)	43 (17.6)	0.154

Values are presented as number (%) or median (interquartile range).

Abbreviations: SGA-P, small for gestational age with placental disorders; HCA, histologic chorioamnionitis; PDA, patent ductus arteriosus; BPD, bronchopulmonary dysplasia; NEC, necrotizing enterocolitis; IVH, intraventricular hemorrhage; ROP, retinopathy of prematurity; VEGF, vasculo-endothelial growth factor; iNO, inhaled nitric oxide.

* $P < 0.05$ versus no SGA-P nor HCA.

Table 3. Multivariable Analysis of Mortality and In-hospital Outcomes according to the Presence of SGA-P or HCA (Reference: No SGA-P nor HCA)

	SGA-P only		HCA only		Both SGA-P and HCA	
	aOR (95% CI)	P-value	aOR (95% CI)	P-value	aOR (95% CI)	P-value
Death	3.15 (1.13, 8.80)	0.029	0.88 (0.42, 1.87)	0.741	2.76 (0.73, 10.41)	0.133
Moderate to severe BPD or death	9.12 (3.98, 20.90)	<0.001	1.05 (0.61, 1.81)	0.853	1.53 (0.44, 5.32)	0.509
Severe BPD or death	3.73 (1.62, 8.58)	0.002	0.68 (0.39, 1.21)	0.191	1.82 (0.55, 6.03)	0.325
PDA treatment	0.98 (0.51, 1.90)	0.961	1.14 (0.74, 1.78)	0.553	1.14 (0.40, 3.28)	0.806
Sepsis	2.12 (1.01, 4.46)	0.046	1.38 (0.84, 2.26)	0.207	1.07 (0.35, 3.27)	0.913
Early sepsis	3.79 (1.04, 13.81)	0.044	2.06 (0.82, 5.15)	0.122	1.70 (0.17, 16.95)	0.651
Late sepsis	1.65 (0.77, 3.54)	0.200	1.19 (0.71, 2.00)	0.499	1.00 (0.33, 3.08)	0.998
IVH \geq grade 3	0.48 (0.13, 1.81)	0.277	1.00 (0.47, 2.12)	0.999	1.34 (0.34, 5.36)	0.675
NEC \geq stage 2b	2.42 (0.79, 7.43)	0.123	0.79 (0.35, 1.75)	0.554	0.47 (0.05, 4.28)	0.499
Pulmonary hypertension	3.26 (1.15, 9.22)	0.026	0.71 (0.33, 1.54)	0.383	2.37 (0.56, 9.97)	0.240
ROP with surgery or VEGF	1.64 (0.51, 5.24)	0.404	1.23 (0.65, 2.33)	0.535	1.65 (0.34, 8.04)	0.536

Adjusted for Gestational age at birth (weeks), cesarean section, 5 minute Apgar score, multiple pregnancy, premature rupture of membranes before 18 hours prior to delivery, and preeclampsia.

Abbreviations: SGA-P, small for gestational age with placental disorders; HCA, histologic chorioamnionitis; aOR, adjusted odds ratio; CI, confidence interval; BPD, bronchopulmonary dysplasia; PDA, patent ductus arteriosus; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis; ROP, retinopathy of prematurity; VEGF, vasculo-endothelial growth factor.

labor, hypertensive disorders of pregnancy, chorioamnionitis, IUGR, and maternal hemorrhage lead to preterm birth. Some epidemiologists group the pregnancy complications ending in preterm birth according to a common etiology and relationship to outcomes: a placental histologic inflammation and poor placentation such as infarcts and an abundance of syncytial knots.² In our study, because we performed a placental biopsy in all the mothers who delivered preterm infants, we collected accurate information about histologic chorioamnionitis. We included SGA infants only associated with placentation disorders because many other factors such as genetic, chromosomal, and maternal nutrition factors can also cause SGA but usually are not accompanied with preterm birth. Most of our SGA-P group represented IUGR; however, because this study was not a prospective study and we could not get accurate information on intrauterine growth, we used the term SGA-P instead of IUGR.

SGA is known to be a significant risk factor of neonatal death, BPD, and nosocomial infection; however, the results are still controversial.^{5,15-17} In our study, the risk of neonatal death, BPD, sepsis, and pulmonary hypertension was higher in infants with SGA-P only; however, the risk of such neonatal outcomes was not increased in infants with both SGA-P and HCA. We could not examine the long-term neurodevelopmental outcome; thus, further study will be needed.

In our study, only 4.2% of infants had both SGA-P and HCA. Recently, the proportion of microbial invasion of the amniotic cavity in pregnancies with SGA detected by the 16S ribosomal DNA polymerase chain reaction method was also 6%, which is smaller than that of other conditions (13% of women with preterm labor, 32% of preterm PROM, and about 50% of cervical insufficiency).¹⁸ Although the proportion of infants with both SGA-P and HCA was low, HCA can have a protective role in SGA patients for mortality and BPD, and there were no significant differences in neonatal outcomes when compared with the control groups.

