Fetal Growth Restriction and a Single Umbilical Artery are Independent Predictors of Hypospadias During Pregnancy

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Abstract

Objective

To investigate the association between hypospadias (HS) and small fetuses using a database on fetal ultrasound and obstetric events.

Methods

A cohort of male singleton infants delivered after 22 weeks of gestation at Keio University Hospital between 2013 and 2019 was retrospectively reviewed. Fetal growth restriction (FGR) was defined by the Delphi criteria. Logistic regression analysis was performed to identify the significant predictors of HS. Placental pathology was reviewed in cases with HS.

Results

2063 male infants delivered during the study period, 27 had HS. The prevalence of a single umbilical artery (SUA), small for gestational age, maternal hypertensive disorders of pregnancy, and a small placenta, were significantly higher in infants with HS. Multiple logistic regression analysis revealed that the presence of FGR and an SUA were independently and significantly associated with HS. The association of FGR with HS was significant regardless of the time of onset. Moreover, the review of placental histological findings suggested that fetal vascular malperfusion might play a role in HS.

Conclusion

Our study suggests that FGR and SUAs are independent prenatal predictors for the development of HS and that fetal vascular malperfusion of the placenta may be involved in the etiology of HS.

Introduction

Hypospadias (HS), a condition where the urethral meatus is present along the ventral aspect of the penis as opposed to the tip of the glans penis, is considered a multifactorial abnormality caused by genetic variation, environmental factors, and fetal endocrine factors.[1–6] It is the second most common congenital malformation in men with an incidence of 0.3–0.8% [6–9] and has increased prevalence in recent years.[9] Many hypotheses have been proposed concerning the etiology of HS. For instance, an incomplete fusion of the urethral folds may occur during the first trimester [10] due to the decreased testosterone levels in the fetus caused by the reduction of placentally-derived human chorionic gonadotropin secondary to placental insufficiency.[11] Large-scale epidemiological studies have suggested that factors associated with preterm birth, low birth weight (LBW), and small for gestational

age (SGA) are the most prominent risk factors among various contributing factors.[8, 12, 13] However, the underlying mechanisms for their association with HS have not been clarified.[1–5, 14]

Many studies have indicated that HS infants are indeed characterized not merely by small size, but also by complications of placental insufficiency.[11–13, 15] Based on the results of a small case series, Hashimoto *et al.* suggested that fetal growth restriction (FGR) due to placental insufficiency rather than the absolute LBW may be a more important factor for HS.[15] Since obstetric ultrasound with Doppler evaluation can differentiate between small fetuses with or without placental insufficiency, SGA infants diagnosed at birth can be classified as having FGR or being constitutionally small and healthy in utero by reviewing their prenatal sonographic data.[16] However, little has is known about the association between HS and small fetuses using prenatal ultrasound data, as well as the pathological implications of FGR, with appropriately selected control groups.

In this study, we aimed to investigate the association between HS and small fetuses by distinguishing pathological FGR and constitutionally small fetuses (CSF) using a database on fetal ultrasound and obstetric events.

Results

Maternal background and obstetrical complications

Of the 2063 singleton male infants, 195 (9.5%) were SGA. A total of 27 infants (1.3%) were diagnosed with HS after birth (Fig. 1). Comparisons of maternal background and obstetrical complications between the HS and non-HS cases are shown in Table 1. In the HS group, 16 (59.3%) cases were conceived spontaneously, whereas 11 cases (40.7%) were conceived by intrauterine insemination or in vitro fertilization. Maternal age, body mass index, mode of conception, and parity were comparable between the HS and non-HS groups. Among the obstetrical complications such as HDP, GDM, placenta previa, and placental abruption, the incidence of HDP alone was higher in the HS group than in the non-HS group (18.5% vs. 4.9%, P = 0.01).

Obstetrical outcomes and prenatal findings

The obstetric outcomes and prenatal findings are summarized in Table 2. The median gestational age at birth was 2.3 weeks shorter in the HS group, compared to the non-HS group (36.4 weeks vs. 38.7 weeks, P < 0.0001). Compared with non-HS, HS infants had significantly higher rates of LBW (40.7%) and preterm delivery (55.5%). A lower PW and a higher incidence of small placenta (weight < 10th percentile) [19] was evident in patients with HS than in those without HS. The incidence of an SUA and FGR were significantly higher in the HS group than in the non-HS group (18.5% vs. 0.6%, P < 0.0001, 48.2% vs. 3.9%, P < 0.0001). In addition, both Eo- and Lo-FGR were more frequently found in the HS group (25.9% vs. 2.2%, P < 0.0001; 22.2% vs 1.7%, P < 0.0001, respectively).

