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Short stature in small-for-gestational-age offspring born to mothers with hypertensive disorders of pregnancy

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ABSTRACT

Objective: To investigate the incidence and risk factors of small-for-gestational age (SGA) short stature at 2 and 3 years of age in SGA offspring born to women with hypertensive disorders of pregnancy (HDP).

Methods: We examined 226 women with HDP whose respective SGA offspring were delivered.

Results: Eighty offspring (41.2%) were diagnosed with SGA short stature. The prematurity before 32 weeks of gestation was the most significant factor for catch-up growth failure.

Conclusion: In SGA offspring born to women with HDP, SGA short stature incidence was high, and the risk factor was prematurity before 32 weeks of gestation.

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Short stature; catch-up growth; small-for-gestational age; premature birth; hypertensive disorders of pregnancy

Introduction

Hypertensive disorders of pregnancy (HDP) occur in approximately 5% of all pregnancies (1). The etiology of HDP, particularly preeclampsia, is clarified by the two-stage disorder theory (2,3), wherein stage 1 involves placental hypoxia because of poor arterial perfusion, and stage 2 involves the subsequent release of hypoxia-induced factors that results in a disordered state, such as preeclampsia (2–4). Anti-angiogenic factors released due to hypoxia further exacerbate the hypoxic placental insufficiency (5,6), causing hypertension and proteinuria in the mother (7) and fetal growth restriction (FGR) and small-for-gestational age (SGA) in the fetus (8).

Appropriate-for-gestational age neonates with birth weights and lengths below the 10th percentile are diagnosed as SGA (9). Approximately 10% of SGA offspring cannot achieve catch-up growth and attain a length of ≥ -2.0 standard deviations (SD) by 2 years of age. Thus, they are diagnosed with short stature in children born SGA (10,11), which reportedly accounts for approximately 20% of cases of adulthood short stature (12). A better understanding of HDP and its association with SGA prevalence can guide preventative and early interventional methodologies to greatly improve the life-course development of SGA short stature neonates.

In the general obstetric population, the reported risk factors for short stature in children born SGA include

the birth length and a preterm birth at <32 weeks (13). Although HDP causes premature delivery at a very early gestational age and severe FGR owing to impaired blood flow during the fetal period associated with placental circulatory failure (8), reports on the incidence of and risk factors for short stature in children born SGA and failure of catch-up growth in SGA offspring born to women with HDP are lacking.

Therefore, we aimed to examine the incidence and risk factors for short stature in children born SGA and failure of catch-up growth in SGA offspring born to women with HDP.

Materials and methods

Participants, groups, and data collection

We retrospectively examined 1918 women with HDP who gave birth between 2009 and 2015 at 13 perinatal medical centers in eight prefectures in Chugoku and Shikoku, Japan. HDP was diagnosed according to the definition of the Japan Society for the Study of Hypertension in Pregnancy (14). HDP is defined as hypertension (blood pressure $\geq 140/90$ mmHg) occurring during pregnancy and includes chronic hypertension, gestational hypertension, preeclampsia, and superimposed preeclampsia. Mothers included in this study had preeclampsia or superimposed preeclampsia.

Preeclampsia is defined as gestational hypertension accompanied by one or more of the following new-onset conditions at or after 20 weeks gestation. These conditions could be proteinuria or other maternal organ dysfunctions, including liver involvement, progressive kidney injury, neurological complications, hematological complications, or uteroplacental dysfunction. However, all symptoms are normalized by 12 weeks postpartum. Superimposed preeclampsia is defined as hypertension that is diagnosed pre-pregnancy or before 20 weeks of gestation and followed by new onset conditions, as in preeclampsia at or after 20 weeks of gestation. A total of 226 SGA offspring (males, 115; females, 111) and their women with HDP were included in this study (Figure 1).

The SGA offspring included in this study had both birth weights and lengths below the 10th percentile and either birth weight or length of < -2.0 SD (weight data alone were used if no length data were available). The SGA definition by the Japanese Society for Pediatrics Endocrinology was adopted (15). This study excluded multiple pregnancies and pregnancies with chromosomal abnormalities and congenital disease in the fetuses and newborns to eliminate other conditions causing FGR. All procedures were performed in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2018. This study was conducted with the approval of the Ethics Committees of Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences (Okayama, Japan). The information used herein, including the research plans, has been previously published online. All data were anonymized before the analysis. The requirement for

informed consent was waived due to the retrospective nature of the study.

