

Surgical Practice in Girls with Congenital Adrenal Hyperplasia: An International Registry Study

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Keywords

Congenital adrenal hyperplasia · Disorders of sexual development · Intersex · Surgery

Abstract

In this article international trends in surgical practice in girls with congenital adrenal hyperplasia (CAH) are evaluated. All cases that had been classified in the I-CAH/I-DSD registry as 46,XX CAH and who were born prior to 2017 were identified. Centers were approached to obtain information on surgical decision making. Of the 330 included participants, 208 (63.0%) presented within the first month of life, and 326 (98.8%) cases were assigned female. Genital surgery had been performed in 250 (75.8%). A total of 64.3, 89.2, and 96.8% of cases residing in Europe, South America and Asia, respectively, had at least one surgery. In a logistic regression model for the probability of surgery before the second birthday (early surgery) over time an increase of probability for early vaginal surgery could be identified, but not for clitoral surgery or both surgeries combined. Genitoplasty in girls with CAH remains controversial. This large international study provides a snapshot of current practice and reveals geographical and temporal differences. Fewer surgeries were reported for Europe, and there seems to be a significant trend towards aiming for vaginal surgery within the first 2 years of life.

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Introduction

Congenital adrenal hyperplasia (CAH) is the most common diagnosis in infants with virilization, 46,XX DSD. The incidence of classic virilising CAH is about 1:15,000 in most populations in the world [Speiser et al., 2010]. More than 95% of cases are caused by 21-hydroxylase deficiency, which is characterized by defective glucocorticoid synthesis in all patients and mineralocorticoid synthesis in some. Precursors to cortisol and aldosterone accumulate and are shunted toward androgen production, starting in fetal life. The prenatal excess of androgens results in virilization of 46,XX infants [Speiser et al., 2010]. Most girls with CAH present with atypical genitalia [Merke and Auchus, 2020], and although they have traditionally been treated by early sex-conforming surgery, this approach has increasingly been debated with clinicians/parents opting not to undertake any surgery before the age of consent [Kolesinska et al., 2014; Wolffen-

buttel and Crouch, 2014; Bougneres et al., 2017]. Studies performed on large data sets from international cohorts such as the International DSD registry (www.i-dsd.org) have been successfully used in different scientific projects [Ahmed et al., 2014]. With the recent extension of this registry platform to include patients with CAH (www.i-cah.org), the current study was designed to evaluate changes over time in CAH-related surgical practice. In particular, we wanted to find out whether there was a change over time in the rate of early feminizing genitoplasty. We divided our dataset of patients into 2 equally distributed groups (1996–2006, 2007–2017). By chance, the distribution coincided with the Chicago consensus of 2006, which was followed by many important consensus and position papers concerning care of patients with DSD (Office of the High Commissioner for Human Rights, United Nations for Intersex Awareness, <https://www.ohchr.org/EN/Issues/LGBTI/Pages/IntersexPeople.aspx>, 2016; Parliamentary Assembly of the Council of Europe, Resolution 2191, <https://assembly.coe.int/nw/xml/XRef/Xref-XML2HTML-en.asp?fileid=24232&lang=en>) [Méndez, 2013; Deutsche Gesellschaft für Urologie (DGU) e.V., 2016; Mouriquand et al., 2016; Cools et al., 2018; Krege et al., 2019].

Material and Methods

The I-DSD and the I-CAH registries are international registries, approved by the National Research Ethics Service of the United Kingdom, for storage of pseudo-anonymized data. Data are collected as part of routine clinical practice following informed consent of the parents or patients [Kourime et al., 2017]. All cases that had been registered until 2018 as 46,XX disorder of androgen excess due to CAH and who were born prior to 2017 were included in this study. We identified 555 patients from 41 centers, who were born between 1953 and 2016. These centers were approached to obtain additional information on factors that influenced the option of performing surgery, timing of surgery, type of surgery, and the length of the follow-up period (the questionnaire for the centers is available in online suppl. Table 1; for online suppl. material, see www.karger.com/doi/10.1159/517055).

