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JSM Sexual Medicine

Research Article

The North American Differences of Sex Development (DSD) Clinician Survey: Changes in Recommendations for 46, XX Congenital Adrenal Hyperplasia

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Submitted: 09 December 2022
Accepted: 20 December 2022
Published: 31 December 2022
ISSN: 2578-3718

Keywords
- Congenital adrenal hyperplasia
- Differences of sex development
- Decision-making
- Gender assignment
- Surgery
- Disclosure
- Clinical practice guidelines

Abstract

Background: Several aspects of clinical management of 46, XX congenital adrenal hyperplasia (CAH) remain unsettled and controversial.

Aim: The aim of the North American Disorders/Differences of Sex Development (DSD) Clinician Survey is to investigate changes over the last two decades in clinical recommendations among experts regarding the management of newborns with CAH.

Methods: Active members of the (Lawson Wilkins) Pediatric Endocrine Society (PES) and the Societies for Pediatric Urology (SPU) participated in a web-based survey at three timepoints: 2003-04 (T1), 2010-11 (T2) and 2020 (T3). Data from 432 participants in T1, 441 in T2, and 272 in T3 are included. The participants were presented with two clinical case scenarios (one with mild/moderate CAH and one with severe CAH) and asked for recommendations for the clinical management of each case.

Outcomes: The main outcomes assessed include recommended gender of rearing, surgical decision-maker (parent or patient), genital surgery timing, and age at which to disclose surgical history and karyotype to the patient.

Results: Most participants recommended rearing the newborn as a girl, that parents (in consultation with physicians) should make surgical decisions, performing early genitoplasty, and disclosing surgical history earlier. Several trends were identified: a small but significant shift toward recommending a gender other than girl in severely virilized CAH; including the patient with either mild/moderate or severe virilization in decision-making; performing surgery at later ages; and disclosing surgical details earlier.

Strengths and Limitations: This is the first study of its kind that monitors the clinical recommendations of physicians in the span of two decades. One limitation is whether responses to vignette-based clinician surveys do accurately reflect what they do in real-life settings.

Conclusion: Despite variability in the recommendations, most experts followed CAH clinical practice guidelines, and these did not change since 2003. While some of the emerging trends align with expert opinion and empirical evidence, others appear to be in conflict. In lieu of compelling evidence regarding best practices, shared decision-making should guide clinical care.

ABBREVIATIONS

CAH: Congenital Adrenal Hyperplasia; PES: Pediatric Endocrine Society; SPU: Societies for Pediatric Urology; CPGs: Clinical Practice Guidelines; DSD: Disorders/Differences of Sex Development

INTRODUCTION

Congenital adrenal hyperplasia (CAH) is an umbrella term for a group of disorders characterized by a mutation in one or more enzymes involved in the biosynthesis of adrenal hormones. In more than 95% of cases, the affected enzyme is 21-hydroxylase (21OH), and its reduced activity leads to decreased cortisol and aldosterone production and increased levels of androgens. The incidence of classic 21OH CAH has been reported to be 1:14,000 to 1:18,000. In patients with 21OH CAH and a 46, XX karyotype, increased prenatal androgens typically result in virilized genitalia at birth which creates several challenges for clinical teams and

parents in managing the psychosexual aspects of the affected newborn [1]. Challenges include, but are not limited to, decisions regarding the child's gender of rearing (particularly in severe cases where the genitalia are extremely virilized), when (if any) surgical interventions should be performed, and the age at which the child should be informed about the surgery they may have experienced during infancy. Considering the relative rarity of this condition and the lack of systematic, standardized, longitudinal assessment of health outcomes among patients with CAH, firm evidence-based answers do not exist for most of these decisions [2].

Disorders (or differences) of sex development (DSD) are defined as congenital conditions in which development chromosomal, gonadal, or anatomic sex is atypical [3]. Classic CAH – associated with genital virilization in females – is the most common cause of 46, XX DSD and is the most extensively studied DSD condition with regard to psychosocial and psychosexual outcomes. Individuals born with CAH have been the focus of study in multiple disciplines including social psychology [4,5], gender studies [6], feminism [7], sports [8], bioethics [9], and gender politics [10].

Regarding gender assignment, in an authoritative review, Speiser & White [11], stated that most females with CAH ultimately identify as women, echoing the evidence for a 2002 statement made by the Joint Workgroup of the Lawson Wilkins Pediatric Endocrine Society (North America) and the European Society for Pediatric Endocrinology that had recommended rearing females with CAH as girl [12]. In contrast, no specific gender of rearing was recommended in Endocrine Society clinical practice guidelines (CPGs) published in 2010 [13] and 2018 [2]. Instead, consultation with a mental health provider with specialized expertise in DSD was recommended for psychosocial issues, including gender assignment at birth, associated with DSD. Within the same month that the Endocrine Society 2010 CPGs were published, Houk and Lee [14], proposed consideration of male assignment for 46, XX patients who developed typical male external genitalia.

