Sex Dimorphism of Birth Weight and Length: Evidence Based on Disorders of Sex Development

Debora Stabile Romero Amais
State University of Campinas: Universidade Estadual de Campinas
Tainara Emilia Rodrigues da Silva
State University of Campinas: Universidade Estadual de Campinas
Beatriz Amstalden Barros
State University of Campinas: Universidade Estadual de Campinas
Juliana Gabriel Ribeiro de Andrade
State University of Campinas: Universidade Estadual de Campinas
Sofia Helena Valente de Lemos-Marini
State University of Campinas: Universidade Estadual de Campinas
Maricilda Palandi de Mello
State University of Campinas: Universidade Estadual de Campinas
Antonia Paula Marques-de-Faria
State University of Campinas: Universidade Estadual de Campinas
Tais Nitsch Mazzola
State University of Campinas: Universidade Estadual de Campinas
Mara Sanches Guaragna
State University of Campinas: Universidade Estadual de Campinas
Helena Fabbri-Scallet
State University of Campinas: Universidade Estadual de Campinas
Tarsis Antonio Paiva Vieira
State University of Campinas: Universidade Estadual de Campinas
Nilma Lucia Viguetti-Campos
State University of Campinas: Universidade Estadual de Campinas
Andre Moreno Morcillo
State University of Campinas: Universidade Estadual de Campinas
Olaf Hiort
University of Lubeck: Universitat zu Lubeck
Andrea Trevas Maciel-Guerra
State University of Campinas: Universidade Estadual de Campinas
Gil Guerra-Junior (gilguer@unicamp.br)
State University of Campinas: Universidade Estadual de Campinas https://orcid.org/0000-0002-2991-7678

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Abstract

The aim of this study was to verify the influence of Y chromosome and intrauterine androgens production/action on birth weight and length of children with Disorders/Differences of Sex Development (DSD). This was a cross-sectional and retrospective study. Cases of Turner syndrome (TS), complete (XX and XY), mixed (45,X/46,XY) and partial (XY) gonadal dysgenesis (GD), complete (CAIS) and partial (PAIS) androgen insensitivity syndromes and XX and XY congenital adrenal hyperplasia (CAH) were included. Such conditions were grouped according to karyotype and to intrauterine production/action of androgens. The sample consisted of 293 cases, 50 with TS, 28 mixed GD, 117 CAH (49 XY and 68 XX), 18 CAIS, 10 PAIS, 30 partial GD, 10 XY and 30 XX complete GD. Birth weight and length were lower in TS and mixed GD when compared to XY and XX. In turn, patients with increased androgen production/action (117 cases) had higher birth weight and length when compared to those with absent (108 cases) and decreased (68 cases) production/action. It was observed a negative influence of the 45,X/46,XY karyotype in birth weight and a positive influence of increased androgen production/action. Regarding birth length, there was a negative influence of the TS karyotype and of decreased androgen production/action. In conclusion, in DSD, both karyotype, especially with a 45,X cell line, and intrauterine androgenic production/action influence sex dimorphism of birth weight and length. It can be inferred that in children with normal karyotype and without a DSD, this dimorphism is mainly due to intrauterine androgenic production or action.

Introduction

Fetal growth and development are determined by several conditions, including maternal and placental factors and those that are inherent to the fetus, such as its genome. The latter appears as the main determinant of growth at the beginning of fetal life, while in the final stage of pregnancy the intrauterine environment, nutrition and hormonal influence assume a fundamental role [1]. It is known that birth weight in boys is higher than in girls in the general population. Differences in birth weight between the sexes have been reported in humans and in non-human primate species [2]. A population-based retrospective study of 574,358 individuals from southern Australia showed that male fetuses had a lower average gestational age at birth and a higher average birth weight [3]. Moreover, it has been shown that girls are slightly smaller between 8 and 12 weeks and remain smaller throughout pregnancy [4, 5].

A large multicenter cross-sectional study evaluated 8,070 low-risk single pregnancies between 16 and 40 weeks of gestation with measurements of biparietal diameter, head and abdomen circumferences and femur length. It was observed that fetal sex was a significant covariate for biparietal diameter and for head and abdomen circumferences, with higher values in male fetuses [6].