The centers were provided a 6-month period to respond, and during this period 21 (51.2%) centers completed and returned the questionnaires on a total of 334 of 555 eligible cases (60.2%). Of the 334 completed questionnaires, 330 (98.8%) from 12 countries in Europe (15 centers, $n = 199$), Asia and Turkey (4 centers, $n = 94$), and South America (2 centers, $n = 97$) were suitable for analysis. In this study, we included only patients born between January 1995 and December 2015 who had their first presentation between January 1996 and December 2016 before their first birthday ($n = 184$) (Fig. 1). Out of the 184 patients included, 104 patients (56%) were registered in European centers, 59 patients (32%) were registered in Asian centers, and 21 patients (11%) were registered in South American centers. Prader score at first presentation was

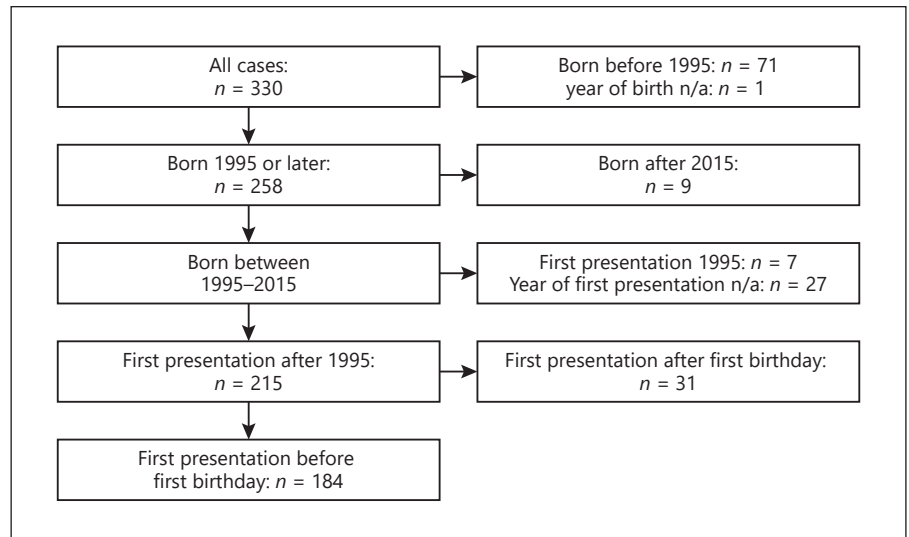


Fig. 1. Inclusion/exclusion flow diagram of the sample.

available for 122 patients (66%), external masculinization score (EMS) [Ahmed et al., 2000] at first assessment was available for 67 patients (36%). A total of 90 patients (49%) had their first presentation before or in 2006, 94 patients (51%) presented in 2007 or later.

Statistical Analysis

Early surgery was defined as surgery before 24 months of life. For univariate analysis, a logistic regression of the probability of early surgery for patients presenting before their first birthday was performed. Patients for which no information about early surgery was available were considered as missing values. Differences in proportions of early surgery before and after 2006 were analyzed by a Pearson's χ^2 test, and correlation between early surgery and Prader score and EMS were investigated by Wilcoxon tests. In a multiple logistic regression model we included the year of first presentation with an interaction term with the cut off at 2006, and the Prader score dichotomized as up to 2 and >2. In a sensitivity analysis, the calculations were repeated in a nonlinear mixed model with the random effect intercept per center. All statistical calculations were performed with R versions 3.5.1 and 3.6.3.

Results

Clinical Characteristics

Of the 184 cases, 160 patients (87%) presented within the first month of life, 15 patients (8%) presented between month 1 and end of month 3, and 9 patients (5%) presented between month 4 and their first birthday. A total of 172 patients (93%) had 21-hydroxylase deficiency, 6 (3%) had 11 β -hydroxylase deficiency, and 6 patients (3%) had other forms of CAH. At birth, 183 (99%) cases were assigned as female, and 1 case was not assigned to any sex.

At latest assessment, all cases had a female sex assignment. Prader score was available in 122 patients (66%) with a median of 4 (IQR: 3–4, range: 0–5; EMS at first assessment was entered for 67 patients (36%) with a median of 7 [IQR: 7–9, range: 4–10]).

