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RESEARCH ARTICLE

Abnormal placental cord insertion, hypertensive disorders of pregnancy and birth length may be involved in development of hypospadias in male fetuses

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Abstract

Objectives: Hypospadias is a congenital disease characterized by morphological abnormalities of the penis, including abnormal urethral opening and penile flexion, which cause urination disorders and/or sexual intercourse difficulty. Various factors have been suggested to cause this anomaly, but evidence concerning risk factors causing this anomaly is insufficient. We evaluated the etiology of hypospadias in Japan using the Common Database of the National Hospitals' Neonatal study group.

Study design: We retrospectively evaluated 7,865 male neonates registered in the NICU Common Database of the National Hospitals' Neonatal study group. The subjects were divided into two groups by the presence ($n = 43$) or absence ($n = 7{,}822$) of hypospadias. Statistical analyses were performed to compare nominal variables between the groups by Fisher's direct establishment calculation method and logistic regression analyses.

Results: A univariate analysis showed significant between-group differences in hypertensive disorders in pregnancy (odds ratio [OR]: 4.02, 95% confidence interval [CI]: 1.95–7.90), placental weight <-1.28 standard deviation (*SD*; OR: 5.06, 95% CI: 2.45–10.32), abnormal placental cord insertion (OR: 4.7, 95% CI: 2.62–9.76), birth length $<-2SD$ (OR: 10.56, 95% CI: 5.00–21.1) and birth weight $<-2SD$ (OR: 8.17, 95% CI: 4.17–15.68). A multivariate analysis showed a significant between-group difference in hypertensive disorders of pregnancy (adjusted OR [AOR]: 2.30, 95% CI: 1.09–4.85), abnormal placental cord insertion (AOR: 3.69, 95% CI: 1.83–7.44) and birth length $<-2SD$ (AOR: 3.44, 95% CI: 1.26–9.42).

Conclusion: Abnormal placental cord insertion, hypertensive disorders of pregnancy and birth length may be involved in hypospadias development

Abbreviations: 95% CI, 95% confidence interval; AOR, adjusted odds ratio; GDM, gestational diabetes mellitus; NHO, National Hospital Organization; NICU, neonatal intensive care unit; SGA, small for gestational age.

in male neonates in conjunction with placental dysfunction in early pregnancy.

KEYWORDS

abnormal placental cord insertion, birth length, hypertensive disorders of pregnancy, hypospadias, NICU

1 | INTRODUCTION

Hypospadias is a congenital disease characterized by an abnormal morphology of the penis, causing urination disorders due to abnormal opening of the urethra and difficulty engaging in sexual intercourse in the future due to penile flexion (van der Horst & de Wall, 2017). The frequency of hypospadias is 5.2–34.2/10,000 males in general (Bergman et al., 2015; Springer, van den Heijkant, & Baumann, 2016; Yu et al., 2019) and 3.9–12.3/10,000 in Japanese boys, showing racial differences (Kurahashi et al., 2004; Michikawa et al., 2019).

The present study evaluated the clinical features of neonates with hypospadias and explored the factors related to hypospadias in males, using the Common NICU Database created for the neonatal study group of the National Hospitals' Organization in Japan.

2 | MATERIAL AND METHODS

A total of 17,250 neonates were registered in the NICU Common Database from 2010 to 2014 and from 2016 to February 2019, and 9,345 of them were males. Among the 9,345 male neonates, 1,480 were excluded due to the exclusion criteria (twins, triplets and cases with deficient data). A total of 7,865 male neonates were thus available for the present study.

The subjects were separated into two groups: 7822 neonates without hypospadias were included in Group A, and 43 neonates with hypospadias were in Group B, and the following clinical features were compared and examined between these groups: maternal information, placenta information, and neonatal information (Figure 1). This information was collected from chart review, and they had been previously reported in relation to be related to fetal development and the advancement development of hypospadias. Maternal age ≥35 years old, fertility treatment, alcohol history, smoking status and presence of gestational diabetes mellitus (GDM) or hypertensive disorders in pregnancy were collected as maternal information. Placental weight <-1.28 standard deviation (*SD*; Ogawa et al., 2016) and abnormal placental cord insertion (velamentous and marginal cord insertions)