Although the cause of the difference in fetal weight and length is not yet fully understood, studies suggest that the presence of the Y chromosome and androgenic action in the prenatal period may play this role [7]. The interference of the Y chromosome on birth weight was already suggested in the past. Chen et al. [8] evaluated the effects of chromosome abnormalities on birth weight. They concluded that in

men with sex chromosome abnormalities birth weight tends to decrease when there is an increase in the number of X chromosomes, while the addition of a Y chromosome does not correlate with low birth weight [8]. In turn, Turner Syndrome (TS) patients are a good example of how this genotype-phenotype relationship can be inferred from anthropometric data. Although most have normal birth parameters, the frequency of TS in newborns with low birth weight and length is higher than expected [9, 10]. This is partly explained by the loss or altered expression of genes on the X chromosome involved with fetal growth [11].

Regarding androgenic action, De Zegher et al. [12] demonstrated that the degree of androgenization is directly related to birth weight, and this factor proved to be superior even to chromosomal sex. In their study, they demonstrated that children with androgen insensitivity syndrome (AIS) with a known mutation in the androgen receptor (*AR*) gene had a mean birth weight comparable to that of girls and significantly lower of that of unaffected boys and concluded that the difference in birth weight between boys and girls is generated by androgen action.

Boys have greater weight and length at birth compared to girls. Starting from the premise that this result may be due to either the chromosomal constitution or the intrauterine androgenic action, Disorders/Differences of Sex Development (DSD) could be an ideal model for assessing the influence of the karyotype and the intrauterine production and action of androgens in the weight and length at birth. In 46,XY DSD there are cases without androgen production [complete gonadal dysgenesis (GD)] and without androgenic action [complete androgen insensitivity syndrome (CAIS) and in 46,XX DSD there are cases with androgenic overproduction and action [congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency] [13, 14].

Children with CAH due to 21-hydroxylase deficiency have an increased secretion of adrenal androgens, which in the prenatal period causes virilization of the female external genitalia. Data in the literature demonstrate that prenatal hyperandrogenism also affects the size at birth in newborns with CAH [15]. This analysis started in 1971, in a Canadian study that compared the birth weight of newborns with CAH with their unaffected siblings and normal newborns and found that only girls with CAH had higher weight than their sisters and female controls [16].

Over the years, several studies have been published comparing anthropometric data of newborns with CAH and healthy ones. A study in Finland reported that boys and girls with CAH were longer at birth than healthy children of the same ethnicity [17]. This fact was also confirmed in the study by Balsamo et al., in Italy [18]. In contrast, data from the United Kingdom and Sweden did not show differences between the standard deviation of birth weight in girls and boys with CAH in relation to national references, and the same occurred in the study by Chalmers et al. [19, 20]. Thus, it is clear that data published so far in literature are scarce and conflicting.

Therefore, the present study aimed to evaluate the influence of Y chromosome and intrauterine androgens secretion and action on birth weight and length of children with DSD.

Casuistic And Methods

The sample consisted of patients diagnosed with DSD evaluated at the Pediatric Endocrinology Outpatient Clinic and the Interdisciplinary Group for the Study of Sex Determination and Differentiation (GIEDDS) at Clinical Hospital of State University of Campinas (UNICAMP), Campinas (Brazil) from June 1988 to December 2017.

Data extracted from the medical files were: gestational age in weeks assessed by Capurro, birth weight and length, presence of genital ambiguity, karyotype and diagnosis of DSD.

In all cases the karyotype was analyzed at the Cytogenetics Laboratory of the School of Medicine of UNICAMP with a count of at least 16 metaphases for homogeneous karyotypes 46,XX and 46,XY and 50 metaphases in cases of mosaicism or a 45,X constitution. All cases with a 45,X karyotype were evaluated for *SRY*, *DYZ3* and *TSPY* genes by polymerase chain reaction at the Human Molecular Genetics Laboratory of the Center for Molecular Biology and Genetic Engineering of UNICAMP. Another inclusion criterion was to have the etiologic diagnosis of DSD confirmed. The non-inclusion criterion was the absence of at least one of the data not available in the medical record.