Surgery

Altogether, 184 patients were born between January 1996 and December 2016 and had their first presentation within the first year of life: 94 patients (51%) presented between 1996 and 2006, 90 patients (49%) presented in 2007 or later. In sum, 51 patients (28%) did not have surgery before their second birthday (no early surgery), 65 patients (35%) had at least 1 operation before their second birthday. For 68 patients (37%) this information was not available: for 3 patients it was unclear whether they had surgery, 6 patients without surgery had their last follow-up before their second birthday, and for 59 patients with surgery the date of surgery remained unknown. Of those 65 patients with at least 1 operation before their second birthday, 54 patients (83%) had vaginal as well as clitoral surgery, 7 patients (10%) had clitoral but no vaginal surgery, 2 patients (3%) had vaginal but no clitoral surgery, and 2 patients (3%) had clitoral surgery with no information about vaginal surgery. Of the 54 cases who had both operations, in 3 (6%) clitoral surgery was performed first, in 48 patients (89%) both surgeries were performed simultaneously, and for 3 patients this information was not available. Age at last follow-up was equally distributed between patients with early surgery (median 10, range 0–20), patients without early surgery (median 10, range

Table 1. Probability of having early surgery did not change over time ($p = 0.59$)

| | Patients (%) presenting in 2006 or before | Patients (%) presenting in 2007 or later |
|----------------------------|--|--|
| No early surgery | 24 (27) | 27 (29) |
| At least one early surgery | 35 (39) | 30 (32) |
| Information not available | 31 (34) unknown date: 28 lost to follow-up: 2 unclear if surgery: 1 | 37 (39) unknown date: 31 lost to follow-up: 4 unclear if surgery: 2 |

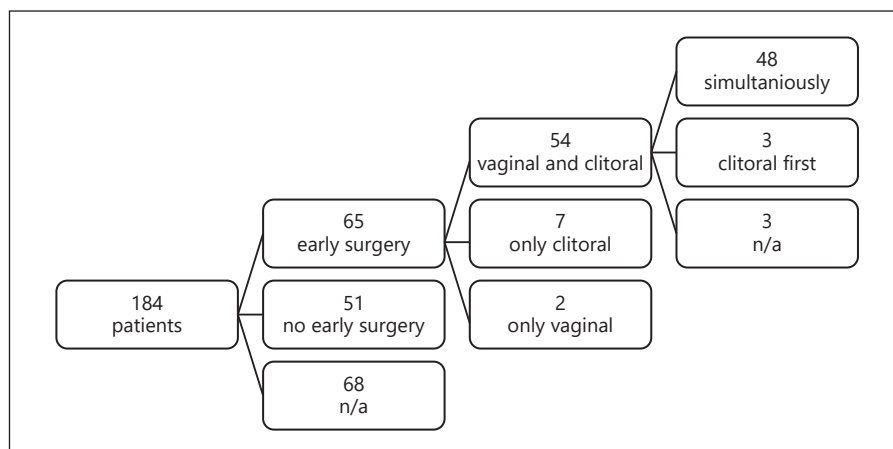


Fig. 2. Estimated trend for proportion of early surgeries over time.

2–19), and patients with unknown early surgery status (median 9, range 0–21). The time at first presentation (before and after 2006) did not show any association with the proportion of early surgeries (Pearson's χ^2 test, $p = 0.59$). No trend in the distribution of missing data could be perceived, therefore we are confident not to have any bias due to missing values (Table 1; Fig. 2).

Surgery and Geography

Of the 184 cases, the number of cases from Europe, South America, and Asia were 104 (56.5%), 21 (11.4%), and 59 (32.1%), respectively, and the number of girls who had surgery reported in these 3 regions was 76 (73.0%), 17 (81.0%), and 58 (98.3%), respectively. The number of girls who had early surgery reported in these 3 regions was 33 (31.7%), 10 (47.6%), and 22 (37.3%), respectively.

The median Prader stage for these 3 regions was 3 (normal female–5), 3 (3–5), and 4 (2–5), respectively. Altogether, 90 girls presented before 2006, 94 presented in 2007 or later. Early surgery was reported for 35 girls of the former group (38.9%) and for 30 girls of the second group (32.9%).

No clear difference in the frequency of reported early surgery before and after 2006 can be perceived, and a χ^2

test identified no difference in proportions before and after 2006. Also, when geographical regions were analyzed separately, proportions of girls with early surgery before and after the statement did not differ substantially (Europe: 18 out of 49 [36.7%] before 2006 vs. 15 out of 57 [27.3%] after 2006; South America: 5 out of 11 [45.5%] before vs. 5 out of 10 [50%] after 2006; Asia: 12 out of 30 [40%] before vs. 10 out of 29 [34.5%] after). Due to the geographic bias of this study no further analysis was performed.

