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Hypospadias in Males With Intrauterine Growth Restriction Due To Placental Insufficiency: The Placental Role in the Embryogenesis of Male External Genitalia

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Our aim was to define the association between early onset intrauterine growth restriction (IUGR) due to placental insufficiency and hypospadias in males. We prospectively studied a cohort of small-for-gestational age (SGA) male infants with hypospadias managed by a multidisciplinary team over a 5-year period. Thirty SGA male infants were diagnosed with hypospadias/abnormal genitalia after birth, and four of them were diagnosed antenatally. Five cases occurred in the smaller pair of discordant IUGR twins, where the larger co-twin had normal male genitalia. Serial ultrasounds demonstrated features of early-onset IUGR in all cases at a median gestational age of 21 weeks (range 14–31weeks). Twenty-one (70%) pregnancies were subsequently complicated by absent/reversed end-diastolic flow in the umbilical arteries indicating severe IUGR, and 17 (57%) women developed severe pre-eclampsia. There were 27 (90%) live births at a median gestational age of 31 weeks (range 27–37); 23 (77%) of the neonates had birth weights <3rd centile. All newborns had normal male karyotypes. In 62% (18/29) the hypospadias was severe. A correlation was found between the severity of the IUGR and the severity of hypospadias as significantly more infants with severe hypospadias were less than the 3rd centile compared to the mild–moderate hypospadias group: 94% (17/18) versus 55% (6/11), respectively ($P = 0.02$). In conclusion, SGA male newborns with hypospadias exhibit a high rate of early -onset severe IUGR due to placental insufficiency. Early placental development likely influences male external genitalia formation. Careful sonographic evaluation of the genitalia is advised when early-onset placentally mediated IUGR is found.

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INTRODUCTION

Hypospadias is a common malformation in males with an incidence of 0.3–0.4% [Gallentine et al., 2001; Brouwers et al., 2007]. It results from an incomplete fusion of the urethral folds between the 7th and

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14th week of gestation. Most cases are isolated and are presumed to be multifactorial traits [Calzolari et al., 1986; Baskin et al., 2001; Manson and Carr, 2003]. Previous epidemiologic studies found a close relationship between low birth weight and hypospadias [Calzolari et al., 1986; Akre et al., 1999; Weidner et al., 1999], yet the underlying mechanism of this association is unclear. Hussain et al. [2002] demonstrated that hypospadias was significantly more common in infants who were small-for-gestational age (SGA), suggesting that intra-uterine growth restriction (IUGR) rather than the absolute birth weight is a more important risk factor for hypospadias. Some evidence suggests that placental insufficiency may be the underlying factor, for example, hypospadias correlates with low weight of the placenta [Stoll et al., 1990], and has been observed in the smaller twin in a mono-chorionic twin pregnancy complicated by discordant growth [Fredell et al., 1998]. These data suggest that the association of low birth weight with hypospadias may be related to placental dysfunction. Since the most severe forms of IUGR have their origins in the first trimester [Smith et al., 1998], we tested the hypothesis that severe hypospadias is associated with early-onset severe placental insufficiency.

METHODS

Institutional research ethics board approval was obtained to audit clinical outcomes and relate these to screening tests of placental function.