From the data collected, the variables were classified into:

- Gestational age: in weeks by Capurro [21]
- Gestational age: preterm (< 37 weeks), term (between 37 weeks and 41 weeks and 6 days, and post-term if > 42 weeks) [22]
- Weight (g) and length (cm) at birth: they were transformed into a z score using the Intergrowth 21st [23] for gestational age and male or female sex according to the presence or absence of Y chromosome in the karyotype, respectively.
- Intrauterine production or action of androgens: assessed according to the presence of genital ambiguity: female genitalia independent of the karyotype = absence of androgens secretion and(or) action; ambiguous genitalia in any karyotype except 46,XX = decreased androgens; male genitalia with karyotype 46,XY or ambiguous with karyotype 46,XX = increased androgens
- Karyotype: 45,X or other karyotypes of TS without a Y chromosome; 45,X and other cell line(s) with a Y chromosome; 46,XY; 46,XX
- Diagnosis: TS (if female genitalia and 45,X karyotype or mosaicism with a 46,XX cell line or with structural X aberration – cases with Y chromosome were excluded), mixed GD (mosaicism 45,X/46,XY with genital ambiguity and absence of ovarian tissue in gonadal histological evaluation), complete GD (46,XX or 46, XY karyotype, typical female genitalia, with uterus and hypergonadotrophic hypogonadism), XY partial GD (46,XY karyotype, ambiguous genitalia and gonadal histological evaluation showing structural alteration), CAIS (46,XY karyotype, female genitalia, two testicles, mutation in the *AR* gene), PAIS (partial AIS = 46,XY karyotype, ambiguous genitalia, two testicles, mutation in the *AR* gene), CAH (46,XX karyotype with genital ambiguity or inferred 46,XY karyotype with male genitalia with biallelic mutations in the *CYP21A2* gene) [13, 14].

The diagnostic groups were divided according to karyotype into: 45,X without Y (TS), 45,X with Y (mixed GD), 46,XY (complete and partial GD, CAIS, PAIS and CAH) and 46,XX (complete GD and CAH). The diagnostic groups were also divided according to intrauterine production and(or) action of androgens in absent (TS, XX and XY complete GD and CAIS), decreased (mixed GD, XY partial GD and PAIS) and increased (XX and XY CAH).

Statistical analysis was performed using SPSS version 21.0 and STATA version 12.0. Quantitative variables were analyzed in median, minimum and maximum and qualitative variables in absolute and relative frequency. Chi-square and Kruskal-Wallis tests and Spearman's correlation coefficient were used. In the multivariate analysis, Quantil Regression was used to model the median. The significance level of 5% was used in the interpretation of the results.

Results

The sample consisted of 293 cases, with 50 cases of TS without a Y chromosome, 28 cases of mixed GD, 117 cases with a 46,XY karyotype (49 cases of CAH, 18 of CAIS, 10 of PAIS, 30 of partial GD and 10 of complete GD) and 98 with a 46,XX karyotype (68 of CAH and 30 of complete GD) (Table 1).

Table 1
Data (n and %) of type of karyotype and intrauterine production and action of androgens in 293 cases of DSD.

Karyotype	Androgens			Total
	Absent	Decreased	Increased	
46,XY	28 (23,9)	40 (34,2)	49 (41,9)	117
46,XX	30 (30,6)	0 (0)	68 (69,4)	98
45,X without Y	50 (100,0)	0 (0)	0 (0)	50
45,X with Y	0 (0)	28 (100,0)	0 (0)	28
Total	108	68	117	293

Regarding karyotype, the z score of birth weight was significantly lower in the TS group without Y compared to the 46,XY karyotype ($p = 0.008$) and 46,XX karyotype ($p = 0.003$), and the same occurred when birth length was compared ($p < 0.0001$ in both). Birth weight and length z score was also significantly lower in 45,X/46,XY cases (mixed GD) when compared to 46,XY and 46,XX karyotypes ($p < 0.0001$ in all analyzes). There was no significant differences between TS without Y and mixed GD in relation to birth weight ($p = 0.06$) and length ($p = 0.186$), the same occurring between XY and XX karyotypes for birth weight ($p = 0.07$) and length ($p = 0.374$) (Table 2).

Table 2
Weight and length z score at birth of 293 cases of DSD according to the karyotype.

Karyotype		z Birth Weight	z Birth Length
TS without Y	n	50	50
	Median	-0,20	-1,02
	Minimum – Maximum	-3,47–1,68	-4,58–1,63
Mixed GD	n	28	28
	Median	-0,66	-1,48
	Minimum – Maximum	-2,98–1,49	-4,90–0,67
XY	n	117	117
	Median	0,03	-0,35
	Minimum – Maximum	-1,78–2,51	-3,25–2,57
XX	n	98	98
	Median	0,20	-0,28
	Minimum – Maximum	-2,21–2,90	-3,57–5,94
Mixed GD: Mixed Gonadal Dysgenesis; TS: Turner syndrome; Kruskall-Wallis test			

According to intrauterine androgens production and(or) action, the groups were divided into absent (108 cases), decreased (68 cases) and increased (117 cases). The group with increased androgens had birth weight ($p < 0.0001$) and length ($p < 0.0001$) significantly higher than the group of absent and decreased androgens. There was no significant difference between the group with absent androgens and decreased androgens in relation to birth weight ($p = 0.064$) and length ($p = 0.071$) (Table 3).