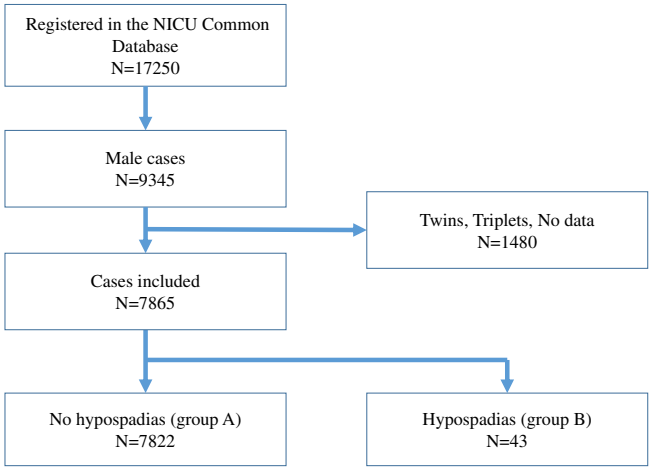

FIGURE 1 Flowchart of the study

were collected as placenta information. Birth length $<-2SD$, birth weight $<-2SD$, head circumference $<-2SD$, small for gestational age (SGA; $<-2SD$ for both weight and height) and cryptorchism were collected as neonatal information.

We declared that this study was approved by an ethics committee and/or follows the tenants of the Declaration of Helsinki and was approved by the Ethics Committee of the National Hospital Organization Kokura Medical Center. (Approval number: REC2021-009). Written informed consent was obtained from the parents.

Statistical analyses were performed to compare nominal variables between the groups by Fisher's direct establishment calculation method and logistic regression analyses. $p < .05$ were considered to indicate statistical significance. A univariate analysis was performed to identify significant factors. Then, all factors with a $p < .05$ in the univariate analysis were included in a multivariate analysis. In this way, we protected the study-wide p value of .05. All statistical analyses were performed using EZR (Kanda, 2013).

3 | RESULTS

The average gestation period for all male neonates registered was 36.7 ± 4.1 weeks, and the average weight at birth was 2,564 ± 725.8 g. The median *SD* of the birth

weight was −0.19*SD* (interquartile range: −0.94 to 0.61), and the median *SD* of the birth length was −0.19*SD* (interquartile range: −0.58 to 0.89). In our data, the rate of abnormal cord insertion was 486 (6.2%) in marginal cases and 121 (1.5%) in velamentous cases. Hypospadias was associated with anal atresia ($n = 2$), hydronephropathy ($n = 1$), bifid scrotum ($n = 1$), cryptorchidism ($n = 1$), and spina bifida ($n = 1$). A univariate analysis showed a significant difference between the two groups with regard to hypertensive disorders of pregnancy as maternal information. Maternal age ≥35 years old, fertility treatment, alcohol habit, smoking habit and a history of GDM did not show any significant difference between the two groups. However, significant differences were observed between the two groups with regard to placental weight <−1.28*SD* and abnormal placental cord insertion (Table 1). There was also a significant difference between the two groups with regard to birth length <−2*SD* and birth weight <−2*SD* as neonatal information. There was no significant difference in the head circumference, SGA or presence of cryptorchism (Table 2).

A logistic regression analysis was then performed for hypertensive disorders of pregnancy, placental weight <−1.28*SD*, abnormal placental cord insertion, birth length <−2*SD* and birth weight <−2*SD*, with all of these factors showing significant differences in a univariate analysis between the two groups. We adjusted five factors in the regression analysis, hypertensive disorders of pregnancy, placental weight <−1.28*SD*, abnormal placental cord insertion, birth length <−2*SD*, and birth weight <−2*SD*. A multivariate analysis revealed significant differences in hypertensive disorders of pregnancy, abnormal placental cord insertion and birth length <−2*SD* between the two groups (Table 3). There was no significant difference in placental weight or birth weight between the two groups according to the multivariate analysis.