First, 194 SGA offspring (males, 102; females, 92) with data for the weight and length at 2 years of age were divided into two groups: those with a length of < -2.0 SD at 2 years of age were assigned to the SGA short stature group, and those with a length of ≥ -2.0 SD at 2 years of age were assigned to the non-SGA short stature group (Figure 1). We examined the incidence of short stature in children born SGA at 2 years of age among SGA offspring born to women with HDP. The initial total of 226 participants decreased because we included only SGA offspring with data at 2 years of age. We compared the maternal and neonatal characteristics of the aforementioned groups. The maternal characteristics were the maternal age, height, type of pregnancy, type of HDP, gestational day of onset of HDP, day of delivery, days from onset of HDP to delivery, and method of delivery. The neonatal characteristics were the birth weight, birth length, birth weight SD, birth length SD, Apgar score at 1 min, Apgar score at 5 min, and neonatal complications; respiratory distress syndrome, chronic lung disease, sepsis, intraventricular hemorrhage, and necrotic enteritis. Breastfeeding, artificial milk feeding, and mixed nutrition during the first 6 months after birth were also compared. Additionally, to identify the factors that most significantly contributed to short stature in children born SGA at 2 years of age, we compared the maternal age, height, type of pregnancy, type of HDP, week of delivery (≥ 32 vs. < 32 weeks), and offspring sex between the groups using multivariate analysis.

Next, 198 SGA offspring (males, 104; females, 94) with data for the weight and length at 3 years of age were divided into two groups: those with a length of < -2.0 SD at 3 years of age were assigned to the SGA short stature group, and those with a length of ≥ -2.0 SD at 3 years of age were assigned to the non-SGA short stature group (Figure 1). We examined the incidence of short stature in children born SGA at 3 years of age among SGA offspring born to women with HDP. The initial total of 226 participants decreased because we included only SGA offspring with data at 3 years of age. We compared the maternal and neonatal characteristics of the aforementioned groups. The maternal characteristics were the maternal age, height, type of pregnancy, type of HDP, gestational day of onset of HDP, day of delivery, days from onset of HDP to delivery, and method of delivery. The neonatal characteristics were the birth weight, birth length, birth weight SD, birth length SD, Apgar score at 1 min, Apgar score at 5 min, and neonatal complications; respiratory distress syndrome, chronic lung disease, sepsis, intraventricular hemorrhage, and necrotic enteritis. Breastfeeding, artificial milk feeding, and mixed nutrition during the first 6 months after birth were also compared. Additionally, to identify the factors that most significantly contributed to short stature in children born SGA at 3 years of age, we compared the maternal age, height, type of pregnancy, type of HDP, week of delivery (≥ 32 vs. < 32 weeks), and offspring sex between the groups using multivariate analysis.

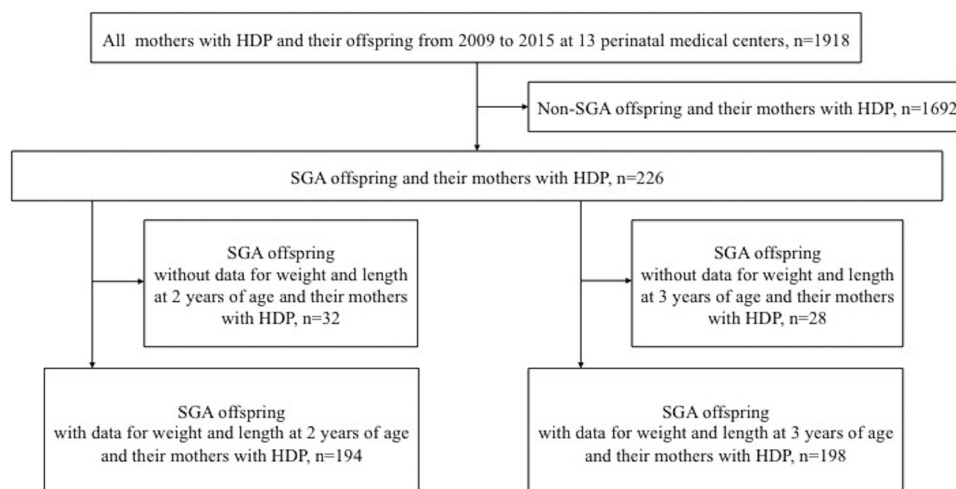


Figure 1. Flowchart of the study population.

−2.0 SD at 3 years of age were assigned to the non-catch-up group, and those with a length of ≥ -2.0 SD at 3 years of age were assigned to the catch-up group (Figure 1). The initial total of 226 participants decreased because we included only SGA offspring with data at 3 years of age. We also compared the maternal age, height, type of pregnancy, type of HDP, week of delivery (≥ 32 vs. < 32 weeks), and offspring sex between the groups to identify the factors that most significantly contributed to the failure of catch-up growth at 3 years of age using multivariate analysis.