Between 2004 and 2008, 1,659 preterm male infants were born at Mount Sinai Hospital, 156 of them were SGA and consisted of our study cohort. Out of this cohort, all male infants who were diagnosed with hypospadias/abnormal genitalia after birth were identified. They all underwent a multidisciplinary assessment and care by a team consisting of geneticists, endocrinologists, neonatologists, and pediatric urologists. All cases of IUGR and hypospadias were followed antenatally in our multidisciplinary placenta clinic, six of them were referred prior to delivery. In this clinic, we screen and follow pregnancies that are considered to be high risk because of medical or obstetric complications for placental dysfunction. This includes first trimester screening at 10–13 weeks of gestation, maternal serum screening at 16–18 weeks, and placental ultrasound examination with uterine artery Doppler evaluation at 19–23 weeks. Pregnancy-associated plasma protein-A (PAPP-A) levels <0.3 multiples of the median (MoM) and alpha-fetoprotein (AFP) >2.0 MoM were considered abnormal as previously reported [Alkazaleh et al., 2006]. Once a diagnosis of IUGR due to placental insufficiency was made, ultrasound examinations were performed every 2 weeks from 24 weeks of gestation, and increased up to 3 per week depending on the gestational age, severity of IUGR (determined by fetal Doppler studies, biophysical profile scores, and amniotic fluid volume), and the presence/severity of pre-eclampsia. Sonographic findings indicating placental insufficiency were recorded including absent or reversed end-diastolic flow velocities (AREDV) in the umbilical arteries; elevated head/abdomen circumference ratio above the 95th centile for gestational age indicating asymmetrical IUGR [Snijders and Nicolaides, 1994]; reduced amniotic fluid volume (amniotic fluid index <5 cm); abnormal placental shape (small/thick) and texture; bilateral abnormal uterine artery Doppler, both as we have previously defined [Viero et al., 2004; Toal et al., 2008]. After delivery, all placentas were examined pathologically, including assignment of chorionicity in the twin pregnancies.

Antenatal data were collected prospectively and included maternal demographic information (age, race, parity, exposure to alcohol, tobacco, substance abuse and other teratogens, and pre-existing chronic diseases), mode of conception, first and second trimester screening as well as fetal karyotype determined by amniocentesis, serial ultrasound findings, and obstetrical complications. Hypertensive disorders were defined according to the American College of Obstetricians and Gynecologist criteria [ACOG, 2002]. Delivery information was reviewed and included birth weight, gestational age at delivery, Apgar scores, head circumference and length at birth, genital findings, neonatal complications, and placental histopathology.

A diagnosis of hypospadias was based on an initial physical examination; confirmation of diagnosis and severity grading were done by a pediatric urologist. The severity of hypospadias was based on the anatomical position of the urethral meatus: glandular, coronal, and penile were defined as mild–moderate and penoscrotal, scrotal and perineal were defined as severe [Boisen et al., 2005]. The evaluation of these infants included abdominal ultrasonography to define the internal genitalia, chromosome analysis, and extensive endocrinology work-up in cases of ambiguous genitalia, which included blood testosterone level, 17-OH progesterone, FSH, LH, thyroid function tests, dehydrotestosterone, cortisol, androstenedione, DHEAS, and sex hormone binding globulin levels. Some of the cases had DNA analysis of the androgen receptor and 7-dehydrocholesterol. All the patients had serial follow-up in the neonatal neurodevelopmental and pediatric urology clinics.

Descriptive statistics are presented as mean $\pm$ 1 SD or median (range). Fisher's exact test was used for statistical comparison of categorical variables. A P-value <0.05 was considered significant.

RESULTS

Thirty SGA male infants were diagnosed with hypospadias/abnormal genitalia after birth during the 5-year period. Maternal demographic data and pregnancy characteristics of these cases are shown in Table I. Twenty-three (77%) of these pregnancies were conceived spontaneously, the remainder were conceived following ovulation induction via clomiphene citrate (1), gonadotropins (3), or in vitro fertilization (3). Five were the smaller IUGR co-twin in discordant twins (three were monochorionic-diamniotic, two dichorionic-diamniotic).

Antenatal evidence of placental dysfunction was common; low PAPP-A levels <0.3 MoM were found in 45% and elevated AFP >2.0 MoM in 71%. Both markers were abnormal in 36% of cases. Abnormal uterine artery Doppler (mean pulsatility index >1.45 and bilateral early diastolic notches) was found in 50% (11/22) of pregnancies that had performed this test.