Clinical Features Associated with the Likelihood of Surgery

Prader score was available for 34 patients without early surgery (median: 3, range: 0–5, IQR: 2–4), 45 patients with early surgery (median: 4, range: 2–5, IQR: 3–4), and 43 patients with unknown early surgery status (median: 4, range: 0–5, IQR: 3–4). A Wilcoxon rank sum test identified differences between Prader scores of patients with and without early surgery ($p = 0.002$). EMS was available for 67 patients. Median EMS reported for those who did not have early surgery ($n = 17$) was 7 (range: 4–10, IQR: 6–8), median EMS for those who had surgery ($n = 28$) was

7 (range: 4–10, IQR: 7–7), median EMS for patients with unknown early surgery status ($n = 22$) was 7 (range: 4–10, IQR: 7–9). A Wilcoxon rank sum test identified no differences between first EMS of patients with and without surgery ($p = 0.55$). First EMS was available for 67 girls and missing for 117 girls, with median 7 and range 4–10. Prader Score was available for 122 girls and missing for 62 girls, with median 4 and range 0–5. For 51 patients (27.7%) neither Prader nor EMS score were available.

Analysis of data regarding the influence of patient, parent, clinician, society, religion, and media for the decision-making process was not possible due to heterogeneity and incompleteness.

Multiple Logistic Regression

Logistic regression was performed for the proportion of early surgery regarding the year of first presentation. No significant change of the proportion of early surgeries over the year of first presentation was identified (OR = 0.99, 95% CI = [0.92, 1.07], $p = 0.780$). Inclusion of an interaction between time and the cut off at 2006 did not identify a change in trend of the proportion of early surgery after 2006 (OR = 1.23, 95% CI = [0.94, 1.62], $p = 0.135$). For those patients with known Prader score, in a logistic regression model with covariates *year of first presentation* and *dichotomized Prader score*, no trend could be identified (OR: 1.05, 95% CI = [1.00, 1.11], $p = 0.067$), but a higher proportion of early surgeries was associated with a Prader score >2 (OR: 6.54, 95% CI = [1.84, 31.11], $p = 0.007$). In a sensitivity analysis, nonlinear mixed models with the random effect center were analyzed which gave the same results (data not shown).

Discussion

Despite the widespread controversy in the medical community, media, and general population, there is a significant lack of reliable or prospective data on genital surgery in CAH. Therefore, the subject of this study was to evaluate the current surgical practice and changes over time in children with CAH within the I-CAH and I-DSD registries. Data from over 184 girls with CAH were accessed and analyzed to investigate trends in early surgery. To our knowledge this is the largest international study of a contemporary approach to surgery in these patients.

Apart from one patient, where information on sex assignment was not available, all patients were raised as girls, and around 35% had at least one reported genital surgery before their second birthday. When early surgery

was performed, the majority of all patients had complete urogenital reconstruction in one step. When a staged approach was followed, clitoroplasty preceded vaginoplasty. Postponing surgery is a concept that is not reflected by our data: no change in the proportion of early surgeries over time could be identified, and there was no change in the probability of having early surgery over time. The current recommendation is to perform surgery only in cases of severe virilization (Prader III, IV, and V) [Hughes et al., 2006]. Wolffenbuttel and Crouch [2014] recommend one stage surgery for severely virilized genitalia and deferring surgery in milder cases whenever possible. Different expert opinion papers recommend early single-stage genital repair for girls with severe virilization, performed by experienced surgeons [Speiser et al., 2010; Yankovic et al., 2013]. On the other hand, non-surgical treatment or delayed surgery is considered to be an option for patients with a phenotypical genital variation. Recently, a study suggested deferring genital surgery in girls with 21-hydroxylase deficiency into adolescence as a feasible option. However, none of these girls have reached puberty so far [Bougnères et al., 2017]. On the contrary, there is information on individuals with complete masculinization, 46,XX karyotype, and CAH raised as boys, with some displaying gender dysphoria and some not. The social support seems to play a crucial role in the development of their sexual identity. de Jesus et al. [2019] reported a higher percentage of gender dysphoria in individuals with 46,XX CAH raised as males compared to those raised as females, 9 and 18.4% respectively, but with a confounding factor considering late diagnosis in most male-raised individuals [Lee et al., 2010; Khattab et al., 2017]. A consensus statement recently published stresses the importance of informed consent and a holistic, multidisciplinary care for the patients, and postponing the genital surgery until the individual is old enough to be actively involved in the decision whenever possible was advised [Cools et al., 2018].

