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RESEARCH PAPER

Sex dimorphism of weight and length at birth: evidence based on disorders of sex development

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ABSTRACT

Background: Males have higher weight and length at birth than females.
Aim: To verify the influence of the Y chromosome and the action of intrauterine androgens on weight and length at birth of children with Disorders of Sex Development (DSD).
Subjects and methods: A cross-sectional and retrospective study. Patients with 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. Weight and length at birth were evaluated.
Results: Weight and length at birth were lower in TS and mixed GD when compared to XY and XX DSD cases. In turn, patients with increased androgen action (117 cases) had higher weight and length at birth when compared to those with absent (108 cases) and decreased (68 cases) production/action. In birthweight, there was a negative influence of the 45,X/46,XY karyotype and a positive influence of increased androgen and gestational age. In birth length, there was a negative influence of the 45,X and 45,X/46,XY karyotypes and also a positive influence of increased androgen and gestational age.
Conclusions: The sex dimorphism of weight and length at birth could possibly be influenced by intrauterine androgenic action.

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Introduction

Foetal growth and development are determined by several conditions, including maternal and placental factors and those that are inherent to the foetus, such as its genome. The latter appears as the main determinant of growth at the beginning of foetal life, while in the final stage of pregnancy the intrauterine environment, nutrition and hormonal influence assume a fundamental role (Cunningham, Gant et al. 2001). It is known that birthweight in males is higher than in females in humans and in non-human primate species (Smith and Leigh 1998; Verburg et al. 2016). Moreover, it has been shown that females are slightly smaller between 8 and 12 weeks and remain smaller throughout pregnancy (Bukowski et al. 2007; Peacock et al. 2012; Rizzo et al. 2016).

However, the cause of the difference in foetal 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 be influential (Poyrazoglu et al. 2017). Patients with Turner Syndrome (TS) 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 weight and length at birth is higher than expected (Even et al. 2000; Hagman et al. 2010). This is partly explained by the loss or altered expression of genes on the X chromosome involved with foetal growth (Wisniewski et al. 2007). On the other hand, Miles et al. showed that newborns with Complete Androgen Insensitivity Syndrome (CAIS) had weight at birth similar to normal male babies and the birthweight in babies with Congenital Adrenal Hyperplasia (CAH) was not higher when compared to healthy ones (Miles et al. 2010).

Regarding androgenic action, De Zegher et al. demonstrated that the degree of androgenization is directly related to birthweight, and this factor proved to be superior even to chromosomal sex. In their study, they demonstrated that children with AIS with a known mutation in the androgen receptor (*AR*) gene had a mean birthweight comparable to

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that of females and significantly lower than that of unaffected boys (De Zegher et al. 1998).

Children with CAH due to 21-hydroxylase deficiency have an increased production 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 (Qazi and Thompson 1971; Dörr et al. 2019). Over the years, several studies have been published comparing anthropometric data of newborns with CAH and healthy ones. A study in Finland reported that males and females with CAH were longer at birth than healthy children of the same ethnicity (Jaaskelainen and Voutilainen 1997). This fact was also confirmed in the study by Balsamo et al. in Italy (Balsamo et al. 2006). In contrast, data from the United Kingdom and Sweden did not show differences between the standard deviation of birthweight in females and males with CAH in relation to national references, and the same occurred in the study by Chalmers et al. (2011). Thus, it is clear that data published so far in the literature are scarce and conflicting.

Males have higher weight and length at birth compared to females. 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] (Lee et al. 2006, 2016).

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

Subjects and methods

Participants and study design

This is a cross-sectional and retrospective study evaluating routinely recorded medical data of DSD patients.

The sample consisted of patients diagnosed with DSD evaluated at the Paediatric 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.

Procedures

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 for this study was obtained from the institutional review board of UNICAMP (CAAE: 0340.0.146.000-06).

Data extracted from the medical files were: gestational age in weeks assessed by Capurro et al. (1978), weight and length at birth, presence of genital ambiguity, karyotype, and diagnosis of DSD.

In all cases, the karyotype was analysed 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 Centre 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 items of data not available in the medical record.

From the data collected, the variables were classified into:

- Gestational age: in weeks by Capurro (Capurro et al. 1978)
- Gestational age: in weeks
- Weight (g) and length (cm) at birth
- Intrauterine production or action of androgens: assessed according to the presence of genital ambiguity: female genitalia independent of the karyotype = absence of androgens production 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). Although 46,XY individuals with CAH due to the classical form of 21-hydroxylase deficiency were not considered DSD, the inclusion of these cases was necessary in the study because there was no model of 46,XY DSD with excess intrauterine androgen production (Speiser and White 2003; Merke and Bornstein 2005). 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).

