



Risk Factors of Overweight or Obesity among 3-year-old Offspring Born to Hypertensive Disorders of Pregnancy

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ABSTRACT

Introduction: Offspring of mothers with hypertensive disorders of pregnancy have a high risk of lifestyle-related diseases, such as obesity and hypertension, during childhood and young adulthood. We investigated the risk factors of overweight or obesity in 3-year-old offspring of mothers with hypertensive disorders of pregnancy.

Materials and methods: This retrospective cross-sectional study included 383 mothers with hypertensive disorders of pregnancy and their offspring delivered between 2009 and 2015 at 13 perinatal centers in Japan. Offspring at 3-years-old were classified according to body mass index into standard (<85th percentile) and “overweight or obese” groups (≥ 85th percentile). We compared maternal and neonatal characteristics between the groups. Logistic regression was used to determine which factors contributed most to the development of offspring overweight or obesity. We also compared differences in offspring physical development and body mass index during the first 3 years of life.

Results: We observed overweight or obesity in 14.3% of 3-year-old offspring. In the “overweight or obese” group, maternal body weight and body mass index before pregnancy and body weight at delivery were significantly greater than those in the standard group. Comparisons between the standard and “overweight or obese” groups using logistic regression analysis revealed a significant difference in body mass index before pregnancy, which was the most influential factor that increased body mass index of offspring by 3 years of age (odds ratio 1.069, 95% confidence interval 1.017-1.123, P=0.01). Significant differences in body mass index were observed between the standard and “overweight or obese” groups from the first 6 months after birth (P<0.001).

Conclusion: Among the “overweight or obese” offspring of mothers with hypertensive disorders of pregnancy, maternal body mass index before pregnancy was the most significant factor for increased body mass index in offspring by 3 years of age. When mothers with hypertensive disorders of pregnancy have obesity, their offspring often demonstrate rapid catch-up growth that has been linked to a high risk of childhood obesity.

Key Words: Overweight; Hypertensive disorders; Pregnancy; Obesity; Body mass index; Childhood; Dietary habits; Maternal; Neonatal

INTRODUCTION

Obesity is considered a serious pandemic, and its influence on morbidity in childhood and adulthood is increasingly important [1]. Overweight and obesity during childhood and adolescence

are among the most important issues in global health [2,3]. The NCD Risk Factor Collaboration reported that the global age-standardized prevalence of obesity increased from 0.7% in 1975 to 5.6% in 2016 among girls and from 0.9% in 1975 to 7.8% in 2016 among boys [4]. In 2016, approximately 40 million

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children aged <5 years were overweight or obese [5]. The increasing prevalence of childhood obesity is associated with lifestyle-related diseases during adulthood, such as diabetes, dyslipidemia, and hypertension. The concept of fetal origin of the adult disease is that fetuses with Fetal Growth Restriction (FGR) are at increased risk of lifestyle-related diseases, such as obesity, diabetes, hypertension, and cardiovascular disorders, during adulthood [6]. Not only prenatal but also various postnatal environmental factors, such as breastmilk and nutrition, are related to lifestyle-related diseases. This situation is widely recognized as a concept of developmental origins of health and disease (DOHaD) [7]. FGR has various causes, including Hypertensive Disorder of Pregnancy (HDP). When the intrauterine environment deteriorates due to maternal complications, such as HDP and malnutrition, the fetus becomes chronically hypoxic, with low nutrition and asymmetrical FGR [8]. Several reports have indicated that offspring of mothers with HDP have higher blood pressure and greater body weight and Body Mass Index (BMI) in childhood and young adulthood than do offspring of healthy mothers [9-11]. However, no extant research has been conducted on risk factors for childhood obesity in consideration of maternal background factors and physical data over time since delivery among offspring of mothers with HDP. Therefore, we investigated the prevalence of overweight or obesity and associated risk factors in 3-year-old offspring of mothers with HDP.