Characteristics of all HS infants and their mothers

Characteristics of the 27 HS infants are summarized in Table 3. The HS infants were born at a median gestational age of 36.4 weeks (range 24–39 weeks). The median birth weight was 2283 g (range 268–3702 g). Thirteen (48.1%) of the neonates were SGA. Preterm delivery at < 35 weeks of gestation occurred in 8 mothers (29.6%); all were iatrogenic, by induction of labor or by cesarean section for the following indications: severe preeclampsia (n = 1), severe FGR associated with non-reassuring fetal status (n = 6), and placental abruption (n = 1).

Of the 27 cases, 5 were prenatally diagnosed as ambiguous genitalia by serial ultrasound observations. Regarding the classification of HS, there were 13 (48.1%) cases with distal HS, 5 (18.5%) cases with middle type HS, and 9 (33.3%) cases with proximal HS. Chordee and foreskin distribution abnormalities were found in 26 cases (96.3%). Bifid scrotum or penoscrotal transposition, and cryptorchidism were found in 5 cases (18.5%) and 4 cases (14.8%), respectively. Thirteen cases were complicated by other abnormalities and/or systemic diseases, such as Prader-Willi syndrome, 46 XY + del(22), 47 XXY, VACTERL complex, horseshoe kidney, mesocardia, tetralogy of Fallot, and cleft lip.

Histopathologic findings of the placenta

Placental pathology in 23 of the 27 HS cases was investigated retrospectively based on the Amsterdam Placental Workshop Group Consensus Statement (Table 4).[20] Of the 23 cases, 21 (91.3%) demonstrated findings of fetal vascular malperfusion, such as perivillous fibrin deposition, intervillous thrombosis, and umbilical cord abnormalities. Maternal vascular malperfusion, a finding related to placentation in early gestation and placental function in later gestation, was also observed in 11 cases (47.8%). Of these, 3 cases were Eo-FGR, 1 had a placental abruption, and 1 case presented with HDP. Umbilical cord abnormalities including an SUA and abnormalities of cord insertion into the placenta, such as a velamentous insertion, were seen in 10 cases (43.5%). As for PW, 9 of the 27 measured cases (33.3%) had small placentas (weight < 10th percentile).[19]

Multivariate logistic regression analysis.

The results of the logistic regression analysis are shown in Table 5. Unadjusted analyses revealed a significant positive association between HS and FGR (OR = 23.0; 95% CI: 10.5–50.6), HDP (OR = 4.4; 95% CI: 1.6–11.9), and an SUA (OR = 38.4; 95% CI: 12.5–118.1). PW was inversely associated with HS; for every 10-gram increase in the PW, there was a 0.92-fold less likelihood of HS presence (95% CI: 0.89–0.94; P < 0.0001). The association between FGR and HS remained significant after adjustments for HDP, an SUA, and PW (OR = 12.9; 95% CI: 3.81–43.8; P < 0.0001). An SUA also remained a significant predictor of HS after adjustments for FGR, HDP, and PW (OR = 39.9; 95% CI: 10.6–150.6; P < 0.0001), suggesting that FGR and an SUA were independently associated with HS. On the other hand, HDP and PW were not significantly associated with HS in the adjusted model (OR = 1.04; 95% CI: 0.36–3.28; P = 0.953; OR = 0.97; 95% CI: 0.93–1.01; P = 0.128, respectively), implying that these two factors did not contribute substantially to the risk of HS. The correlation between two independent variables was estimated to check for multicollinearity, but each phi-coefficient was less than 0.30, which ruled out a high correlation

between any pair. As shown in Table 6, similar results were observed after performing a sub-analysis using data matched for maternal age, mode of conception, and the number of parities in a 1:4 ratio.

Table 7 shows the result of the logistic regression analysis investigating the effect of the onset of FGR on HS. When non-FGR was set as the reference category, both Eo-FGR (crude OR = 22.2, 95% CI: 8.6–57.8, P < 0.0001) and Lo-FGR groups (crude OR = 24.0, 95% CI: 8.7–66.0, P < 0.0001) were significantly associated with HS. The results remained similar after adjustment for the presence of an SUA.