Serial ultrasound examinations established the diagnosis of early onset of growth restriction by the defined criteria at a median gestational age of 21 weeks. Sonographic findings indicating placental dysfunction consisted of absent/reversed end-diastolic flow in the umbilical arteries in 21 (70%) fetuses, oligohydramnios in 15 (50%) pregnancies, asymmetrical pattern of growth restriction as

TABLE I. Baseline and Pregnancy Characteristics

Characteristic	No. of women (n = 30) n (%)
Maternal age (mean ± SD)	33 ± 6
Ethnicity	
Caucasian	19 (63)
Asian	8 (27)
African	3 (10)
Parity (mean ± SD)	0.6 ± 0.9
Mode of conception	
Spontaneous	23 (77)
Clomiphene/ovulation induction	4 (13)
IVF	3 (10)
Type of pregnancy	
Singleton	25 (83)
Twins[a]	5 (17)
Prenatal screening	
PAPP-A (MoM, mean ± SD)	0.5 ± 0.4
Low PAPP-A (<0.3 MoM)	5/11 (45)
AFP (MoM, mean ± SD)	3 ± 1.9
Increased AFP (>2 MoM)	12/17 (71)
hCG (MoM, mean ± SD)	2.5 ± 1.5
Increased hCG (>2.5 MoM)	5/13(38)
US findings	
Gestational age at onset of growth restriction (median, range)	21 (14 – 31)
Head/abdomen ratio prior to delivery (median, range)	1.2 (1.1 – 1.44)
Oligohydramnios	15 (50)
AREDV in the umbilical artery	21 (70)
Abnormal placental morphology	15 (50)

[a]Three monochorionic-diamniotic and two dichorionic-diamniotic twins.

TABLE II. Obstetrical and Neonatal Outcome

Outcomes	No. of pregnancies (%) (n = 30)
Obstetric outcome	
Pre-eclampsia	17 (57)
Placental abruption	2 (7)
GA at delivery (median, range)[a]	31 (27 – 37)
Pre-term delivery ≤34 weeks	28/30 (93)
Pre-term delivery ≤28 weeks	6/30 (20)
Fetal/neonatal outcome	
Birth weight (grams, mean ± SD)	970 ± 446
Fetal death/stillbirth[b]	3 (10)
Neonatal death[c]	2 (7)
Perinatal survival	24(80)

[a]Only cases, which resulted in live birth, were included.
[b]At 18, 27, and 28 weeks of gestation.
[c]At 5 min and 24 hr.

evident by head/abdomen circumference ratio above the 95th centile in 15 fetuses (50%), and abnormal placental shape or texture in 15 (50%) cases.

The obstetrical and neonatal outcomes are summarized in Table II. Of the 30 pregnancies, 27 (90%) were live born at a median gestational age of 31 weeks (range 27–37 weeks). Preterm delivery at <34 weeks of gestation occurred in 28 women (93%); all were iatrogenic by induction of labor or by cesarean section for the following reasons: severe pre-eclampsia (14), severe IUGR (accompanied by pre-eclampsia in two of them), and non-reassuring fetal condition by ultrasound and/or non-stress test (9), placental abruption (2), intra-uterine fetal death (IUFD) (2), and pre-eclampsia with IUFD (1).

Mean birth weight was 970 g (range 460–2,195); 23 (77%) of the neonates were below the 3rd centile for sex and gestational age according to birth weight data for Canadian infants [Kramer et al., 2001], and the rest were below the 10th centile.

The placental histopathologic findings are summarized in Table III. Twelve (45%) had a small placenta (weight <10th centile). Findings consistent with ischemic–thrombotic placental pathology were found in 22 (81%) cases including accelerated villous maturation, perivillous fibrin deposition, decidual vasculopathy, infarction, and fetal thrombotic vasculopathy.

Postnatal genitalia findings are summarized as individual cases in Table IV.

In four cases the genital abnormality was diagnosed antenatally (Fig. 1). In two cases a diagnosis of a female fetus was made and only after a male karyotype was found by amniocentesis, the diagnosis of abnormal genitalia was established. Chromosome analysis was performed postnatally on peripheral blood lymphocytes and all showed a normal male karyotype (46, XY). In 11, the karyotype was determined prenatally in amniocytes and confirmed after birth.