Data analysis

SPSS version 21.0 and STATA version 12.0 were used. In this sample, weight and length at birth did not show normal distribution, so these variables were expressed in median, minimum, and maximum. In this sample, gestational age, weight, and length at birth did not show normal distribution, therefore the Kruskal-Wallis test was used to analyse the differences in these variables in relation to the groups of karyotype and intrauterine production or action of androgens. When necessary, a non-parametric multiple comparison test was used to identify the differences between the groups. Spearman's test was used to analyse the correlation between gestational age and weight and length at birth. In the multivariate analysis, Quantil Regression was used to model the median to verify the influence of karyotype, androgens, and gestational age in the weight and length at birth. For this model, dependent (weight and length at birth) and predictor variables (gestational age, karyotype, and production or action of androgens) were used. The predictor variables were divided into quantitative (gestational age in weeks) and qualitative (karyotype = 46,XX was the reference; and androgens = absent was the reference). Qualitative predictor variables were classified as dummy (1 = yes; 0 = no). The analysis was started with a saturated model and later the non-significant variables were removed one by one. For all the statistical results, a p-value <0.05 was considered significant.

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).

Therefore, there were no differences in the gestational age between the groups of karyotype ($p = 0.078$) and of production or action of androgens ($p = 0.061$).

Regarding karyotype, the birthweight was significantly lower in the TS group without Y compared to the 46,XX and 46,XY karyotype ($p < 0.0001$ in both), and the results were similar when birth length was compared ($p < 0.0001$ in both). Weight and length at birth 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 analyses). There were no significant differences between TS without Y and mixed GD in relation to weight ($p = 0.094$) or length ($p = 0.636$) at birth, with the same occurring between XY and XX karyotypes for weight ($p = 0.625$) and length ($p = 0.594$) at birth (Table 1 and Figure 1).

According to intrauterine androgen 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 birthweight ($p < 0.0001$) and length ($p < 0.0001$) significantly higher than the groups of absent and decreased androgens. There was no significant difference between the group with absent androgens and decreased androgens in relation to weight ($p = 0.482$) and length ($p = 0.918$) at birth (Table 1 and Figure 2).

The multivariate analysis with Quantile regression for the median presented the following models (Table 2):

$$\text{Birthweight (g)} = 2,971 - (257 \times 45,\text{X with Y karyotype}) - (161 \times 45,\text{X karyotype}) + (180 \times \text{increased androgen}) + (157 \times \text{gestational age})$$

$$\text{Birth Length(cm)} = 19 - (1.25 \times 45,\text{X with Y karyotype}) - (1 \times 45,\text{X karyotype}) + (0.75\ 46,\text{XY karyotype}) + (0.75 \times \text{increased androgen}) + (0.75 \times \text{gestational age})$$

Table 1. Weight and length at birth of 293 cases of DSD according to the karyotype and to intrauterine production or action of androgens.

Karyotype		Birthweight (g)	Birth Length (cm)	Gestational age (weeks)
TS without Y	*n*	50	50	50
	Median	2821	45.8	37.7
	Minimum–maximum	1400–3850	37.0–50.0	35.0–50.0
Mixed GD	*n*	28	28	28
	Median	2532	44.4	36.9
	Minimum–maximum	645–3730	28.0–51.0	32.0–41.0
XY	*n*	117	117	117
	Median	3099	48.1	37.9
	Minimum–maximum	615–4265	31.0–53.5	26.0–42.0
XX	*n*	98	98	98
	Median	3093	47.7	38.0
	Minimum–maximum	1560–4245	42.0–52.0	32.0–41.0
Androgens production/action				
Absent	*n*	108	108	108
	Median	2902	46.7	37.7
	Minimum–maximum	1400–3850	37.0–50.0	35–40
Decreased	*n*	68	68	68
	Median	2790	46.0	37.3
	Minimum–maximum	615–3850	26.0–52.5	26.0–42.0
Increased	*n*	117	117	117
	Median	3201	48.5	38.3
	Minimum–maximum	1560–4265	42.0–53.5	32.0–42.0

Mixed GD: mixed gonadal dysgenesis; TS: Turner syndrome.

