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Birth Sizes of Neonates with Congenital Adrenal Hyperplasia Secondary to 21-Hydroxylase Deficiency
Dörr HG et al. Androgens and Birth Sizes

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What is already known on this topic?
Prenatal weight gain and birth weight are partially influenced by androgen action. Some reports in the literature show higher birth weight and length in CAH newborns. However, data on this topic are inconsistent in the literature.

What this study adds?
We studied birth sizes of term newborns with classic CAH who were followed in our hospital. Our data support the assumption that prenatal hyperandrogenism has no effect on fetal growth.

Abstract
Objective: Classic congenital adrenal hyperplasia secondary to 21-hydroxylase deficiency (CAH) is characterized by increased prenatal adrenal androgen secretion. There are few reports in the literature showing higher birth weight and length in CAH newborns.
Methods: We analyzed birth weight and length data of 116 German newborns (48 boys, 68 girls) with classic CAH who were born during the period from 1990 to 2017. All children have been followed or are currently treated as outpatients in our clinic. All children were born at term. The mothers were

healthy, and their pregnancies were uneventful. The diagnosis of CAH was confirmed by molecular analyses of the CYP21A2 gene. Birth data were calculated as standard deviation scores (SDS) according to German reference values.
Results: (Mean ± SD): Weight and length in male CAH newborns (3601 ± 576 g; 52.4 ± 2.85 cm) were statistically significantly higher than in female CAH newborns (3347 ± 442 g; 51.2 ± 2.55 cm), but male-female differences in the CAH cohort were lost when data were converted into SD scores. The birth sizes of the CAH newborns did not differ from the reference group. The birth sizes were not different in relation to the different CAH genotypes. Maternal age, mode of delivery and maternal parity had no influence on birth sizes.
Conclusions: Our data show that prenatal hyperandrogenism does not affect fetal growth.
Keywords: Term newborn, congenital adrenal hyperplasia, 21-hydroxylase deficiency, genotype

Introduction

Classic congenital adrenal hyperplasia (CAH) is the most common form of inherited disorders of cortisol biosynthesis in the adrenal cortex. It is due to mutations in the active gene CYP21A2 causing varying degrees of impairment of 21-OH activity. Classic CAH with 21-OH-deficiency occurs in two forms, a three-times more frequent form with salt wasting (cortisol + aldosterone deficiency) and a simple virilizing form without aldosterone deficiency (1-3). Both forms are characterized by increased adrenal androgen secretion which prenatally causes virilization of the external female genitalia and, postnatally in both sexes without treatment, results in pseudoprecocious puberty, accelerated growth and bone maturation.

Since term-born male newborns are heavier than females, it has been speculated that prenatal weight gain and birth weight are also at least partially influenced by androgen action (4). In contrast, there are also data showing that birth size is not explained by the effects of prenatal androgen exposure (5).

Some reports in the literature show higher birth weight and length in CAH newborns. According to data from Finland, both girls and boys with classic CAH are significantly longer at birth than healthy newborns of the same ethnic origin (6). Italian authors confirmed these results and speculated that birth sizes of newborns with classic CAH correlate with the severity of the phenotype (7). In another study from UK and Sweden no differences between birth weight SDS in CAH girls and boys in relation to the national references and no correlation to the severity of the gene mutation were found (5).

Overall, the data on this topic is inconsistent in the literature. The objective of our study was to analyse birth weight and length of children with classic CAH who were treated in the outpatient department of our hospital. The severity of the CAH phenotype was determined by molecular genetic classification of the common mutations (8-11). We tried to exclude most factors that might additionally affect birth weight and length.

Methods

Birth weight and length data of 116 German newborns (48 boys, 68 girls) with classic CAH who were born during the period from 1990 to 2017 was analyzed. All children have been followed or are currently treated as outpatients in our endocrinology clinic. All children were born at term (gestational age: 38 to 41 weeks) either spontaneous vaginally (n = 95) or by caesarean section (n = 21). The mothers (age: 20 to 42 years) were healthy, primipara (n = 77) or multipara (n = 39), and their pregnancies were uneventful. Data on maternal body mass index (BMI) at delivery were not available.