Severe proximal hypospadias occurred in 62% (18/29) of the newborns and mild–moderate hypospadias was seen in 38% (11/29). Of the 18 infants with severe hypospadias, 17 (94%) were below the 3rd centile compared to 6 (55%) infants with mild–moderate hypospadias ($P = 0.02$). The incidence of AREDV in the umbilical artery was similar in both groups: 67% (12/18) in the severe hypospadias group versus 82% (9/11) in the mild hypospadias group ($P = 0.7$). Associated genital abnormalities included micro-

TABLE III. Histopathologic Findings of the Placenta

Histopathologic findings	No. of cases (n = 27)[a]
Normal	2
Placental weight <10th centile	12
Cord <2 cm from nearest edge	7
Decidual vasculopathy	4
Accelerated villous maturation	5
Lesions of the parenchyma	
Infarction	9
Fetal thrombotic vasculopathy	6
Increased perivillous fibrin deposition	6

[a]Placental pathology was not available for three cases.

TABLE IV. Genital Findings

Case	Pregnancy complications	GA at delivery	Birth weight (centile)	Placental pathology	Genital findings	Long-term outcome[a]
1	Severe pre-eclampsia, REDV, and oligohydramnios	30 + 3	880 (<3)	250 g (<10%) and villi with irregular maturation infarction	Severe hypospadias, small phallus, and descended testes	Normal at 4 months
2	Severe pre-eclampsia and REDV in UA	32 + 6	1,200 (<3)	Placental weight <10th centile and increased perivillous fibrin deposition	Proximal midscrotal hypospadias, severe chordee, penoscrotal transposition, descended testicles, and bifid scrotum	Normal at 11 months
3	Severe pre-eclampsia	33	1,450 (5)	213 g (<10%), excessive intervillous fibrin deposits, and fetal thrombotic vasculopathy	Penoscrotal hypospadias, penoscrotal transposition, chordee of 40°, and undescended testes	Normal at 24 months
4	Severe pre-eclampsia	32	1,300 (<3)	Vellamentous cord insertion, 2-vessel cord, and accelerated villous maturation	Severe penoscrotal hypospadias, bifid scrotum, small phallus (17 mm), severe chordee, and descended testes	Mild delay in gross motor development at 5 months
5	AEDV in UA and oligohydramnios	28	570 (<3)	Vellamentuous insertion, accelerated villous maturation, and distal villous hypoplasia	Severe perineal hypospadias and undescended testes	Neonatal death at 5 min
6	AEDV in UA and oligohydramnios	33 + 5	1,160 (<3)	Laterally inserted cord, circummarginate insertion of the membranes, and fetal thrombotic vasculopathy	Perineal hypospadias, bifid scrotum, short phallus (1.5 cm), and undescended testes	Death at 9.5 months respiratory failure. Bronco-pulmonary dysplasia and hydrocephalus
7	Oligohydramnios	31 + 6	940 (<3)	Placental weight <10th centile, marginal cord insertion, and increased perivillous fibrin deposition	Mild hypospadias with double opening at tip of penis and descended testes	Not available
8	AEDV	26 + 6	460 (<3)	Small placenta <10th centile, chronic deciduitis, and areas of infarction	Ambiguous genitalia: broad short phallus, an urethral opening along the ventral aspect, bifid scrotum, and undescended testes	Stillbirth
9	Oligohydramnios	36	1,980 (<3)	Subchorionic fibrin deposition and intervillous thrombus	Severe hypospadias, bifid scrotum, and undescended testes	Normal at 12 months
10	Severe pre-eclampsia, oligohydramnios, PPROM, and AEDV in UA	31 + 3	930 (<3)	Marginal cord insertion, circummarginate membranes, and decidual vasculopathy	Mild hypospadias and undescended testis	Normal at 25 months