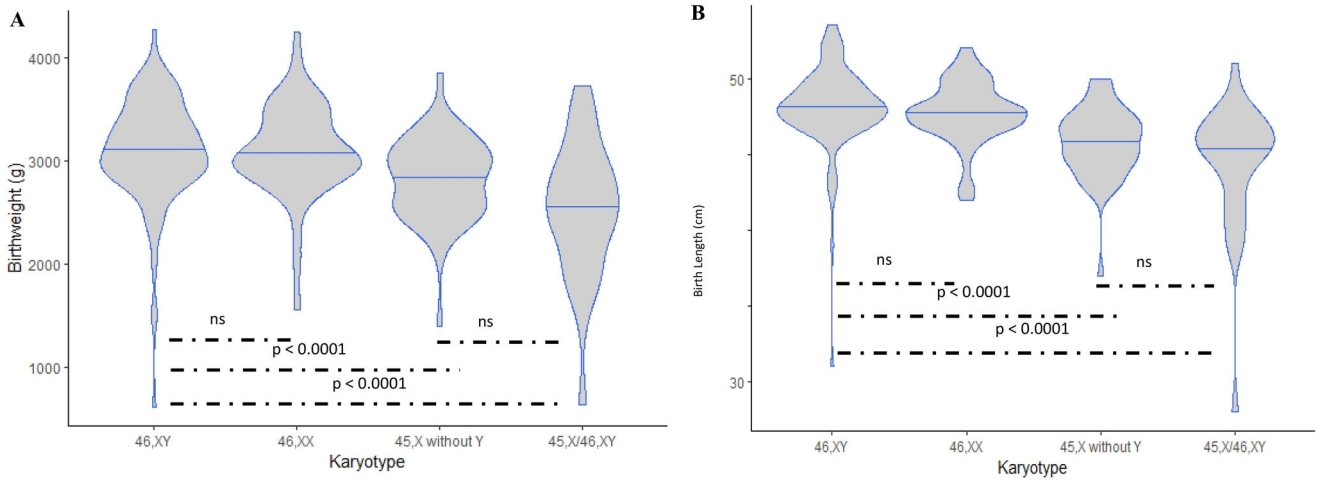

Figure 1. (A) Distribution of weight (g) and (B) length at birth according to karyotype from 293 cases of DSD. The data were represented by violin plots.

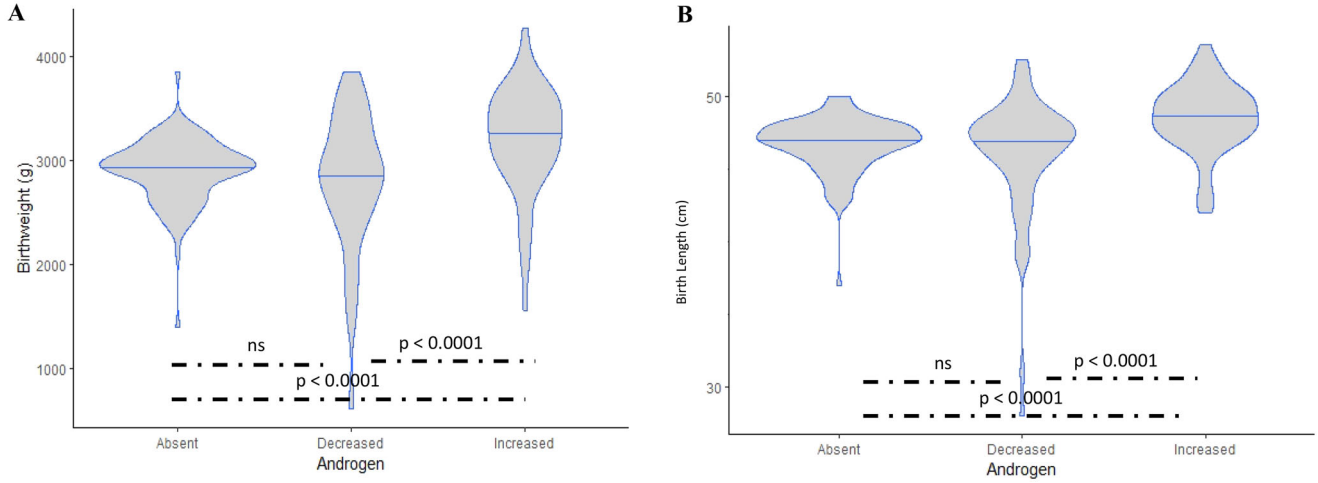

Figure 2. (A) Distribution of weight (g) and (B) length at birth according to androgen production or action from 293 cases of DSD. The data were represented by violin plots.

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

Discussion

In the present study, using DSD cases, it was possible to verify the influence of the Y chromosome and the production and(or) action of intrauterine androgens on weight and length at birth.