Statistical analyses

For statistical analyses, the Mann-Whitney U and χ^2 tests were performed to determine statistical differences between the groups (first: the SGA short stature group and the non-SGA short stature group, second: the non-catch-up group and the catch-up group) using GraphPad Prism, version 8.0 (Graph Pad Software Inc., Los Angeles). Multivariate analysis using binomial logistic regression was performed using SPSS software, version 25.0 (SPSS Japan, Tokyo, Japan). A *P*-value of < 0.05 was considered statistically significant.

Results

First, of the 194 SGA offspring for whom 2-year data were available, the incidence of short stature in children born SGA was 41.2% among SGA offspring born to women with HDP. Regarding the comparisons of maternal characteristics between the SGA short stature group and the non-SGA short stature group, significant differences were observed in height ($P = 0.01$), types of HDP ($P = 0.03$), gestational day of onset of HDP ($P <$

0.001), and day of delivery ($P < 0.001$). The commonest gestational age at delivery was at 27–31 weeks in the SGA short stature group and 32–36 weeks in the non-SGA short stature group (Table 1).

Regarding the comparisons of neonatal characteristics between the SGA short stature group and the non-SGA short stature group, significant differences were observed in the birth weight ($P < 0.001$), birth length ($P < 0.001$), birth weight SD ($P < 0.001$), birth length SD ($P = 0.003$), Apgar score at 1 min ($P < 0.001$), Apgar score at 5 min ($P = 0.001$), and chronic lung disease ($P < 0.001$) (Table 2). However, the nutritional status during the first 6 months after birth did not significantly differ (data not shown).

In multivariate analysis, significant differences were found in the maternal height (0.87–0.98; odds ratio [OR], 0.93; 95% confidence interval [CI]) and day of delivery (OR, 3.93; 95% CI, 2.09–7.40;) (Table 3).

Next, of the 198 SGA offspring for whom 3-year data were available, 72 (36.4%) were assigned to the non-catch-up group and 126 (63.6%) to the catch-up group. The multivariate analysis revealed a significant difference in the day of delivery (OR, 2.75; 95% CI, 1.43–5.26;) and a tendency of difference in the maternal height (OR, 0.95; 95% CI, 0.89–1.00;) and offspring sex (OR, 1.85; 95% CI, 0.99–3.45;) (Table 4).

Discussion

Reportedly, approximately 90% of SGA children achieve catch-up growth after birth and are expected to reach normal height within 2 years of age (12,16). However, in this study, 80 (41.2%) of the SGA offspring born to women with HDP could not catch-up within 2 years of age and were diagnosed with short stature in

Table 1. Comparison of maternal characteristics between the SGA and non-SGA short stature groups.

Maternal characteristics	SGA short stature group (<i>n</i> = 80)	Non-SGA short stature group (<i>n</i> = 114)	<i>P</i> -value
Age (years)	32.5 (22.0–46.0)	33.5 (19.0–45.0)	0.31
Height (cm)	154.0 (142.0–169.0)	156.0 (140.0–171.0)	0.01
Types of pregnancy			
Primigravida	52 (65.0%)	81 (71.1%)	0.43
Multigravida	28 (35.0%)	33 (28.9%)	
Types of HDP			
PE	68 (85.0%)	108 (94.7%)	0.03
SPE	12 (15.0%)	6 (5.3%)	
Gestational day of onset of HDP	197.0 (103.0–267.0)	216.5 (135.0–281.0)	< 0.001
Day of delivery	211.5 (169.0–267.0)	230.0 (174.0–288.0)	< 0.001
22–26 gestational weeks	18 (22.5%)	5 (4.4%)	
27–31 gestational weeks	35 (43.8%)	36 (31.6%)	
32–36 gestational weeks	23 (28.8%)	61 (53.5%)	
37–41 gestational weeks	4 (5.0%)	12 (10.5%)	
Days from onset of HDP to delivery	5.0 (0.0–117.0)	9.0 (0.0–87.0)	0.13
Methods of delivery			
Vaginal delivery	8 (10.0%)	18 (16.8%)	0.29
Cesarean section	72 (90.0%)	96 (84.2%)	

SGA: small-for-gestational age, HDP: hypertensive disorders of pregnancy, PE: preeclampsia, SPE: superimposed preeclampsia.

Table 2. Comparison of neonatal characteristics between the SGA and non-SGA short stature groups.