11	Severe pre-eclampsia and REDV in UA	32 + 5	780 (<3)	No significant pathology	Bifid scrotum, posterior scrotal fusion and severe perineal hypospadias, penoscrotal transposition, severe chordee, and descended testes	Normal at 36 months
12	Placental abruption and oligohydramnios	32	1,050 (<3)	One focus of recent intervillous thrombosis	Severe perineal/scrotal hypospadias, very small penis with severe chordee, penoscrotal transposition, bilateral descended testis, and bilateral large inguinal hernias	Not available
13	REDV in UA	28 + 3	850 (<3)	Placental weight <10th centile, area of villous infarction, and slightly increased perivillous fibrin deposition	Bifid scrotum, perineal hypospadias, penoscrotal transposition, severe chordee, phallus of 3 cm (5 months), descended testes, and bilateral inguinal hernia	Normal at 36 months
14	IUFD at 18 weeks	18	23.3(correlates with 14 weeks)	Retroplacental hemorrhage with associated villous infarction	Hypospadias	Stillbirth (Ebstein's anomaly and coarctation, malrotation of the bowel)
15	REDV in UA and oligohydramnios (DC/DA twins)	30	540 (<3)	No significant pathology	Glanular hypospadias	Not available
16	Severe pre-eclampsia, REDV in UA, and oligohydramnios (MC/DA twins)	28 + 3	600 (<3)	Unequal sharing of parenchyma, twin A-30%, B-70%, and small area of infarction	Subcoronal (distal shaft) hypospadias with significant chordee, rt. Inguinal hernia and descended testes	Global delay at 48 months and PVL
17	Oligohydramnios and gestational diabetes (DC/DA twins)	33 + 3	1,130 (<3)	Circummarginate membranes and amnion nodosum of the amniotic epithelium	Midshaft hypospadias and descended testes	Mild delay in fine motor skills at 24 months
18	Severe pre-eclampsia, oligohydramnios, and REDV in UA (MC/DA twins)	30 + 6	760 (<3)	Weight <10th centile	Distal hypospadias and descended testes	Not available
19	Twin to twin transfusion syndrome, severe pre-eclampsia, AEDV, and oligohydramnios (MC/DA twins)	31	780 (<3)	Monochrionic diamniotic twin placenta with area of infarction	Penoscrotal hypospadias, mild chordee (25–30°), descended testes, and left inguinal hernia	Delayed in motor skills and language skills at 18 months and congenital hypothyroidism
20	Chronic hypertension, REDV in UA, and gestational diabetes	33	1,430 (5)	Small chorioangioma and focal thrombosis	Mild hypospadias and descended testes	

(*Continued*)

TABLE IV. (*Continued*)

Case	Pregnancy complications	GA at delivery	Birth weight (centile)	Placental pathology	Genital findings	Long-term outcome[a]
21	Severe pre-eclampsia and AEDV in UA	30	1,110 (10)	Weight <10th centile, foci of avascular villi, multiple infarcts, and hemorrhagic endovasculitis	Mild distal hypospadias and undescended testis	Normal at 6 months
22	Severe pre-eclampsia and AEDV in UA	29	920 (5–10)	Focal infarction	Mild hypospadias with chordee and descended testes	Normal at 7 months
23	Severe pre-eclampsia, oligohydramnios, and AEDV	28	558 (<3)	Weight <10th centile and severe decidual vasculopathy	Complete penoscrotal hypospadias and no fusion of scrotal folds and right undescended testes	Stillbirth
24	REDV in UA and oligohydramnios	29	580 (<3)	Weight <10th centile, massive perivillous fibrin deposition, and early decidual vasculopathy	Severe proximal (?) hypospadias and undescended testes	Massive intra-cranial hemorrhage and neonatal death after 24 hr
25	Severe pre-eclampsia	37	2,195 (<3)	Not available	Scrotal hypospadias, chordee-marked ventral curvature, and low inguinal testes	Normal at 12 months
26	Severe pre-eclampsia and AEDV in UA	29 + 3	760 (<3)	Not available	Penoscrotal hypospadias, bifid scrotum, ventral chordee, small penis (2 cm at 2 months), and both testes in the scrotum at normal size	Normal at 5 months
27	Placental abruption and AEDV in UA	34	1,480 (<3)	Not available	Severe perineal hypospadias, minor penoscrotal transposition and severe chordee, micropenis (2–2.5 cm at 3 months), bifid scrotum, and bilateral undescended testes	Normal at 48 months
28	Chronic hypertension, superimposed pre-eclampsia, REDV in UA, and oligohydramnios	27	670 (<3)	Placental weight 10–25 centile, multifocal infarction, and no decidual vasculopathy	Ambiguous genitalia: small phallus (1 cm), severe perineal hypospadias, and undescended testes	Normal at 3 months
29	Severe pre-eclampsia and REDV in UA	29	860 (5)	Placental weight 10–25 centile, focal chronic villitis, and chronic intervillositis	Glanular hypospadias, mild chordee, and descended testes	Small left sided IVH and neurologically normal at 2 months
30	Severe pre-eclampsia and AEDV	30	1,100 (10)	Two areas of infarction and no fetal or decidual vasculopathy	Mild hypospadias	Neurologically normal at 2 months

