Incidence of hypospadias in severe small-for-gestational-age infants: A multicenter Asian population study

Ashina, Mariko
Fujioka, Kazumichi
Yoshimoto, Seiji
Ioroi, Tomoaki
Iijima, Kazumoto

(Citation)
Pediatrics and Neonatology,61(5):548-550

(Issue Date)
2020-10-01

(Resource Type)
journal article

(Version)
Version of Record

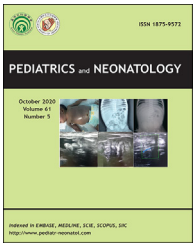
(URL)
https://hdl.handle.net/20.500.14094/90009531

Pediatrics and Neonatology (2020) 61, 548–550

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: http://www.pediatr-neonatol.com



Short Communication

Incidence of hypospadias in severe small-for-gestational-age infants: A multicenter Asian population study

Mariko Ashina [a], Kazumichi Fujioka [a,*], Seiji Yoshimoto [b], Tomoaki Ioroi [c], Kazumoto Iijima [a]

[a] Department of Pediatrics, Kobe University Graduate School of Medicine, Kobe, Japan
[b] Department of Neonatology, Hyogo Prefectural Kobe Children's Hospital, Kobe, Japan
[c] Department of Pediatrics, Japanese Red Cross Society Himeji Hospital, Himeji, Japan

Received Nov 24, 2019; received in revised form Apr 17, 2020; accepted Jul 1, 2020
Available online 25 July 2020

1. Introduction

Intrauterine growth restriction is a consequence of the deterioration of the fetal environment[1] and results in small-for-gestational-age (SGA) newborns with a birthweight less than 10th percentile for gestational age. Fujita et al. reported that the incidence of severe SGA (birthweight less than −2 standard deviations (SD) for gestational age) was 1.2% in their population-based study conducted in Kobe.[2] Fujioka et al. reported that infants with severe SGA have abnormal placental DNA methylation, which suggested of disturbed epigenetic control *in utero*.[3] These findings suggest that severe SGA is more frequently complicated by hypospadias.

The incidence of hypospadias increases with fetal growth restriction (FGR) and in infants with low birth weight.[4,5] In early embryogenesis, the secretion of testosterone, which is required for fetal vulvar masculinization, is induced by placental human chorionic gonadotropin (hCG). SGA typically results from FGR or placental dysfunction; therefore, insufficient placental hCG secretion may play a role in the development of hypospadias.[4] In this study, we hypothesized that the risk of developing hypospadias may increase with increasing severity of SGA.

While the prevalence of hypospadias shows considerable regional disparities, there have been recent reports of an increase in the incidence of hypospadias in Western countries, and some environmental factors are presumed to be involved.[3] However, to the best of our knowledge, no large cohort data are available in the Asian population. Therefore, this study aimed to clarify the incidence of hypospadias in severe SGA infants from three tertiary perinatal centers in Japan.

2. Methods

The protocol of this retrospective study was approved by the ethics committee of Kobe University Graduate School of Medicine (approval number 170127). Severe SGA was defined as birthweight of less than −2 SD for gestational age.[3,6] Records of 592 male infants who were admitted to three study facilities from 2008 to 2017 with birthweight less than −2 SD were reviewed; patients with chromosomal anomalies (n = 61) were excluded. Clinical data, including

* Corresponding author. Department of Pediatrics Kobe University Graduate School of Medicine, 7-5-2 Kusunoki-cho, Chuo-ku, Kobe, 650-0017, Japan.
E-mail address: fujiokak@med.kobe-u.ac.jp (K. Fujioka).

https://doi.org/10.1016/j.pedneo.2020.07.011

Table 1 Clinical characteristics of the hypospadias and non-hypospadias groups.

Characteristics	Hypospadias group n = 34	Non-hypospadias group n = 497	P
GA, weeks	36 (27–40)	36 (22–41)	0.64
BW, g	1415 (452–2352)	1750 (314–2720)	0.16
BW Z-score, SD	**−3.03 (-5.96 to -2.01)**	**−2.65 (-4.67 to -2.01)**	**0.002**
Asymmetrical SGA (%)[a]	**19/19 (100.0)**	**122/225 (54.2)**	**0.0001**
Apgar score at 1 min	8 (2–9)	8 (0–10)	0.19
Apgar score at 5 min	9 (4–10)	9 (1–10)	0.18
Asphyxia (%)[b]	11 (32.4)	134 (27.0)	0.49

Data are expressed as median (range) or number (%).
BW, birthweight; GA, gestational age; SD, standard deviation.
Differences were deemed statistically significant for $p < 0.05$ which are mentioned in bold.
[a] Asymmetrical SGA is defined as a head circumference ≥10th percentile for gestational age.
[b] Neonatal asphyxia is defined as an Apgar score ≤ 6 at 1 min.

gestational age, birthweight, birthweight Z-score, Apgar scores, neonatal asphyxia, and incidence of hypospadias, were collected from electronic medical records. Neonatal asphyxia was defined as an Apgar score ≤6 at 1 min. Asymmetrical SGA was defined as head circumference ≥10th percentile for gestational age.