MATERIALS AND METHODS

We assessed 383 mothers with HDP and their respective offspring delivered between 2009 and 2015 at 13 perinatal medical centers in Japan. HDP was diagnosed according to the definition of HDP by the Japan Society for the Study of Hypertension in Pregnancy [12]. Chronic hypertension, gestational hypertension, preeclampsia, and superimposed preeclampsia were included in HDP. From the medical records, we retrospectively investigated the prevalence of overweight or obesity among 3-year-old offspring of mothers with HDP. The offspring were classified according to BMI into standard (<85th percentile) and “overweight or obese” groups (≥ 85th percentile) [13]. Maternal and neonatal characteristics were compared between the standard and “overweight or obese” groups. The following maternal characteristics were also compared: Maternal age, parity, height, pre-pregnancy body weight, pre-pregnancy BMI, body weight at delivery, body weight gain during pregnancy, hypertension type, gestational days of onset, gestational days of delivery, days from onset to delivery, modes of delivery, and frequencies of FGR. The following neonatal characteristics were also compared: Body weight at birth, height at birth, BMI at birth, body weight standard deviation (SD) at birth, height SD at birth, Apgar score at 1 min, Apgar score at 5 min, and neonatal complications. Infant feeding practices (breastfeeding, artificial milk feeding, and mixed feeding) during the first 6 months after birth were also compared. Furthermore, to determine factors that contribute most to the development of overweight or obesity, we compared maternal characteristics (maternal age, height, and pre-pregnancy BMI), gestational days of delivery, frequencies of FGR, and sex of the offspring between the groups using logistic regression analysis. Differences in physical development and BMI during the first 3 years of life were also

compared among the offspring groups. The exclusion criteria were multiple pregnancies, chromosomal abnormalities in the fetus, and congenital diseases in newborns. The Mann-Whitney U test, Fisher’s test, the χ^2 test, and logistic regression analysis were used for statistical analyses; $P < 0.05$ (two-tailed P -value) was considered significant. The D’Agostino-Pearson test was used to assess the normality of the distribution of continuous variables. Graph Pad Prism 8.2.0 (Graph Pad Software Inc., La Jolla, CA, USA) and SPSS software, version 25.0 (SPSS Japan, Tokyo, Japan), were used to perform the statistical analyses. This study conforms to the provisions of the Declaration of Helsinki of 1975, as revised in 1983, and was conducted with the approval of the Ethics Committees of Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences. The research plan approved by the Ethics Committees has been previously published online. All data were anonymized prior to analysis. The requirement for informed consent was waived due to the retrospective nature of the study.

RESULTS

The prevalence of overweight or obesity among 3-year-old offspring of mothers with HDP was 14.3%, which was a very high rate. We compared the maternal and neonatal characteristics and nutrition between the standard and “overweight or obese” groups. With regard to the maternal characteristics, pre-pregnancy body weight and BMI were significantly greater among mothers of “overweight or obese” offspring ($P < 0.001$ and $P = 0.002$, respectively) than among mothers of standard offspring. Maternal body weight at delivery was also significantly greater among mothers of “overweight or obese” offspring than among mothers of standard offspring ($P = 0.001$). As regards neonatal characteristics, the BMI at birth and body weight SD at birth were significantly greater in the “overweight or obese” group than in the standard group ($P = 0.02$ and $P = 0.03$, respectively). No significant intergroup differences were found in terms of neonatal complications. The offspring nutritional status during the first 6 months after birth was not significantly different (Table 1). Logistic regression analysis revealed a significant difference in pre-pregnancy BMI between the standard and “overweight or obese” groups (odds ratio or 1.069, 95% confidence interval [CI] 1.017-1.123, $P = 0.01$), and this significantly influenced the BMI of 3-year-old offspring (Table 2). With respect to the physical development and BMI of the offspring, significant differences in body weight and BMI were observed between the standard and “overweight or obese” groups from 6 months after birth ($P < 0.001$) (Table 3). Figure 1 shows that the BMI in the “overweight or obese” group rapidly increased by 6 months after birth. By the first 6 months, the “overweight or obese” group displayed rapid catch-up growth in comparison with the standard group.

DISCUSSION

HDP, especially the pathogenesis of preeclampsia, has been made apparent by the 2-stage disorder theory [14]. Utero placental circulatory failure is caused by remodeling failure of the spiral arteries during early pregnancy. This circulatory failure causes hypoxia in the placenta and increases the production of hypoxia-inducible factors, including anti-angiogenic factors [15,16]. Utero placental circulatory failure

is then exacerbated further, and maternal hypertension and proteinuria occur, while FGR occurs in the fetus [17,18]. Thus far, we have reported that infants with FGR of mothers with HDP experience rapid catch-up growth after birth [19].

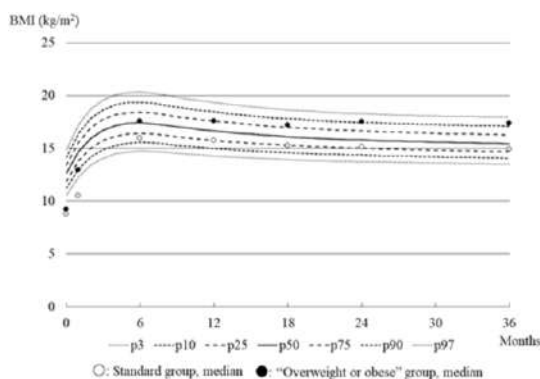


Figure 1: Transition of the BMI of offspring in the standard group and "overweight or obese" group.