[a]Based on assessment done at our neurodevelopment follow-up clinic.

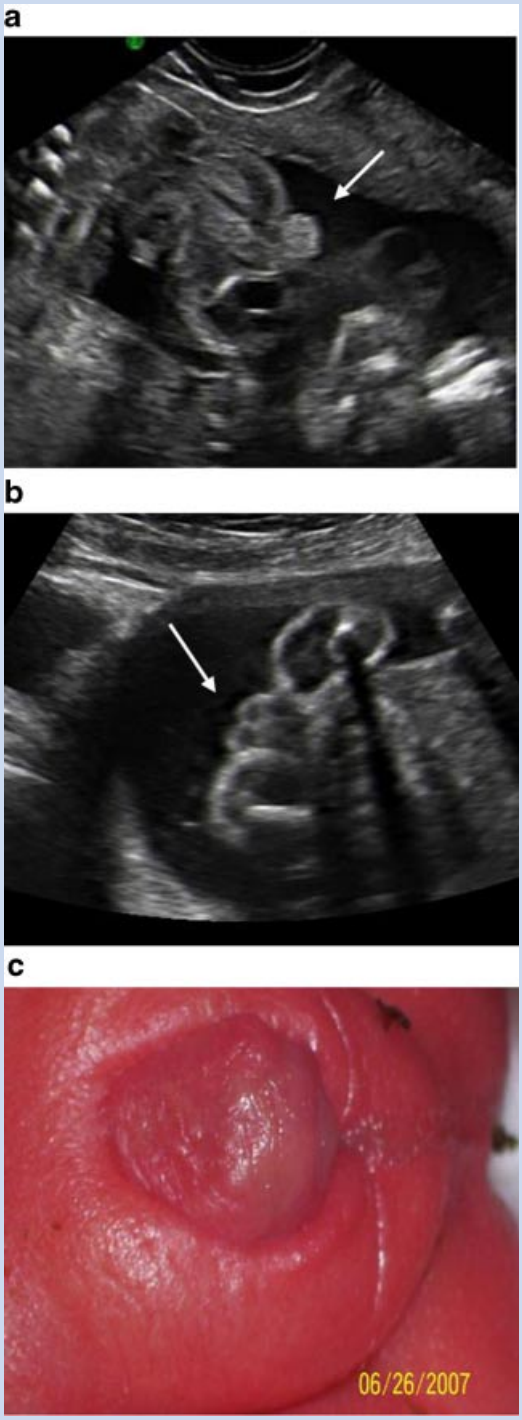

FIG. 1. Ultrasound image at 28 weeks of gestation of an IUGR fetus with AEDV demonstrating micropenis, hypospadias (a), and bifid scrotum (b); postnatal examination confirmed the antenatal diagnosis (c). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

penis (8), bifid scrotum (9), penoscrotal transposition (6), severe chordee (11), and cryptorchidism (14).

In 11 infants the hypospadias was so severe that the gender could not be determined. All were investigated by our Multidisciplinary Urogenital Team, and DNA analysis of the androgen receptor gene (regarding the possibility of partial androgen insensitivity) was performed. At the completion of these investigations a male gender was assigned in all cases, and none of them had evidence of incomplete androgen insensitivity.