The diagnosis of CAH was confirmed by molecular analyses of the CYP21A2 gene. Molecular genetic classification of the severity of CAH was performed according to Krone et al. (8). The genotype 'Null' included patients with biallelic mutations that resulted in completely inactive enzymes (e.g. gene deletions), genotype A included patients with homozygous I2G or heterozygous I2G in trans with a null mutation, and B patients with homozygous p.I173N mutation or heterozygous p.I173N mutation in trans with a mutation from group 'Null' or group A. Genotype 'Null' was found in 43 children, genotype A in 51 children, and 22 children were identified with genotype B.

Birth weight (g) and length (cm) data were obtained from the patient records ("Vorsorgeheft"). As birth weight we used the weight measured at birth, and for the length we used the data obtained between 3 and 7 days after birth. The length measurement at that age is part of the clinical examination of the newborn, usually before discharge from the hospital, and the value obtained is more reliable than the length measured at birth. Birth data were calculated as standard deviation scores (SDS) according to German reference values as follows (12): SDS = (patient's measured value – mean value for age- and sex-matched normal subjects) ÷ SD of the values for age- and sex-matched normal subjects. The used German references based on the perinatal data of 2.3 million singleton newborns from 1995-2000 (12). We defined all neonates with the parameter birth weight and length < – 2 SDS as small for gestational age (SGA) and with the same parameters > 2 SDS as large for gestational age (LGA).

The study design (retrospective analysis of the data) was approved by the Ethical Committee of our Hospital without an approval number. Informed consent has been obtained from the parents after full explanation of the purpose and nature of all procedures used.

Statistical analysis was performed using SPSS, Version 21 (IBM). Data are expressed as mean ± SD and median. Kruskal Wallis test was used to compare values between different genetic groups. Student t test for unpaired samples was used to compare weight and length values between status of maternal parity and mode of delivery.

Results

Birth sizes (weight and length) of term newborns with classic CAH are shown in Tables 1 and 2. We found no statistically significant difference between the birth sizes of the CAH newborns in relation to the used reference group. In terms of birth weight, three children of the CAH cohort were classified as small-for-gestational age and six as large-for-gestational age newborns. The mean birth sizes (weight in grams and length in centimeters) in male CAH newborns were statistically significantly higher than in females (weight: $p < 0.01$; length $p < 0.02$). However, when calculating the data in SDS, neither weight-SDS nor length-SDS values were significantly different between both sexes. The birth sizes were also not different between the different CAH genotypes. We analyzed the data also according to genotype and sex and found no difference. Moreover, maternal age, mode of delivery and maternal parity had no influence on birth sizes.

Discussion

The androgen action on birth sizes is documented by the fact that healthy male newborns are longer and weigh more than female newborns (13). Children with classic congenital adrenal hyperplasia and 21-hydroxylase deficiency (CAH) have increased adrenal androgen secretion which already prenatally causes virilization of the external female genitalia. Additionally, there are some reports in the literature showing that prenatal hyperandrogenism also affects birth sizes in CAH newborns.

Already in 1971, a study from Canada compared the birth weights of CAH newborns with their unaffected siblings and normal newborns and found that only females with CAH were heavier than the female controls and female siblings (14). Jaaskelainen and Voutilainen from Finland reported that both girls and boys with classic CAH are significantly longer at birth than healthy newborns of the same ethnic origin (6). The authors did not make any distinction between the different clinical forms of classic CAH.

Italian authors found that the average birth length in both boys and girls with classic CAH was significantly greater than the mean birth length in healthy Italian children, and speculated that the birth data correlate with the severity of the phenotype (7). Data from UK and Sweden found no differences between birth weight SDS in CAH girls and boys in relation to the national references and no correlation to the severity of the gene mutation (5). In a study from Munich, mean birth “height” SDS data of 51 newborns with classic CAH diagnosed by newborn screening was found to be slightly above average (15). Chalmers et al. identified 105 CAH newborns over a long period of 50 years and found no difference in birth weight from the standard population median and also no sex difference in favour of heavier males (16). They speculated that these differences were ameliorated because of increased levels of prenatal androgens experienced by the female infants.