By the first 6 months, the "overweight or obese" group displays rapid catch-up growth in terms of BMI compared with the standard group. BMI: Body Mass Index

In addition, some studies have reported that rapid catch-up growth is associated with lifestyle-related diseases, such as obesity and hypertension in adulthood [20,21]. In this study, infants born to mothers with HDP displayed rapid catch-up growth, and especially in the overweight or obese offspring, both body weight and BMI rapidly increased by 6 months after birth. It is considered that this rapid catch-up growth is due to environmental maladaptation as a result of an external environment that is different from the intrauterine environment. With regards to proposed that developmental plasticity, trade-off, and predictive adaptive responses of the environment in the developmental phase are associated with various diseases in adulthood [22,23]. In this study, maternal pre-pregnancy body weight, pre-pregnancy BMI, and body weight at delivery were significantly higher among the overweight or obese

offspring of mothers with HDP. Additionally, maternal pre-pregnancy BMI was the most influential factor that increased the BMI of offspring by 3 years of age. Sun et al. reported an additive interaction of maternal pre-pregnancy overweight or obesity and HDP on offspring with a high BMI [24]. Thus, it is suggested that physical development and the BMI of the offspring after birth may be greatly influenced by the dietary habits and obesity of the mother, which is an environmental factor after birth. Several risk factors for HDP have been reported, including family history, obesity, and hypertension. If there is a maternal family history of preeclampsia, the risk of developing preeclampsia is 20%-40% [25]. The risk of developing HDP by obesity is proportional to the BMI of the mother, and the relative risk of developing HDP at a BMI of $\geq 25 \text{ Kg/m}^2$ is reported as 1.9 [26]. Given that maternal obesity is associated with a high risk of HDP, and perhaps childhood overweight or obesity, pregnant women with pre-pregnancy obesity should attempt improving their dietary habits, and clinicians should closely monitor childhood overweight or obesity of the offspring of mothers with HDP during post-delivery follow-ups. Children with overweight or obesity are considered at a high risk of developing future lifestyle-related diseases; therefore, careful follow-up is required. This study has some limitations. This is a retrospective study from multiple perinatal medical centers. There is a risk of bias inherent to the retrospective design that affects the generalizability of the findings to other populations. This study investigated only physical development, such as body weight, height, and BMI in offspring. Future research should examine lipid and hormone levels in the offspring. To the best of our knowledge, this is the first study to show the prevalence and risk factors for childhood obesity in consideration of maternal background factors and physical data over time since delivery among offspring of mothers with HDP. Because mothers with HDP as well as with obesity are more likely to be complicated with FGR, offspring of mothers with HDP and obesity have rapid catch-up growth. Thus, offspring of mothers with HDP are considered at a high risk of childhood obesity.

Table 1: Comparison of maternal and neonatal characteristics and nutrition after birth between the standard group and "overweight or obese" group

Maternal characteristics	Standard (n=328)	Overweight or obese (n=55)	P-value
Age, median (range), years	34.0 (19.0-46.0)	33.0 (20.0-43.0)	0.52
Parity, n (%) with data			
Primigravida	213 (64.9%)	39 (70.9%)	0.44
Multigravida	115 (35.1%)	16 (29.1%)	
Height, median (range), cm	156.0 (143.0-174.0)	156.0 (144.0-171.0)	0.09
Pre-pregnancy body weight, median (range), kg	51.0 (34.0-106.0)	57.4 (40.0-126.0)	<0.001
Pre-pregnancy BMI, median (range), kg/m ²	21.4 (14.1-42.7)	23.2 (17.7-47.4)	0.002
Body weight at delivery, median (range), kg	60.2 (37.8-117)	67.0 (48.8-129.0)	0.001
Body weight gain during pregnancy, median (range), kg	7.8 (-4.0-30.3)	8.1 (-6.6-19.6)	0.73
Hypertension type, n (%) with data			
Chronic hypertension	4 (1.2%)	2 (3.6%)	0.29
Gestational hypertension	33 (10.1%)	7 (12.7%)	
Preeclampsia	254 (77.4%)	37 (67.3%)	