Three of the cases had non-genital anomalies: the first was a patient with hydrocephalus, minor facial anomalies, and clinodactyly of the 5th fingers, feeding difficulties and developmental delay who died at the age of 9 months. The second was a neonate who was born at 28 weeks gestation, weighed 570 g and had facial anomalies, and died 5 min after birth. The third was a patient with Ebstein anomaly and coarctation of the aorta who died in utero at 18 weeks of gestation. In all three extensive investigations were done but no specific diagnosis could be made. The possibility that the hyposdpadias was secondary to a syndrome in these three cases could not be excluded.

Our cohort included five sets of discordant twins, in which the IUGR twin had hypospadias and the healthy co-twin had normal male genitalia (Table III, cases 15–19). Three of these twins were monochorionic-diamniotic and all were complicated with severe pre-eclampsia. Interestingly, the severity of the hypospadias appeared to be milder in the IUGR twins: four of the five IUGR twins had mild hypospadias, whereas only 7 of the 25 IUGR singletons had mild hypospadias.

DISCUSSION

This study describes the association between hypospadias and early onset IUGR in 30 fetuses over a 5-year-time period in a single center. This cohort of patients is unique as all had antenatal follow-up showing early onset of IUGR with sonographic findings indicating severe placental dysfunction in most of these pregnancies. Moreover, our cohort represents the more extreme cases of IUGR as most of the fetuses (77%) were below the 3rd centile. The nature and severity of the underlying placental disease was substantiated by postnatal histopathologic examination of the placentas by a perinatal pathologist. Nearly half had chorion regression (small placentas with eccentric cords) [Proctor et al., 2009] and most had some evidence of ischemic–thrombotic injury to the gas-exchanging placental villi. Of these infants, 62% had severe hypospadias and 11 had ambiguous genitalia. All these infants had normal male karyotypes, and none had evidence of an underlying genetic cause for hypospadias.

The association between low birth weight and hypospadias has been described before [Calzolari et al., 1986; Akre et al., 1999; Weidner et al., 1999], and two previous studies have reported on the association between IUGR and hypospadias [Hussain et al., 2002; Fujimoto et al., 2008]. However, in these studies a diagnosis of IUGR was inferred due to a postnatal diagnosis of SGA infant at birth. Our study progresses the findings of these earlier reports by establishing a clear link both to severely impaired fetal growth and to an underlying diagnosis of severe placental dysfunction. Fetal growth restriction can result from a variety of intrinsic or extrinsic insults, yet all our cases had sonographic findings indicating placental dysfunction as the cause of growth restriction.

Hussain et al. showed a 3.83% incidence of hypospadias among SGA male infants compared to 1.27% among AGA infants [Hussain et al., 2002]. Recently, Fujimoto et al. reported on a series of 104

extremely low birth weight (<1,500 g) male infants, and 16 (15.3%) of them having hypospadias [Fujimoto et al., 2008]. Our study design is not able to determine the true incidence of hypospadias among IUGR fetuses due to the inherent selection bias in our tertiary clinical practice. However, since during the study period, 156 IUGR male infants less than 37 weeks of gestation were delivered at our hospital, the rough estimate for the incidence of hypospadias in IUGR fetuses is 19% (30/156) compared to a background incidence of 0.3% [Gallentine et al., 2001; Brouwers et al., 2007]. Therefore, it is likely that severe placental dysfunction is causally associated with disruption of normal male external genital development. During the study period no case of term IUGR with hypospadias was identified, indicating that this association is more common among the severe cases of growth restriction, requiring preterm delivery.

In the Fujimoto et al. [2008] study, 16 male infants with hypospadias and birth weight below 1,500 g were compared to 62 controls whose birth weight was less than 1,500 g but did not have hypospadias. The patients with hypospadias demonstrated a significantly higher placenta-to-fetal ratio associated with placental infarction compared to controls [Fujimoto et al., 2008]. Moreover, placental histopathologic findings in the hypospadias cases revealed severe degenerative changes, infarction, and calcification, similar to the findings in our study. However, the prevalence of pregnancy-induced hypertension in their study was significantly lower in the hypospadias group than in controls (14.2% vs. 26%, respectively), whereas 57% of the pregnancies in our series were complicated by severe pre-eclampsia, as expected in the presence of severe placental dysfunction. Similarly, in a large population-based case-control study hypospadias was shown to be associated with severe pre-eclampsia with an odds ratio of 2.1 [Akre et al., 1999]. The association between pre-eclampsia and hypospadias reflects abnormal placental function.