Discussion

Main findings from the objectives

To the best of our knowledge, this was the first cohort study, with appropriate controls, to investigate the association between HS and its prenatal features, especially focusing on fetal growth combined with fetal and maternal blood flow. Each SGA infant was classified as either FGR or CSF, and the FGR phenotype was classified according to its time of onset.[16] By doing so, our study indicated that both Eo- and Lo-FGR, but not CSF, were significantly associated with the presence of HS. Additionally, our multivariate analysis revealed that an SUA was also a significant predictor of HS, independent of FGR. Frequent observations of fetal vascular malperfusion in the histopathologic placental findings of HS infants also suggested that fetal vascular malperfusion might be involved in the development of HS during pregnancy.

Clinical and research implications and comparison to other studies

The prevalence of HS has been reported as 0.3–0.8% worldwide.[6–9] The prevalence in this study, 1.3% (27 cases among 2063 births), was slightly higher than that in previous reports, and this might be attributed to our institution being a tertiary care hospital. A five-fold increased risk of HS was reported in neonates conceived by assisted reproductive technologies (ART);[5] indeed, a recent increase in HS prevalence has been reported, which may be partly due to recent advances in neonatal intensive care and ART which have led to an increase in preterm births, LBW, and SGA infants.[8, 13] In our study, there was no difference in the frequency of HS depending on the mode of conception. A comparison of obstetric complications and outcomes showed that LBW, SGA, preterm births, low PW, an SUA, and maternal HDP could also be contributing factors for the development of HS, most of which were consistent with findings from previous studies.

Although the relationship between LBW and HS has been proposed for a long time, few studies have described the association of HS with prenatal features such as growth, blood flow, and the environment in utero.[1–15] In this study, FGR was thoroughly and accurately assessed by differentiating between pathological FGR and non-pathological CSF based on the Delphi criteria in the ISUOG guidelines, which include not only fetal growth assessment but also uteroplacental blood flow evaluation.[16} Correspondingly, we clarified that FGR and not CSF was an independent predictor of HS development. Our

data also suggested that HDP, also known as a placental-mediated disease, and PW themselves did not elevate the risk of HS independently. Thus, our data provide stronger evidence for the hypothesis that there is an association between FGR and HS, and pathological FGR, not merely a small fetus, is a predictor of the development of HS.

Another interesting finding of our study is that Lo-FGR was as related to HS as Eo-FGR. The differences between the two phenotypes based on the time of FGR onset may be reflected in the pathological features of the placenta.[20] Among multiple pathophysiologic processes of placental injury known to be associated with FGR, including small placenta, maternal vascular malperfusion, fetal vascular malperfusion, and chronic villitis,[20] a report by Spinillo *et al.* indicated that maternal vascular malperfusion lesions were less typical of Lo-FGR than Eo-FGR, whereas the fetal vascular malperfusion pattern was comparable between the two.[21] In our study, fetal vascular malperfusion (91.3%) was more highly prevalent than maternal vascular malperfusion (47.8%) in HS patients. Taken together with our result that Lo-FGR was just as significant a predictor as Eo-FGR for HS, it may be implied that fetal vascular malperfusion contributes more profoundly to the development of HS than maternal vascular malperfusion.

In the present study, we also found that an SUA was another independent predictor of HS development. An SUA was reported to be diagnosed in 0.5% of all pregnancies and was thought to result from primary agenesis or thrombotic atrophy of one umbilical artery.[22] A study showed that an SUA not only affected umbilical cord blood flow but also induced wider pathological changes of fetal vascular malperfusion in the placenta.[23] The strong association between an SUA and HS may also be indicative of the possible association of fetal vascular malperfusion of the placenta with HS development.

The findings of this study will also contribute to the management of HS infants after birth. Severe cases can cause confusion in sex assignment and are often associated with complicated malformations, requiring prompt referrals to specialized hospitals. Considering that more than 80% (22/27) of our HS infants could not be diagnosed in utero, careful ultrasound examination of the external genitalia in cases with the risk factors indicated by this study is expected to improve the diagnosis accuracy.

Strengths of the study

Several points can be emphasized as strengths in this study. First, the independent prenatal predictors of HS were collected from a reliable database and statistically derived from a cohort using a relatively well-defined population undergoing perinatal care at a single institution, adjusted to minimize the effects of confounding factors. As a result, we were able to conclude that FGR and an SUA were independent predictors of HS development. Secondly, we strictly followed the diagnostic criteria of FGR as per the ISUOG guideline to exclude the effect of merely a small fetus and to investigate the impact of FGR onset. Finally, our study included a review of a placental pathological examination performed within the same institution, showing that these prenatal features might be induced by fetal vascular malperfusion of the placenta.