In turn, in a large retrospective observational cohort study from France heavier male than female CAH newborns were reported, but overall normal mean birth weight and birth length (17). Our data confirm this sex-related difference. In our

analysis, male CAH newborns had statistically significantly higher birth weight (g) and length (cm) values than females. When transforming the data into SDS values, the male newborns still had slightly higher values than the females, but the difference was not statistically significant. Birth sizes of our cohort were not different from the used German reference population. The severity of CAH, maternal age, parity and mode of delivery had no influence on birth sizes. In terms of birth weight, three children of our cohort were classified as small-for-gestational age and six as large-for-gestational age newborns.
It is not surprising that the results in the literature are inconsistent. Most reports on birth sizes in CAH newborns do not provide data on the course of pregnancy, maternal age, maternal status of parity, or mode of delivery. The somatic classification of neonates is primarily based on birth weight. Birth weight is affected by a multitude of different factors such as socio-economic status, maternal age, and concomitant diseases of the mother in pregnancy, as well as placental, fetal and environmental conditions (18-21). Additionally, the correct interpretation of birth sizes is complicated by the methodological heterogeneity and limitations of birth size charts available worldwide. Also, secular trends in birth size over the 25 year period might play a role. In all, there are numerous factors that limit the interpretation of birth sizes in CAH newborns.

Study limitations

There were some limitations to our study. The sample size is too small to exclude a Type 2 statistical error. The study is retrospective. The data analyzed are covering a period from 1990 to 2017. It was not possible to exclude all the different factors which might affect birth sizes of newborns with CAH.

Conclusions

Altogether, data on birth sizes of newborns with CAH secondary to 21-hydroxylase deficiency are rare in the literature. We tried to clarify existing conflicting published data on this topic. Our data support the assumption that prenatal hyperandrogenism has no effect on fetal growth.

List of Abbreviation

CAH = congenital adrenal hyperplasia

Declaration of interest

There is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Ethical approval

The study was approved by the local ethics committee of the Dept. Pediatrics of Erlangen.

Consent has been obtained from the parents after full explanation of the purpose and nature of all procedures used.

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Table 1
Birth sizes of term newborns with classic CAH according to sex
Values shown as mean ± SD (median); * $p < 0.02$; ** $p < 0.01$

	All N =116	Male N = 48	Female N = 68
Birth weight (g)	3452 ± 515 (3410)	3601 ± 576 ** (3510)	3347 ± 442 ** (3355)
Birth weight (SDS)	-0.07 ± 1.12 (-0.19)	0.06 ± 1.26 (-0.08)	-0.17 ± 1.02 (-0.24)
Birth length (cm)	51.7 ± 2.73 (52.0)	52.4 ± 2.85 * (52.1)	51.2 ± 2.55 * (50.9)
Birth length (SDS)	- 0.07 ± 1.15 (-0.21)	0.05 ± 1.20 (-0.20)	-0.16 ± 1.12 (-0,24)

Table 2
Birth sizes of newborns with classic CAH according to genotype
Values shown as mean ± SD (median)

	Genotype		
	0 N = 43	A N = 51	B N = 22
Birth weight (g)	3397 ± 491 (3410)	3474 ± 466 (3410)	3511 ± 665 (3420)
Birth weight (SDS)	-0.19 ± 1.04 (-0.22)	-0.01 ± 1.04 (-0.22)	-0.03 ± 1.44 (-0.22)
Birth length (cm)	51.4 ± 2.68 (51.2)	51.9 ± 2.45 (51.7)	51.2 ± 3.44 (51.2)
Birth length (SDS)	- 0.19 ± 1.13 (-0.39)	0.04 ± 1.05 (-0.11)	-0.10 ± 1.42 (-0.40)