The most severe forms of placenta-mediated IUGR originate in the early part of the first trimester, around weeks 7–8, when the male external genitalia are forming. This has been supported by studies showing that low maternal circulating levels of PAPP-A at 8–14 weeks of gestation are significantly predictive of IUGR, and more so when measured prior to 13 weeks [Smith et al., 2002, 2006; Dugoff et al., 2004]. However, the underlying mechanism of the association between hypospadias and placental insufficiency is unclear. The development of the human male urethra, which occurs between 7 and 14 weeks of gestation, is the result of androgen action on the external genitalia. Lack of testosterone, 5-alpha reductase deficiency, complete or incomplete androgen receptor insensitivity, and steroidogenic enzyme deficiencies are known to result in ambiguous genitalia. The earlier the disruption, the more severe the hypospadias [Main et al., 2006]. Since fetal testosterone secretion is under the influence of placental hCG during the first 14 weeks of gestation [Brouwers et al., 2007], placental dysfunction leading to insufficient hCG supply, may theoretically result in hypospadias [Fredell et al., 2002]. However, placental dysfunction is known to be associated with high maternal serum hCG. Thus, it seems that there is another placental enzyme involved in normal placental function, which also produces androgens, necessary for the normal development of male external genitalia. This mechanism may be similar to the placental esterase deficiency that causes masculinization of the female external genitalia. An alternative explanation is that one or more of the growing array of genes controlling early fate decisions in placentation [Rawn and Cross, 2008] either directly or indirectly affects the formation of the male external genitalia.

A large proportion (62%) of the infants in our study had severe hypospadias compared to only 6% in the Fredell et al. cohort of 2,500 boys with hypospadias [Fredell et al., 2002] and 23% in Hussain's study, which included SGA infants with hypospadias [Hussain et al., 2002]. This may reflect the early onset as well as the severity of the placental dysfunction in our cohort of patients, in view of the fact that our center is a tertiary facility involved in the more severe cases of IUGR. Unlike previous studies, which did not show a correlation between the severity of hypospadias and the severity of growth restriction [Hussain et al., 2002; Fujimoto et al., 2008], our data do support such relationship as significantly more infants with severe hypospadias were below the 3rd centile compared to the ones with mild–moderate hypospadias.

Another indication for an association between IUGR and hypospadias comes from monozygotic twins. A study of 18 twin pairs in which one twin had hypospadias and one did not, found that in 16 pairs, the healthy co-twin weighed at birth 500 g more than the twin with hypospadias [Fredell et al., 1998]. In our study five of the cases were twins (three monochrionic and two dichorionic with unknown zygosity), in which the IUGR twin was the one with hypospadias. Since monozygotic twins share the same intrauterine environment and genotype as well as the same placenta, the discordance for the hypospadias is difficult to explain. Conditions, for which monozygotic twins are discordant, are usually multifactorial or the result of a new dominant mutation that affected one of the twins or discordance for a chromosome abnormality, which was ruled out in our cases. However, these data support the hypothesis that fetal growth and risk of hypospadias are strongly associated and may indicate an epigenetic phenomena as the cause of the association between IUGR and hypospadias.

Since there is substantial evidence for increased risk of hypospadias/ambiguous genitalia in IUGR male fetuses, in patients with early placental dysfunction an US study directed to the fetal genitalia should be considered, and if amniocentesis is done correlation between the fetal phenotypic sex and chromosome sex should be determined. A discrepancy between the two should be discussed among the specialists involved in the investigation and treatment of babies with ambiguous genitalia and presented to the women/couples in view of the above findings. This will allow the women/parents to make an informed decision regarding the pregnancy and to prepare them for the delivery and the postnatal investigation and treatment required. An attempt should be made to obtain a piece of cord and cord blood to allow in depth postnatal investigation since obtaining sufficient amount of blood for DNA extraction, in these cases, may be difficult.

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