Limitations

There are several limitations to this study. The single institutional, retrospective nature might have led to possible selection and information biases. The placental pathology was not examined in all cases, including the control group. The sample size was also small, and thus, statistical analysis, such as the association of preeclampsia, which affects placental changes more than HDP, was difficult to conduct. A multi-institutional approach with a prospective design is needed to confirm our results in the future.

Conclusions

To the best of our knowledge, this is the first cohort study, with appropriate controls, to investigate the association between HS and small fetuses during pregnancy. Our findings statistically clarified that FGR, not a CSF, was an independent predictor of the development of HS, irrespective of the timing of FGR onset. We also found that an SUA is another independent prenatal predictor of HS. Both could be diagnosed by prenatal ultrasound and might be associated with fetal vascular malperfusion of the placenta. Careful examination of the external genitalia in FGR and SUA cases will enhance appropriate interventions beginning with perinatal counseling from specialists in the DSD team.

Methods

Study population

Our study cohort consisted of 2063 females with singleton pregnancies who gave birth to male infants at Keio University Hospital between 2013 and 2019. Since our institution is a tertiary care hospital, the cohort consisted of females who had undergone prenatal checks at the hospital from the beginning of pregnancy, as well as those who were referred to our hospital during pregnancy due to maternal and fetal complications such as hypertension or a small fetus. The females who delivered non-singleton or female infants and those in whom the placental weight (PW) could not be measured, such as those with placenta accreta, were excluded from the analysis. A flow diagram of patient selection is shown in Fig. 1.

This study was conducted according to the guidelines of the Declaration of Helsinki, and all procedures were approved by the institutional Ethics Board of Keio University, School of Medicine (Accession NO. 2015 – 0103), which exempted obtaining informed consent because our study design was retrospective and all identifying information was removed. Therefore, opt-out informed consent was employed in this study. All information about the patient is processed anonymously in accordance with the De-Identification Standard of the HIPAA Privacy Rule.

Data collection

Antenatal data, such as maternal demographic information (age, race, parity, pre-existing chronic diseases, exposure to alcohol, tobacco, and other teratogens), mode of conception, ultrasound findings, and obstetrical complications, were collected retrospectively. Delivery information, including birth weight, gestational age at delivery, Apgar scores, genital findings, neonatal complications, and placental histopathology, was reviewed. Diagnoses of hypertensive disorders of pregnancy (HDP), gestational

diabetes mellitus (GDM), and placenta previa were based on the clinical criteria given by the Japan Society of Obstetrics and Gynecology (JSOG).[17]

Diagnosis of HS

A diagnosis of HS was based on an initial physical examination; confirmation of the diagnosis and classification was done by a pediatric urologist.[18] The classification of HS was based on the anatomical position of the urethral meatus: glanular, coronal, and subcoronal were defined as the distal type. Distal and proximal penile were defined as the middle type. Penoscrotal, scrotal, and perineal were defined as the proximal type. In addition, those with chordee and foreskin distribution abnormalities, bifid scrotum or penoscrotal transposition, and cryptorchidism were also investigated.[18] Infants with HS were managed by a multidisciplinary team belonging to The Center for Differences of Sex Development (DSD), which consisted of geneticists, endocrinologists, neonatologists, and pediatric urologists.

Diagnosis of FGR

Fetal ultrasound screenings were routinely performed at 20, 28, and 34 weeks of gestation. When abnormal findings such as an estimated fetal body weight (EFBW) or abdominal circumference (AC) less than − 1.5 standard deviation (SD) or abnormal blood flow were observed, fetal ultrasound examinations were performed by several maternal-fetal medicine specialists at weekly to biweekly intervals. The fetuses were categorized into three groups based on the prenatal ultrasound findings: appropriate for date (AFD), CSF, and FGR. FGR and its phenotypes based on onset (early-onset [Eo] and late-onset [Lo]) were defined by the Delphi criteria in the International Society of Ultrasound in Obstetrics & Gynecology (ISUOG) guidelines.[16] A CSF was defined as a fetus with EFBW less than − 1.5 SD, but not meeting the definition of FGR in the Delphi criteria. The remaining cases were categorized as AFD.

Statistical analysis

Characteristics of infants with and without HS were compared by a t-test or Wilcoxon test for continuous variables depending on their distribution and a chi-squared test or Fisher's exact test for categorical variables. Data were presented as the median (range) or the number of cases (percentage). Multiple logistic regression analysis was performed, and odds ratios (ORs) and their 95% confidence intervals (CIs) were evaluated for the relative contributions of various maternal and perinatal factors associated with HS.

Additionally, the HS and non-HS groups were matched for maternal age, mode of conception, and the number of parities in a 1:4 ratio using propensity scores, and the same analyses were performed to eliminate their possible confounding effects.