Neonatal characteristics	SGA short stature group (n = 80)	Non-SGA short stature group (n = 114)	P-value
Sex			
Male	46 (57.5%)	56 (49.1%)	0.31
Female	34 (42.5%)	58 (50.9%)	
Birth weight (g)	825.5 (316.0–2052.0)	1237.0 (432.0–2327.0)	<0.001
Birth length (cm)	33.5 (24.5–45)	37.6 (36–47.5)	<0.001
Birth weight (SD)	–2.9 (–6.3–2.0)	–2.6 (–7.8–1.3)	<0.001
Birth length (SD)	–2.6 (–6.0–1.3)	–2.2 (–6.7–1.3)	0.003
Apgar score, 1 min	5 (1–8)	7 (1–10)	<0.001
Apgar score, 5 min	8 (1–10)	9 (1–10)	0.001
Complications			
Respiratory distress syndrome	32 (40.0%)	33 (28.9%)	0.17
Chronic lung disease	22 (27.5%)	8 (7.0%)	<0.001
Sepsis	6 (7.5%)	1 (0.9%)	0.02
Intraventricular hemorrhage	4 (5.0%)	2 (1.8%)	0.23
Necrotic enteritis	2 (2.5%)	2 (1.8%)	>0.99

SGA: small-for-gestational age, SD: standard deviation.

Table 3. Comparison of the maternal age, height, types of pregnancy, types of HDP, gestational age, and sex of the offspring between the SGA and non-SGA short stature groups by logistics regression analysis.

	SGA short stature group (n = 80)	Non-SGA short stature group (n = 114)	OR	95% CI
Maternal age (years)	32.5 (22.0–46.0)	33.5 (19.0–45.0)	0.97	0.91–1.03
Height (cm)	154.0 (142.0–169.0)	156.0 (140.0–171.0)	0.93	0.87–0.98
Types of pregnancy				
Primigravida	52 (65.0%)	81 (71.1%)	1.28	0.65–2.51
Multigravida	28 (35.0%)	33 (28.9%)		
Types of HDP				
PE	68 (85.0%)	108 (94.7%)	0.92	0.37–2.30
SPE	12 (15.0%)	6 (5.3%)		
Day of delivery	211.5 (169.0–267.0)	230.5 (174.0–288.0)	3.93	2.09–7.40
Sex				
Male	46 (57.5%)	56 (49.1%)	1.35	0.73–2.52
Female	34 (42.5%)	58 (50.9%)		

HDP: hypertensive disorders of pregnancy, SGA: small-for-gestational age, OR: odds ratio, CI: confidence interval.

Table 4. Comparison of the maternal age, height, types of pregnancy, types of HDP, day of delivery, and sex of the offspring between the non-catch-up and catch-up groups by logistics regression analysis.

	Non-catch-up group (n = 72)	Catch-up group (n = 126)	OR	95% CI
Maternal age (years)	32.0 (23.0–46.0)	33.5 (19.0–45.0)	0.95	0.90–1.01
Height (cm)	155.0 (144.0–168.0)	156.0 (140.0–171.0)	0.95	0.89–1.00
Types of pregnancy				
Primigravida	48 (66.7%)	86 (68.2%)	0.87	0.44–1.70
Multigravida	24 (33.3%)	40 (31.8%)		
Types of HDP				
PE	61 (84.7%)	117 (92.9%)	1.72	0.62–4.76
SPE	11 (15.3%)	9 (7.1%)		
Day of delivery	209.5 (170.0–258.0)	227.0 (169.0–288.0)	2.75	1.43–5.26
Sex				
Male	45 (62.5%)	59 (46.8%)	1.85	0.99–3.45
Female	27 (37.5%)	67 (53.2%)		

HDP: hypertensive disorders of pregnancy, OR: odds ratio, CI: confidence interval.

children born SGA. The incidence of short stature in SGA offspring born to women with HDP was higher than in previous reports. In a 3-year prospective study of 604 preterm offspring born before 32 weeks of gestation, 27 (36.5%) of 74 offspring diagnosed with SGA at

birth developed short stature in children born SGA at the age of 2 years, and 14 (18.9%) were targeted for treatment with growth hormone (17). Engstrom et al. reported a positive correlation between the insulin-like growth factor 1 (IGF-1) concentration and postnatal

growth (18). The IGF-1 concentration increased at 30 weeks of gestational age (19), although premature offspring born before 32 weeks of gestation had low plasma IGF-1 levels in mid-childhood (20). These reports suggest that a short gestation increases the risk of short stature after birth. Here, the commonest gestational age at delivery was at 27–31 weeks in the SGA short stature group and 32–36 weeks in the non-SGA short stature group. Additionally, according to the multivariate analysis, the most influential factor for the high incidence of short stature in children born SGA and failure of catch-up growth within 3 years of age was the gestational age. Thus, it is suggested that the most important factor affecting the incidence of short stature in children born SGA and failure of catch-up growth among SGA offspring born to women with HDP is the gestational age. Such offspring are associated with severe intrauterine growth restriction and preterm birth and are at a high risk of short stature in children born SGA and failure of catch-up growth within 3 years of age.