Table 3
Weight and length z score at birth of 293 cases of DSD according to the intrauterine production or action of androgens.

Androgens		z Birth Weight	z Birth Length
Absent	n	108	108
	Median	-0,02	-0,53
	Minimum – Maximum	-3,47–1,68	-4,58–1,63
Decreased	n	68	68
	Median	-0,31	-0,92
	Minimum – Maximum	-2,98–1,47	-4,90–2,12
Increased	n	117	117
	Median	0,47	0,01
	Minimum – Maximum	-2,21–2,90	-3,57–2,57
Kruskall-Wallis test			

An association was observed between the intrauterine androgens production and(or) action and gestational age (premature or term) ($\chi2 = 39.511$; DF = 2; $p < 0.0001$), with more term cases with increased androgens and more premature cases with absent androgens (Table 4).

Table 4
Association data between gestational age and intrauterine production or action of androgens in 293 cases of DSD.

Gestational Age	Androgens			Total
	Absent	**Decreased**	**Increased**	
Premature	**49 (66,2)***	14 (18,9)	11 (14,9)	74
Term	59 (26,9)	54 (24,7)	**106 (48,4)***	219
Total	108	68	117	293
Chi-square test; *p < 0.0001				

There was no association between the karyotype and gestational age (premature or term) ($\chi2 = 6.328$; DF = 3; $p = 0.097$). There was also no correlation between gestational age (in weeks) with birth weight ($r = -0.14$; $p = 0.811$) or length ($r = 0.17$; $p = 0.767$).

The multivariate analysis with Quantile regression for the median presented the following models (Table 5):

Qualitative variables assume the value 1 for yes and 0 for no; and gestational age in weeks.

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Table 5
Data of Quantile regression for the median z score of weight and length at birth in 293 cases of DSD.

z Birth Weight	Coefficient	SD	t	p	CI 95%
45,X with Y	-0,702	0,18	-3,95	0,0001	-1,057 a -3,455
Increased androgen	0,559	0,11	5,00	0,0001	0,338 a 0,778
Gestational age	-0,665	0,03	-2,27	0,024	-0,127 a -0,009
Constant	2,517	1,14	2,21	0,028	0,276 a 4,758
z Birth Length					
45,X with Y	-0,964	0,402	-23,59	0,0001	-1,044 a -0,883
45,X without Y	-0,638	0,322	-19,77	0,0001	-0,701 a -0,574
Increased androgen	0,35	0,026	13,18	0,0001	0,297 a 0,402
Decreased androgen	-0,166	0,034	-4,63	0,0001	-0,233 a -0,098
Gestational age	-0,032	0,005	-5,39	0,0001	-0,043 a -0,020
Constant	0,866	0,225	3,84	0,0001	0,422 a 1,309

Discussion

In the present study, the use of DSD cases allowed to verify the influence of the Y chromosome and the intrauterine androgens production and(or) action on birth weight and length.

Regarding karyotype, it was demonstrated that TS patients without a Y chromosome had significantly lower birth weight and length compared to the 46,XY and 46,XX karyotypes. Similar findings in the literature show that girls with TS are 3.1 to 8.8 times more likely to be born with lower weight than in the general population, in addition to being shorter at birth, with growth deficit due to haploinsufficiency of the *SHOX* gene *(Short Stature Homeobox, OMIM* *312865) located on the short arm of the X chromosome (Xp22.33) [24–26].

There was no significant difference between TS without Y and mixed GD in relation to birth weight and length, due to the fact that patients with 45,X/46,XY karyotype share the 45,X cell line with TS and can also share some or all of its comorbidities, such as prenatal growth deficit [27, 28]. Analyzing these two groups, TS and mixed GD, an important influence of the chromosomal constitution is evidenced when compared to the hormonal synthesis, since in mixed GD there is some androgenic secretion (decreased androgens), while in TS there is no androgen synthesis (absent androgens).