4 | DISCUSSION

Various factors have been described as causes of hypospadias, including synthetic abnormalities of androgen in fetal testes (Batch, Evans, Hughes, & Patterson, 1993), deficient secretion of hCG due to placental dysfunction (Toufaily, Roberts, Westgate, Hunt, & Holmes, 2018), maternal elderly childbirth (Fisch et al., 2001), low birth weight (Hashimoto et al., 2016; Hussain et al., 2002), oral contraceptives (Nørgaard, Wogelius, Pedersen, Rothman, & Sørensen, 2009) and genetic abnormalities (e.g., FOXO3 [Ross et al., 2011], FGF10 [Haid et al., 2020]).

In the present study, a data-based analysis using the NICU Common Database of NHO neonatal centers

TABLE 1 A univariate analysis of the maternal and placental information in Groups A and B

	N	Group A	%	Group B	%	Odds ratio	95% CI		*p* Value
Maternal age ≥35 years	7,678	2,306/7,635	30.2	14/43	32.6	1.11	0.54	2.18	.74
Multipara	7,636	3,851/7,594	50.7	18/42	42.9	0.72	0.37	1.4	.35
Fertility treatment	7,450	807/7,407	10.9	3/43	7	0.61	0.12	1.93	.62
Alcohol	5,834	209/5,794	3.6	3/40	7.5	2.16	0.42	6.92	.17
Smoking	5,817	401/5,777	6.9	1/40	2.5	0.34	0.01	2.04	.52
GDM	7,647	555/7,604	7.3	0/43	0	0	0	1.14	.07
Hypertensive disorders of pregnancy	7,650	814/7,607	10.7	14/43	32.6	4.02	1.95	7.9	<.01
Placental weight <−1.28*SD*	5,715	853/5,679	15	17/36	47.2	5.06	2.45	10.3	<.01
Abnormal placental cord insertion	5,292	593/5,255	11.3	14/37	37.8	4.7	2.62	9.76	<.01

Abbreviations: CI, confidence interval; GDM, gestational diabetes mellitus.

TABLE 2 A univariate analysis of the neonatal information in Groups A and B

	N	Group A	%	Group B	%	Odds ratio	95% CI		*p* Value
Birth length <−2*SD*	7,865	308/7,822	3.9	13/43	30.2	10.56	5	21.1	<.01
Birth weight <−2*SD*	7,865	633/7,822	8.1	18/43	41.9	8.17	4.17	15.6	<.01
HC <−2*SD*	7,865	117/7,822	1.5	1/43	2.3	1.56	0.03	9.39	.47
SGA	7,865	38/7,822	0.5	1/43	2.3	4.87	0.11	30.3	.19
With cryptorchidism	7,865	29/7,822	0.4	1/43	2.3	6.39	0.15	40.4	.15

Abbreviations: CI, confidence interval; HC, head circumference; SGA, small for gestational age; *SD*, standard deviation.

	AOR	95% CI		*p* Value
Hypertensive disorders of pregnancy	2.30	1.09	4.85	.029*
Placental weight <−1.28*SD*	2.04	0.88	4.67	.092
Abnormal placental cord insertion	3.69	1.83	7.44	.000263*
Birth length <−2*SD*	3.44	1.26	9.42	.016*
Birth weight <−2*SD*	1.58	0.55	4.51	.392

TABLE 3 A multivariate analysis of factors associated with hypospadias

Abbreviations: AOR, adjusted odds ratio; CI, confidence interval; *SD*, standard deviation.
*$p < .05$.

showed that abnormal placental cord insertion, hypertensive disorders of pregnancy, and birth length were significantly correlated with the occurrence of hypospadias. Several author reported that placenta cord insertion is established around 15 week's gestation. (Knofler et al., 2019; Turco & Moffett, 2019), and the onset of penile formation hypospadias occurs at 10–14 weeks' gestation (Blaschko, Cunha, & Baskin, 2012) under stimulation of testosterone. At 10–14 weeks' fetal gestation, the secretion of hCG and fetal testosterone in the placenta are both increased, and placental dysfunction at this time may cause abnormal formation of the urethra (Toufaily et al., 2018). Although small placentas are more prone to placental dysfunction than larger ones (Longtine & Nelson, 2011), there was no significant difference in the placental weight by the presence of hypospadias in this study. A decrease in placental weight at birth does not always indicate placental dysfunction during the critical period of penile formation in the early stage of pregnancy, as placental size is affected by various effects, such as calcification and blood flow abnormalities (Longtine & Nelson, 2011), throughout pregnancy. However, the presence of abnormal placental cord insertion reportedly causes placental dysfunction from early pregnancy and induces nutritional damage to fetuses, easily resulting in SGA or a low-birth-weight infant (Ismail, Hannigan, O'Donoghue, & Cotter, 2017). Abnormal placental cord insertion is completed at 9–11 weeks' gestation (Hasegawa et al., 2006), after which the adhesion site of the umbilical cord is not moved. Therefore, male fetuses with abnormal placental cord insertion may develop hypospadias due to placental dysfunction and nutritional disorders from the early stage of pregnancy.