Genital surgery has become the most controversial part of DSD management. Reconstructive surgery of the genitalia, historically thought to be in the individual's best interest by normalizing the phenotype and defining an acceptable gender role, has been appraised extremely critical over the years until in 2012 the UN Report of the Special Rapporteur on torture and other cruel, inhuman, or degrading treatment or punishment underlines the importance of non-discriminating, no forced gender-confirming surgery and specialized holistic care [Méndez, 2013]. Finally, in 2017 the Council of Europe published the resolution 2191 called "Promoting the human rights of and

eliminating discrimination against intersex people resolution” (available at <https://assembly.coe.int/nw/xml/XRef/Xref-XML2HTML-en.asp?fileid=24232&lang=en>) emphasizing the right of physical integrity in children or infants who are unable to give consent and whose gender identity is unknown. This practice has largely been adopted in DSD management. However, there is controversy whether this strict policy is also applicable to individuals with CAH raised as females: on one hand there is a tendency to exclude CAH from the umbrella term DSD (pushed by affected individuals themselves) and on the other hand the majority of individuals with CAH raised as females and their families still support early surgery [Deutsche Gesellschaft für Urologie (DGU) e.V., 2016; Szymanski et al., 2020; Shalaby et al., 2021].

In a recent German interdisciplinary consensus paper, adolescents and young women with CAH from a group of about 600 patients with CAH declared agreement with surgery performed early in childhood, and they do not consider early correction of urogenital sinus as cosmetic procedures [Krege et al., 2019]. Jesus [2018] also supports these findings. In a study performed in 2015 in the USA, only 219/573 (38.2%) received feminizing genitoplasty over a 4-year period of surveillance. Median patient age was <1 year at first procedure in the combined genitoplasty cohort and 74% of combined procedures were performed at <2 years [Sturm et al., 2015]. In other US centers management and timing of surgery differs significantly. In a study from 2010 it was shown that feminizing genitoplasty procedures were performed in 46% of girls and 60% of all procedures were performed by the age of 2 years [Da]justa et al., 2010].

Ethics of allowing parents to consent for genital surgeries that could permanently impair the genital sensation of the child are difficult [Schoer et al., 2018]. Due to the poor quality of data, our survey was not able to analyze trends whether media, society, religion, and others influence the decision-making process significantly. However, the role of cultural, religious, and social attitudes in the decision-making process as well as patients’ and parents’ opinion will require a more detailed investigation [Joint LWPES/ESPE CAH Working Group, 2002; Mouriquand et al., 2016].

Conclusion

In summary, our study shows no change of practice over time in feminizing genitoplasty in girls with 46,XX CAH. Global disease registries such as the I-DSD and I-

CAH registries represent an important resource for long-term monitoring of surgical practice and its outcomes. Inclusion of patient-reported outcome parameters in the I-DSD/I-CAH registries will be of tremendous importance in order to obtain feedback from individuals with DSD directly and not only through caring DSD teams.

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Statement of Ethics

Patient and/or parental consent was obtained prior to registration of cases in the I-DSD Registry. The I-DSD Registry is approved by the National Research Ethics Service of the UK.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Conception and design of the work: D.H., F.S.A., N.K., A.S. Data acquisition: D.H., F.S.A., N.K., C.K., J.B., S.A., R.O., M.L., N.B., W.B., H.C., E.C.C., S.P., L.V., C.E.F., T.G., F.B., A.G., V.I., B.K., J.-T.S., D.K., E.G., R.K., T.M., A.V., R.R., R.T.C., I.H., C.A. Data analysis and interpretation: D.H., F.S.A., N.K., C.K., A.S. Drafting the work or revising it critically for important intellectual content: D.H., F.S.A., N.K., C.K., A.S. Final approval of the version to be published and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: D.H., F.S.A., N.K., C.K., J.B., S.A., R.O., M.L., N.B., W.B., H.C., E.C.C., S.P., L.V., C.E.F., T.G., F.B., A.G., V.I., B.K., J.-T.S., D.K., E.G., R.K., T.M., A.V., R., R.T.C., I.H., C.A., A.S.

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