There were no significant differences between the XY and XX karyotypes for birth weight and length. It must be considered that in groups XX and XY there were different types of DSD with increased, decreased or absent androgenic production or action, therefore the difference described in the literature, that boys (46,XY) have higher birth weight and length compared to girls (46,XX), is not applicable. Thus, it can be inferred that the androgenic effect may play an important role in birth weight and length and may even be more important factor than chromosomal sex [12].

Regarding the androgenic influence on birth weight and length, data in the literature are conflicting. In the present study, in relation to groups classified according to the intrauterine androgens production and(or) action, patients with increased androgens had significantly higher birth weight and length in relation to those in which androgens are absent or decreased.

Hughes et al. showed a significantly higher proportion of boys with hypospadias with birth weight less than 2,500 g (19.6%) compared to the other boys (5.5%) and girls (6%) [29], reflecting the influence of decreased androgen level (presence of hypospadias). Twin pregnancies are another possible model to assess the androgenic effect, revealing that the weight of the female twin is higher when her partner is male, possibly due to the androgenic effect [30].

On the other hand, Miles et al. showed that the anthropometric difference between the sexes at birth is not due to prenatal exposure to androgens, but due to the presence of the Y chromosome. Their results showed that newborns with CAIS had weight at birth similar to normal male babies and the birth weight in babies with CAH was not higher when compared to healthy ones [19]. Dorr et al. found similar results when comparing data on babies with CAH and the population reference group [15].

The association observed between the karyotype and the intrauterine production or action of androgens, with more cases of increased androgens in 46,XY (CAH in males) and 46,XX karyotypes and more cases of absent androgens in cases 45,X without Y and decreased androgens in cases 45,X with Y, is probably due to the types of DSD selected for this study.

There were no androgens in TS (cases 45,X without Y) due to the gonadal abnormality of these patients, even leading to estrogen deficit [26, 31]. A similar situation occurs in mixed GD (45,X with Y), characterized by a hormonal profile with increased gonadotropins due to GD and decreased androgen production, regardless of the degree of genital ambiguity [32].

Regarding the association between the intrauterine androgens production and(or) action and gestational age, there were more patients born at term with increased androgens and more premature patients with absent androgens. Studies have shown the influence of androgen on birth weight and length, but not an influence on prematurity. The etiology of premature birth is not completely understood due to the complex interaction between genetic, environmental and host factors [33]. However, advances are being achieved in this elucidation. Studies also report that there are more premature births among boys than girls between 24 and 37 weeks of gestational age [34].

In animal models, it was identified the *IGF1R* gene (*Insulin-like Growth Factor receptor 1, OMIM * 147370*) related to the predisposition to premature birth and two other genes linked to X chromosome – *AR (Androgen Receptor, OMIM * 313700)* and *IL2RG* gene (*γ subunit of the receptor of IL-2, OMIM * 308380*) (35). CAG repeats of *AR* exon-1 have been associated with premature delivery, with more CAG repeats in premature birth when compared to term birth. CAG repetition encodes a polyglutamine present in the *AR* transactivation domain and longer chains stop *AR* transactivation activity *in vitro*, while short chains lead to increased *AR* activation, resulting in hyperandrogenism [36]. Thus, hypoandrogenism may be associated with prematurity as demonstrated in this sample.

As a synthesis of the results of the present study, quantile regressions were created for the median birth weight and length. In relation to the median birth weight, there was a negative influence of the karyotype 45,X/46,XY and gestational age and a positive influence of androgen. In relation to the median birth length, there was a negative influence of the karyotype 45,X/46,XY, gestational age, TS karyotype without Y and decreased androgen and positive influence of increased androgen.

Conclusion

In children with DSD, birth weight and length were associated with the karyotype and the etiology of DSD evidenced by the intrauterine production or action of androgens. It can be inferred that in children without DSD and with a normal karyotype, the sex dimorphism of weight and length at birth is related to the production or action of androgens in intrauterine life.

Abbreviations

AIS: androgen insensitivity syndrome

CAH: congenital adrenal hyperplasia

CAIS: complete androgen insensitivity syndrome

DSD: disorders/differences of sex development

GD: gonadal dysgenesis

PAIS: partial androgen insensitivity syndrome

TS: turner syndrome

Declarations

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Ethics Declarations:

Ethics Approval:

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Approval of this study was obtained from the institutional review board of State University of Campinas (UNICAMP) (CAAE: 0340.0.146.000-06).

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