In our study, we classified our study population into 4 groups according to the presence of SGA-P and HCA. Actually, hypertensive disorders of pregnancy including preeclampsia are also known to be due to abnormal placentation. SGA can be an indicator of the severity of preeclampsia and has been attributed to a restricted arteriolar supply of the uterine-placental interface.¹⁹ When we also assessed the difference in neonatal

outcomes between infants with preeclampsia or SGA-P only, HCA only, both preeclampsia/SGA-P and HCA, and no preeclampsia/SGA-P or HCA, the risks of moderate to severe BPD or death and sepsis were higher only in infants with preeclampsia or SGA-P when compared with the no preeclampsia/SGA or HCA group, which was similar to our results (data not shown). However, when we classified our study population into infants with preeclampsia only, HCA only, both preeclampsia and HCA, and no preeclampsia or HCA, there were no significant associations between neonatal outcomes and preeclampsia only, HCA only or both preeclampsia and HCA (data not shown). We suggest that SGA-P is a potent risk factor of mortality and major adverse outcomes in preterm infants.

According to the annual report of the Korean neonatal network (KNN) released on 2015, HCA is a more prevalent antenatal condition in extreme premature infants. HCA accounts for 46.5% of the causes of preterm birth among preterm infants born less than GA 24 weeks.²⁰ Our results also show the same distribution of pregnancy disorders according to GA, and when there were both HCA and SGA-P, the GA and birth weight were the lowest between the 4 groups. Although we wanted to match the GA and birthweight in the 4 groups, because of the small number of study subjects, we could not match our cohort, and multiple logistic regression analysis was done instead of matching.

In our cohort, HCA had no association with any neonatal morbidities, which somewhat contrasted other previous results. Previous studies have reported that HCA can increase the incidence of mortality, BPD, early sepsis, and long-term adverse neurodevelopmental outcomes.^{8,21-23} Some evidence supports that the incidence of RDS was decreased in infants with maternal HCA, and in animal studies, intraamniotic injection of *Escherichia coli* increased surfactant protein synthesis.²⁴ Such reports classified their study population according to the presence of HCA only; thus, the control group patients could be mixed up with other significant pregnancy disorders which did not represent a 'normal' control group. Our control group did not have any infants with maternal SGA-P or HCA, which could give such different results for the influence on neonatal outcomes.

In many reports, neonatal mortality was higher in pregnancy disorders associated with placental dysfunction than in those

disorders with intrauterine inflammation.² When Gagliardi et al.¹ compared the disorders of placentation including hypertensive disorders of the pregnancy and the IUGR group to the presumed infection/inflammation group, the risk of mortality, BPD and ROP was higher especially in growth-restricted infants, and the risks of IVH and periventricular leukomalacia were lower in the disorders of placentation group.

In our study, the frequency of sepsis was higher in infants with SGA-P when compared with infants with no diagnosis of SGA-P or HCA. Tröger et al.²⁵ reported that SGA increased the incidence of late onset culture proven sepsis in VLBW infants. Thymic atrophy and lymphopenia and deficiencies in humoral responses in SGA infants were reported.^{26,27} Additionally, in the first week from birth, white blood cell counts are usually decreased in infants with SGA or preeclampsia which is common.

Pulmonary hypertension is known to be associated with BPD.²⁸ Recently, there have been some reports that placental pathologic changes of maternal vascular underperfusion in BPD are associated with increased risk of pulmonary hypertension,²⁹ and after a systematic review and meta-analysis, oligohydramnios and SGA were shown as significant risk factors of pulmonary hypertension in infants with BPD.³⁰ Additionally, in our study, SGA-P was a significant risk factor of pulmonary hypertension.

Our study has some limitations. First, this is a retrospective study with a small number of patients in a single center. Second, when compared to the prospective EPIPAGE-2 study, we could not include all the antenatal factors causing preterm delivery in the classification of the groups because of incomplete medical records due to the retrospective study design. Thus, we decided not to differentiate our whole study population according to the classification guided by antenatal pregnancy complications such as in the EPIPAGE study, and we only used SGA-P and HCA as a standard to classify our groups. A prospective study with a more sophisticated grouping according to the antenatal pregnancy disorders should be done in the future.

In our study, the proportion of infants with both SGA-P and HCA was very small in preterm infants, and there were no significant differences in neonatal outcomes when compared to the control group. SGA-P was a significant risk factor of mortality and moderate to severe BPD or death, sepsis, and pul-

monary hypertension in preterm infants. We should give attention to the close monitoring and prevention of sepsis, BPD, and pulmonary hypertension in the care of preterm infants with SGA-P.

Acknowledgements

This study was approved by the institutional review board (IRB No. 26-2013-126). The need for informed consent was exempted because of the retrospective nature of this study.

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