To investigate the effect of the FGR onset on HS, a logistic regression analysis was also performed with HS being the dependent variable and the FGR phenotype (Eo, Lo, or none) as the independent variable.

In all tests, $P < 0.05$ was considered significant, and statistical analyses were performed using SAS 9.4 (SAS Institute Inc, Cary, NC).

Declarations

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Tables

Due to technical limitations, table 1,2,3,4,5,6,7 is only available as a download in the Supplemental Files section.

Figures

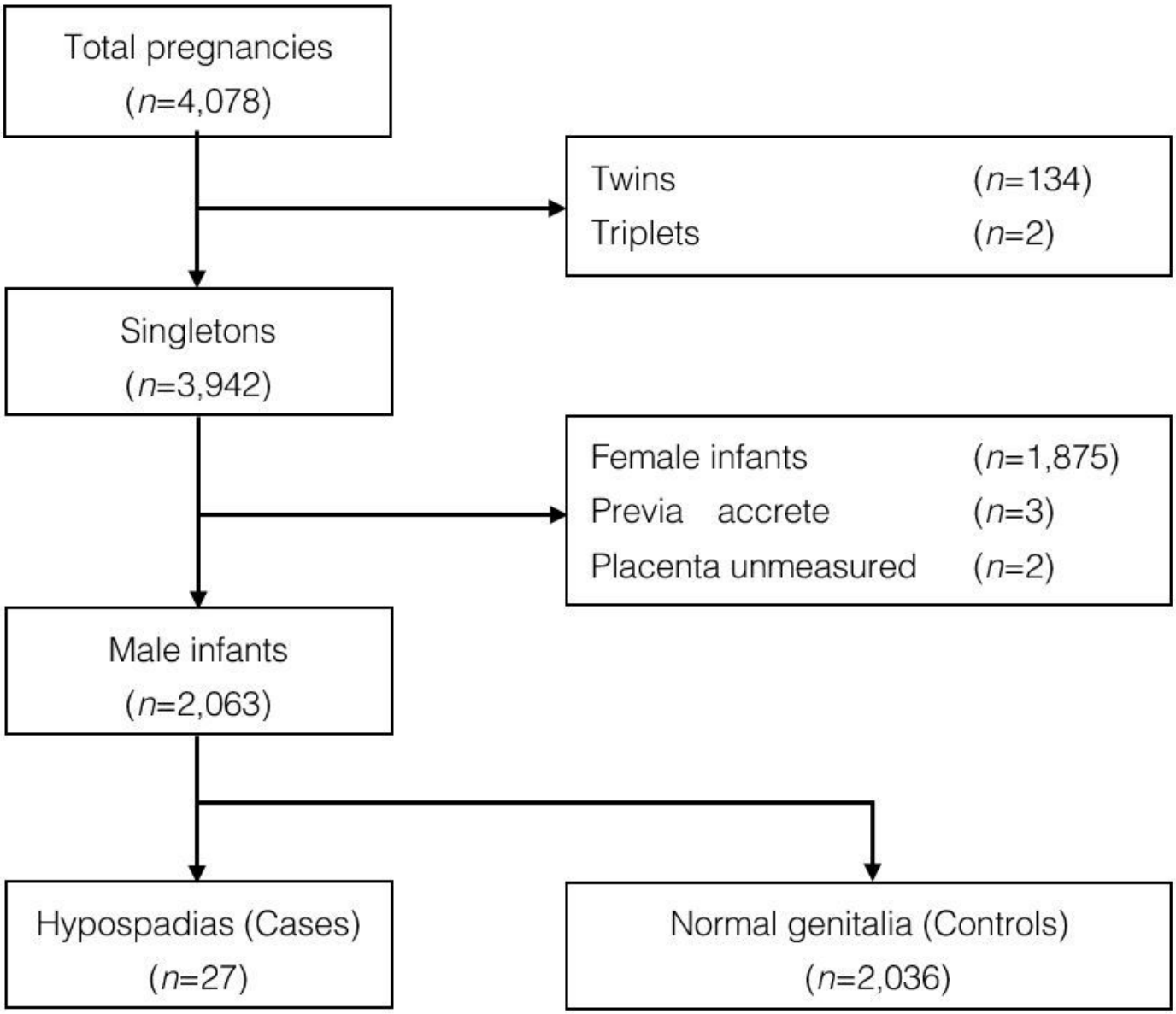

Figure 1

Flow diagram illustrating the selection of the cases and controls

Supplementary Files

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