Superimposed preeclampsia	37 (11.3%)	9 (16.4%)	
Gestational days of onset, median (range), days	213 (61-291)	218 (103-218)	0.27
Gestational days of delivery, median (range), days	226 (165-294)	231 (169-290)	0.14
Days from onset to delivery, median (range), days	7 (0-190)	4 (0-117)	0.17
Modes of delivery, n (%) with data			
Vaginal delivery	46 (14.0%)	11 (20.0%)	
Cesarean section	282 (86.0%)	44 (80.0%)	0.29
Fetal growth restriction	202 (61.6%)	31 (56.4%)	0.46
Neonatal characteristics	Standard (n=328)	Overweight or obese (n=55)	P-value
Sex, n (%) with data			
Male	163 (49.7%)	33 (60.0%)	
Female	165 (50.3%)	22 (40.0%)	0.16
Body weight at birth, median (range), g	1294.0 (350.0-3558.0)	1438.0 (316.0-3326.0)	0.05
Height at birth, median (range), cm	38.5 (24.0-52.3)	39.3 (24.5-51.0)	0.15
BMI at birth, median (range), kg/m ²	8.7 (4.8-14.2)	9.2 (5.3-14.3)	0.02
Body weight SD at birth, median (range)	-2.0 (-7.0-1.9)	-1.5 (-4.4-1.5)	0.03
Height SD at birth, median (range)	-1.5 (-5.3-1.8)	-1.3 (-4.2-1.0)	0.15
Apgar score at 1 min, median (range)	7 (0-10)	7 (1-9)	0.36
Apgar score at 5 min, median (range)	8 (2-10)	9 (4-10)	0.51
Complications, n (%) with data			
Respiratory distress syndrome	110 (25.7%)	21 (38.2%)	0.05
Transient tachypnea of the newborn	46 (14.0%)	12 (21.8%)	0.15
Apnea	68 (20.7%)	16 (29.1%)	0.16
Chronic lung disease	31 (9.5%)	6 (10.9%)	0.8
Respiratory-related pneumonia	6 (1.8%)	0 (0.0%)	0.6
Pneumonia	7 (2.1%)	0 (0.0%)	0.6
Sepsis	10 (3.1%)	0 (0.0%)	0.37
Intraventricular hemorrhage	14 (4.3%)	3 (5.5%)	0.72
Patent ductus arteriosus	38 (11.6%)	8 (14.6%)	0.51
Late neonatal circulatory failure	20 (6.1%)	1 (4.8%)	0.33
Periventricular leukomalacia	9 (2.7%)	3 (5.5%)	0.39
Gastrointestinal perforation	0 (0.0%)	0 (0.0%)	>0.99
Necrotic enteritis	1 (0.3%)	1 (1.8%)	0.27
Jaundice	197 (60.1%)	30 (54.6%)	0.46
Premature bone metabolic disease	60 (18.3%)	5 (9.1%)	0.12
Retinopathy of prematurity	52 (15.9%)	10 (18.2%)	0.69
Anemia	141 (43.0%)	21 (38.2%)	0.56
Infant feeding practices	Standard (n=328)	Overweight or obese (n=55)	
Up to 1 month, n (%) with data	277 (84.5%)	43 (78.2%)	

Mainly breastfeeding	118 (36.0%)	19 (34.5%)	0.19
Mainly artificial milk feeding	34 (10.4%)	6 (10.9%)	
Mixed feeding	125 (38.1%)	18 (32.7%)	
Up to 3 months, n (%) with data	214 (65.2%)	34 (61.8%)	0.18
Mainly breastfeeding	87 (26.5%)	19 (34.5%)	
Mainly artificial milk feeding	37 (11.3%)	6 (10.9%)	
Mixed feeding	90 (27.4%)	9 (16.3%)	0.53
Up to 6 months, n (%) with data	196 (59.8%)	31 (56.4%)	
Mainly breastfeeding	70 (21.3%)	14 (25.4%)	
Mainly artificial milk feeding	58 (17.7%)	9 (16.4%)	0.53
Mixed feeding	68 (20.7%)	8 (14.5%)	

Table 2: Comparison of maternal and neonatal characteristics between the standard group and the "overweight or obese" group using logistic regression analysis