Data are expressed as median (range) or mean ± SD. The Mann–Whitney nonparametric rank test and Chi-squared test were used to compare the data of the hypospadias and non-hypospadias groups. Differences were deemed statistically significant for $p < 0.05$. Analyses were performed using GraphPad Prism version 7.00 (GraphPad Software, La Jolla, CA).

3. Results

The overall incidence of hypospadias in severe SGA infants was 6.4% (34/531). The clinical characteristics of the hypospadias and non-hypospadias groups are described in Table 1. The birthweight Z-scores were significantly lower, and the incidence of asymmetrical SGA was significantly higher in the hypospadias group than in the non-hypospadias group ($p = 0.002$ and 0.0001). The incidences of hypospadias at each hospital were 4.9%, 7.7%, and 5.5%, and no significant differences were found among the hospitals (Supplementary Table).

4. Discussion

In the present study, the incidence of hypospadias among severe SGA infants in the Japanese population was 6.4%, which was >10-fold greater than the reported incidence in the general population (0.3%–0.4%).[4]

Several studies have assessed hypospadias in North American populations. Yinon et al. reported an incidence of 19.2% (30/156) in preterm SGA male infants[4] and Gatti et al. reported an incidence of 11% (17/154) in SGA male infants[5] based on their single-center experiences. Conversely, Hussain et al. reported that only 3.83% (43/1122) of SGA infants admitted to two tertiary centers had hypospadias.[7] Because our multicenter study included a larger sample, it may reflect the actual incidence more accurately, specifically for the Asian population. While these previous studies targeted conventional SGA (<10th percentile), our study was novel in revealing the incidence of hypospadias in severe SGA infants. Furthermore, the birthweight Z-score was significantly lower in the hypospadias group than in the non-hypospadias group, suggesting that the severity of FGR correlates with the development of hypospadias.[4] Further, the increased incidence of asymmetrical SGA in the hypospadias group may reflect the deterioration of the fetal environment in this group.

This study has some limitations. First, it used information extracted from discharge summaries; therefore, detailed data on the severity of hypospadias and perinatal characteristics including those pertaining to maternal placental factors were not available. Second, the testosterone levels of the infants were not measured because of the retrospective study design. We plan to perform a prospective study including hormonal analysis.

In conclusion, the incidence of hypospadias in severe SGA infants was 6.4% in the Japanese population. Birthweight Z-scores were significantly lower in the hypospadias group than in the non-hypospadias group, indicating a possible relationship between more severe SGA and a higher risk of hypospadias. Severe SGA might suffer from disturbed hormonal regulation *in utero*, and thus careful postnatal management is warranted.

Declarations of Competing Interest

None.

Acknowledgements

This work was supported by grants for Scientific Research from JSPSK AKENHI (Grant Number: 23791225 (KF), and 19K17360, (MA)), Kawano Masanori Memorial Public Interest Incorporated Foundation for Promotion of Pediatrics (MA), and The Morinaga Hoshikai (KF).

References

1. Cohen E, Wong FY, Horne RS, Yiallourou SR. Intrauterine growth restriction: impact on cardiovascular development and function throughout infancy. *Pediatr Res* 2016;**79**:821—30.
2. Fujita K, Nagasaka M, Iwatani S, Koda T, Kurokawa D, Yamana K, et al. Prevalence of small for gestational age (SGA) and short stature in children born SGA who qualify for growth hormone treatment at 3 years of age: population-based study. *Pediatr Int* 2016;**58**:372—6.
3. Fujioka K, Nishida K, Ashina M, Abe S, Fukushima S, Ikuta T, et al. DNA methylation of the Rtl1 promoter in the placentas with fetal growth restriction. *Pediatr Neonatol* 2019;**60**:512—6.
4. Yinon Y, Kingdom JC, Proctor LK, Kelly EN, Salle JL, Wherrett D, et al. Hypospadias in males with intrauterine growth restriction due to placental insufficiency: the placental role in the embryogenesis of male external genitalia. *Am J Med Genet* 2010;**152A**:75—83.
5. Gatti JM, Kirsch AJ, Troyer WA, Perez-Brayfield MR, Smith EA, Scherz HC. Increased incidence of hypospadias in small-for-gestational age infants in a neonatal intensive-care unit. *BJU Int* 2001;**87**:548—50.
6. Itabashi K, Miura F, Uehara R, Nakamura Y. New Japanese neonatal anthropometric charts for gestational age at birth. *Pediatr Int* 2014;**56**:702—8.
7. Hussain N, Chaghtai A, Herndon CD, Herson VC, Rosenkrantz TS, McKenna PH. Hypospadias and early gestation growth restriction in infants. *Pediatrics* 2002;**109**:473—8.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pedneo.2020.07.011.