However, it is well established that low-birth-weight infants are more likely to develop non-communicable diseases (NCDs), including cardiovascular diseases, later in life (21). SGA and preterm infants are at a higher risk of NCDs if they exhibit rapid catch-up growth (22). It is important to note that both rapid catch-up growth and overnutrition in low-birth-weight infants could lead to NCDs (23).

There is a correlation between the maternal and newborn physique, and offspring born to short-statured women often become SGA (24,25). It has been reported that the risk factors for failure of catch-up growth in SGA offspring born at >32 weeks of gestation are a shorter maternal height and smaller fetal head circumference at birth (14). However, another report concluded that the outcome of SGA offspring is not necessarily correlated with maternal height (26). It has also been reported that the final height of preterm offspring is less affected by genetic factors and that the height at 2 years of age is important (27). In this study, maternal height contributed to the catch-up growth at 3 years of age in SGA offspring born to women with HDP. Additionally, one report described strong associations between maternal short stature and severe types of preeclampsia (28). Maternal height influences the physical development of SGA offspring through the onset and severity of HDP, suggesting that maternal short stature is a risk factor for intrauterine and extrauterine growth restrictions.

As previously stated, it is difficult for pregnant women who develop HDP to extend the gestational period after the onset, and many of them deliver

prematurely. In this study, many women delivered at <32 weeks of gestation, and it has been reported that this factor tends to hinder postnatal growth. Here, several offspring did not achieve catch-up growth at the ages of 2 and 3 years, despite the gestational age being close to term and their physique at birth being almost normal. No differences were recorded among these cases regarding maternal and neonatal characteristics. Thus, along with the gestational age and physique at birth, postnatal environmental factors (living environment, post-weaning nutrition, and others) may be involved in the growth of the offspring.

In this study, sex differences were observed between the catch-up and non-catch-up groups at 3 years of age. We found that the male sex was a risk factor for catch-up growth failure at 3 years of age. Reese et al. showed that the independent factors contributing to the incidence of extrauterine dysgenesis are male sex, the need for 1-day-old assisted ventilation, a history of necrotizing enterocolitis, the need for respiratory assistance at 28 days of age, and in-hospital administration of steroids (29). Moreover, it was reported that the female offspring with FGR born to women with HDP caught up faster than the male offspring, suggesting the presence of a sex difference in the risk of future obesity in offspring born to women with HDP (30). Vatten et al. reported that the female offspring born to women with preeclampsia had a significantly higher body weight, body mass index, and blood pressure at 13–19 years of age than those born to women without preeclampsia (31). It was also reported that although the female offspring born to women with preeclampsia had a higher body mass index and larger waist circumference than those born to women with normal pregnancies, no difference was recorded in the male offspring (32). Therefore, male sex at birth from women with HDP may be a risk factor for failure of catch-up growth, while female sex at birth from women with HDP may be a risk factor for obesity and hypertension in adulthood.

This is the first report focusing on catch-up growth in SGA offspring born to HDP women. However, this study had limitations that should be acknowledged. This was a retrospective study conducted at multiple perinatal medical centers. Thus, there is a risk of bias inherent to the retrospective design that could affect the generalizability of the findings to other populations. In addition, the 13 participating perinatal medical centers in this study were limited to those located in the Chugoku-Shikoku region in Japan; therefore, the environmental factors were not examined. Furthermore, we only measured the mothers' height and not the fathers.' Our study was also limited to studies conducted among children up to the age of 3 years. Future studies should

monitor the growth of offspring until adolescence and collect information on environmental factors and lifestyle choices; this would help account for potential confounding factors in such a longitudinal study.

In conclusion, the incidence of short stature in SGA offspring born to mothers with HDP was high (41.2%) in our study. SGA offspring born to women with HDP are at risk of early preterm birth, suggesting a high risk of short stature in children born SGA and catch-up growth failure within 3 years of age. In SGA offspring born to women with HDP, the gestational age was the most important factor affecting the incidence of short stature in children born SGA and failure of catch-up growth. Our findings present an opportunity to develop guidance for specialized care for women at risk who are pregnant or planning for pregnancy.

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Consent to participate

The requirement for informed consent was waived due to the retrospective nature of the study.

Disclosure statement

No potential conflict of interest was reported by the authors.

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