Clinical values	Standard (n=328)	Overweight or obese (n=55)	OR	95% CI	P-value
Age, median (range), years	34.0 (19.0-46.0)	33.0 (20.0-43.0)	0.969	0.915-1.025	0.27
Height, median (range), cm	156.0 (143.0-174.0)	156.0 (144.0-171.0)	1.054	0.999-1.111	0.06
Pre-pregnancy BMI, median (range), kg/m ²	21.4 (14.1-42.7)	23.2 (17.7-47.4)	1.069	1.017-1.123	0.01
Gestational days of delivery, median (range), days	226 (165-294)	231 (169-290)	0.162	0.997-1.018	0.16
Fetal growth restriction, n (%) with data	202 (61.6%)	31 (56.4%)	0.893	0.556-1.959	0.89
Sex, n (%) with data					
Male	163 (49.7%)	33 (60.0%)	1.22	0.771-2.543	0.27
Female	165 (50.3%)	22 (40.0%)			

Table 3: Comparison of the transition of body weight, height, and BMI of offspring, who were born to mothers with HDP, between the standard group and "overweight or obese" group

Physical development and BMI	Standard	Overweight or obese	P-value
Body weight, median (range), g			
At birth (n=328 vs. n=55)	1294.0 (350.0-3558.0)	1438.0 (316.0-3326.0)	0.05
1 month (n=306 vs. n=51)	1730.0 (469.0-4980.0)	2062.0 (520.0-5140.0)	0.02
6 months (n=271 vs. n=49)	5840.0 (1374.0-10250.0)	6720.0 (2316.0-9120.0)	<0.001
12 months (n=285 vs. n=49)	7565.0 (2975.0-11345.0)	8885.0 (4272.0-11505.0)	<0.001
18 months (n=261 vs. n=47)	8765.0 (4835.0-12400.0)	10220.0 (6205.0-12200.0)	<0.001
24 months (n=283 vs. n=49)	10000.0 (5313.0-14200.0)	11600.0 (8821.0-13700.0)	<0.001
36 months (n=328 vs. n=55)	11775.0 (7970.0-16100.0)	14300.0 (9744.0-17900.0)	<0.001
Height, median (range), cm			
At birth (n=321 vs. n=55)	38.5 (24.0-52.3)	39.3 (24.5-51.0)	0.15
1 month (n=186 vs. n=33)	43.5 (27.9-57.2)	46.9 (29.6-55.1)	0.08
6 months (n=223 vs. n=46)	60.2 (40.4-73.8)	61.6 (40.5-70.6)	0.05
12 months (n=278 vs. n=47)	69.5 (49.0-78.9)	70.1 (50.0-76.9)	0.06
18 months (n=253 vs. n=46)	75.8 (60.6-89.4)	76.6 (57.5-84.0)	0.12
24 months (n=276 vs. n=47)	81.1 (64.9-90.1)	81.7 (71.5-88.9)	0.22
36 months (n=328 vs. n=55)	88.9 (73.8-106.2)	90.7 (74.6-99.1)	0.05
BMI, median (range), kg/m²			
At birth (n=321 vs. n=55)	8.9 (4.8-14.2)	9.2 (5.3-14.3)	0.02
1 month (n=186 vs. n=33)	10.5 (4.2-17.6)	12.9 (4.9-16.7)	0.02
6 months (n=222 vs. n=46)	16.0 (9.9-19.9)	17.6 (11.4-21.0)	<0.001
12 months (n=276 vs. n=47)	15.8 (11.2-19.7)	17.6 (13.8-20.3)	<0.001
18 months (n=252 vs. n=46)	15.2 (11.9-18.5)	17.2 (14.1-21.3)	<0.001

24 months (n=276 vs. n=47)	15.1 (11.8-18.2)	17.5 (15.8-19.4)	<0.001
36 months (n=328 vs. n=55)	14.9 (11.6-16.8)	17.3 (16.8-22.1)	<0.001

CONCLUSION

The prevalence of overweight or obesity among 3-year-old offspring of mothers with HDP was 14.3%. Maternal pre-pregnancy BMI was the most influential factor that increased the BMI of offspring by 3 years of age. Among offspring of mothers with HDP, rapid catch-up growth by 6 months caused by the change from the fetal to the external environment after birth may significantly affect BMI when the offspring are 3 years old. Childhood overweight or obesity of the offspring of mothers with HDP should be closely monitored during post-delivery follow-ups.

AUTHORS CONTRIBUTION

PC-A designed the study, interpreted the data and wrote the manuscript; MB designed the study, analyzed the data, revised and approved the manuscript; PM collected and analyzed the data; AS-S designed the study, revised and approved the manuscript. All authors have read and agreed to the published version of the manuscript.

DATA AVAILABILITY STATEMENT

All data generated or analyzed during this study are included in this published article.

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CONFLICT OF INTEREST

The authors declare no conflict of interests for this article.

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