A short length at birth and hypertensive disorders of pregnancy were also significantly and independently correlated with the onset of hypospadias in our study. While previous reports have shown that SGA is related to the development of hypospadias, our study showed that a short birth length was more closely associated with the occurrence of hypospadias than a low birth weight in male neonates. A short birth length is associated with placental and umbilical cord abnormalities in early pregnancy (Burton & Jauniaux, 2018; Ismail et al., 2017). In addition to the placental function, the birth weight is greatly affected by maternal factors, such as GDM and the fetus's condition, such as subcutaneous edema in the late stage of pregnancy; however, the birth length is less markedly affected by those factors and may instead be strongly influenced by placental dysfunction in the early stage of pregnancy. Therefore, the birth length may be significantly related to hypospadias. Hypertensive disorders of pregnancy is also thought to cause placental dysfunction. In hypertensive disorders of pregnancy, remodeling failure of the spiral arterioles of the placenta reduces the oxygen supply from the mother and causes hypoxic chorionic mesothemble and placental dysfunction (Roberts & Hubel, 2009). Hypertensive disorders of pregnancy might thus be significantly associated with the occurrence of hypoplasia. Consequently, both abnormal placental cord insertion and hypertensive disorders of pregnancy may induce placental dysfunction, which can cause deficient secretion of hCG and testosterone in the early stage of pregnancy and lead to hypospadias in male fetuses. A short length at birth may be induced by placental dysfunction in the early stage of pregnancy and is independently associated with the formation of hypospadias. On the other hand, in female babies, abnormal placental cord insertion was also significantly associated with short birth length in females ($p < .05$ data not shown). While there have been many reports that hypospadias is strongly associated with cryptorchism (Arendt et al., 2016), no significant correlation was noted in the present study. The occurrence of cryptorchism is also thought to be related to the lack of testosterone activity. Penile formation occurs under the action of testosterone in early pregnancy, while testosterone affects testicular descent in the latter half of pregnancy (Hutson, Li, Southwell, Newgreen, & Cousinery, 2015). Therefore, we only noted a low association of hypospadias and cryptorchidism in our study.

4.1 | Limitations

Several limitations associated with the present study warrant mention. First, the NICU Common Database was established based on patients who were transferred to the

intensive care unit of NHO hospitals. Second, a pathological examination of the placenta was not performed. Third, the degree of hypospadias was not determined. Therefore, further studies will be necessary to verify the etiologically related factors of hypospadias.

5 | CONCLUSION

Abnormal placental cord insertion, hypertensive disorders of pregnancy and birth length are significantly related to the occurrence of hypospadias in neonates hospitalized in the NICU. These factors are strongly correlated with placental dysfunction in the early stage of pregnancy and may induce hypospadias in male fetuses.

MEMBERS OF COLLABORATIVE RESEARCH IN NATIONAL HOSPITAL ORGANIZATION NETWORK: PEDIATRIC AND PERINATAL GROUP OF 2021

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Yoshihiro Sakemi and Takeshi Shono designed the study protocol and drafted the initial manuscript. Noriko Sugino and Motoki Bonno statistical support and designed the analysis. Toshinori Nakashima and Hironori Yamashita coordinate data collection; conceptualized and designed the study, reviewed the analysis. Yoshihiro Sakemi and Takeshi Shono reviewed and revised the manuscript. All authors approved the final manuscript as submitted.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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