Regarding karyotype, it was demonstrated that TS patients without a Y chromosome had significantly lower weight and length at birth compared to the 46,XY and 46,XX karyotypes. Similar findings in the literature show that girls with TS are 3.1–8.8 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) (Bernasconi et al. 1994; Rongen-Westerlaken et al. 1997; Gravholt et al. 2017). In the present study, all included 45,X TS patients were analysed to rule out a Y mosaicism. Probably, the 45,X patients had an occult X mosaicism (Held et al. 1992).

There was no significant difference between TS without Y and mixed GD (45,X/46,XY with sex ambiguity) in relation to weight and length at birth, 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 (Ounsted and Ounsted 1970; Tosson et al. 2010). Upon analysing 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 production (decreased androgens), while in TS there is no androgen synthesis (absent androgens). Furthermore, the 45,X/46,XY mosaicism found in peripheral blood does not reflect its frequency in different tissues, like heart, kidneys, and bones, among others, which can explain this similarity in pre and postnatal growth between 45,X and 45,X/46,XY patients (Fiot et al. 2016).

There were no significant differences between the XY and XX karyotypes for weight and length at birth. It must be considered that in groups XX and XY there were different types

Table 2. Data of quantile regression for the median of weight and length at birth in 293 cases of DSD.

Birthweight (g)	Coefficient	*SD*	*t*	*p*	CI 95%
45,X with Y	−257	55	−4.65	0.0001	−366 to −148
45,X	−161	45	−3.55	0.0001	−250 to −72
Increased androgen	180	36	5.01	0.0001	109 to 250
Gestational age	157	9	17.60	0.0001	139 to 175
Constant	−2971	337	−8.80	0.0001	−3635 to −2307
Birth length (cm)					
45,X with Y	−1.25	0.6	−2.20	0.0001	−2.36 to −0.13
45,X without Y	−1.00	0.49	−2.04	0.0001	−1.96 to −0.04
46,XY	0.75	0.35	2.16	0.0001	0.06 to 1.43
Increased androgen	0.75	0.35	2.16	0.0001	0.07 to 1.43
Gestational age	0.75	0.09	8.58	0.0001	0.58 to 0.92
Constant	18.75	3.32	5.65	0.0001	12.22 to 25.28

of DSD with increased, decreased, or absent androgenic production or action, therefore the difference described in the literature, that males (46,XY) have higher birthweight and length compared to females (46,XX), is not applicable. Thus, it can be inferred that the androgenic effect may play an important role in weight and length at birth and may even be a more important factor than chromosomal sex (De Zegher et al. 1998).

Regarding the androgenic influence on weight and length at birth, data in the literature are conflicting in humans and non-humans (Gill and Hosking 1995; More et al. 2016). In the present study, in relation to groups classified according to the production and(or) action of intrauterine androgens, patients with increased androgens had significantly higher birthweight 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 birthweight <2500 g (19.6%) compared to the other boys (5.5%) and girls (6%) (Hughes et al. 2002), 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 (Jahanfar and Lim 2016).

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 birthweight in male and female babies with CAH was not higher when compared to healthy ones (Miles et al. 2010). Dörr et al. found similar results when comparing data on male and female babies with CAH and the population reference group (Dörr et al. 2019).

There were no androgens in TS (cases 45,X without Y) due to the gonadal abnormality of these patients, even leading to oestrogen deficit (Gravholt et al. 2017, 2019). A similar situation occurs in mixed GD (45,X with Y), characterised by a hormonal profile with increased gonadotropins due to GD and decreased androgen production, regardless of the degree of genital ambiguity (Johansen et al. 2012).

As a synthesis of the results of the present study, quantile regressions were created for the median weight and length at birth. In relation to the median birthweight, 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, weight and length at birth were associated with the karyotype, mainly with 45,X lineage, and the aetiology of DSD was evidenced by the intrauterine production or action of androgens. It is likely that in children without DSD and with a normal karyotype, as in the general population, the sex dimorphism of weight and length at birth could be influenced by the production or action of androgens in intrauterine life. More studies are necessary to confirm this data.

Author contributions

DSTA, TER, ATM-G, and GG-J reviewed the literature. DSTA, TER, BAB, JGRA, APM-F, AMM, OH, ATM-G, and GG-J designed the study. MPM, TNM, MSG, HF-S, TAPV, and NLV performed experiments for the disease diagnosis (karyotype, FISH, and molecular studies). All authors co-wrote and revised the paper.

Disclosure statement

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Data availability statement

Data are available in a public, open access repository at https://doi.org/102524/redu/URVCSI.

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