Regarding genital surgery and its timing, the 2002 consensus statement [12] recommended that surgery be performed in infancy, between 2-6 months. The consensus statements and CPGs that followed in 2010 [13], and 2018 [2] suggested that genital surgery be restricted to cases with severe forms of genital virilization (i.e., Prader stage 3 or greater), and in cases where a decision in favor of surgery was made, performing the procedure in infancy was recommended (Table 1). The 2018 CPG indicated counseling parents that the genital surgery can be postponed, particularly in females with minimal virilization. This CPG [2], also advised that timing of surgery in infancy should be discussed with parents in cases presenting with severe virilization. Finally, the CPG "advise (d) that all surgical decisions remain the prerogative of families (i.e., parents and assent from older children) in joint decision-making with experienced surgical consultants." [2] Worthy of note, all feminizing surgery recommendations in the 2018 CPG were labeled as an "Ungraded Good Practice Statement." [15], Timing of disclosing early medical interventions to the child was not addressed in any of these CPGs. Although not a CPG, per se, the 2006 Consensus Statement on Management of Intersex Disorders stated that "The process of disclosure concerning facts about karyotype, gonadal status, and prospects for future fertility is a collaborative, ongoing action that requires a flexible individual-based approach. It should be planned with the parents from the time of diagnosis" [3].

Growing cautiousness in the tone of clinical recommendations may reflect the inconclusive evidence supporting a specific approach. It may also reflect shifts in sociopolitical conceptualizations of sex and gender that have happened in the last two decades. It has been claimed, mostly by social science scholars, that gender is not an essential biologically-determined quality nor an inherent identity, rather, it is repeatedly performed and reinforced by societal norms; sex is similarly culturally constructed [16]. According to this doctrine, just as binary gender categories are maintained through social conditioning (via enforcing clear negative and stigmatizing consequences for failing to follow gender codes), binary sex categories are maintained by surgically reconstructing those who do not fit into the culturally constructed dichotomy of males and females [16,17] The example frequently used to support this notion is that the majority of newborns with "intersex traits" undergo surgery and are raised as either male or female, protecting and maintaining the binary construction of sex [18]. Based on these theoretical underpinnings, the United Nations [19], and the Commissioner for Human Rights of the Council of Europe [20] declared that the practices of early gonadal and genital surgery – which less than 10 years before were regarded as widely accepted clinical norms – are human rights violations and forms of torture. These statements and their theoretical foundations have been challenged by the American Medical Association and several other medical specialty organizations [21-24].

The aim of this study, which is part of a larger project, is to explore how medical and surgical experts whose specialties lie at the core of clinical management of CAH (i.e., pediatric endocrinology and urology), recommend managing various aspects of the clinical care of children born with 46, XX CAH, and how (if at all) these recommendations have changed over the last two decades. We investigate associations between participants' medical specialty and their clinical recommendations and hypothesize that the physicians' recommendations are based on the published CPGs at the time of the study.

MATERIALS AND METHODS

Participants

Active members of the (Lawson Wilkins) Pediatric Endocrine Society (PES) [1], and the Societies for Pediatric Urology (SPU), as listed in the respective membership directories, were targeted for participation at three timepoints: 2003-2004 (T1), 2010-2011 (T2), and 2020 (T3). Due to restrictions imposed by PES, recruitment for the 2020 wave of the survey was restricted to members who had previously been invited to participate in either 2003 or 2010. Inclusion criteria were 1) active membership of PES or SPU; 2) working within North America (US, Canada, Mexico); 3) having a specialty in endocrinology or urology; and 4) caring for patients with DSD. Unique survey links were emailed to a total of n = 706 (PES: 516; SPU: 190), n = 995 (PES: 777; SPU: 218), and n = 715 (PES: 434; SPU: 281) individuals in 2003,

Table 1: Evolution of clinical practice guidelines on gender assignment and feminizing surgery: 2002 to 2018.

Years	Gender Assignment	Surgery
2002-2003	Most females with CAH are heterosexual, and their sexual identity is almost invariably female [11].[a] Even in females with psychosexual problems, general psychological adjustment seems to be similar to that of females without CAH. Currently, there is insufficient evidence to support rearing a 46,XX infant at Prader stage 5 as male[12].	Early single-stage surgery between two and six months of life in girls with 21-hydroxylase deficiency, a time when the tissues are maximally pliable and psychological trauma to the child is minimized. Surgery during adolescence is often fraught with psychological and technical difficulties[11]. Based on recent clinical experience, the recommended time for surgery is at age 2–6 months; although, at present, this is not universal practice. It is important to note that surgery at this stage is technically easier than at later stages[12].
2010	We suggest that patients with CAH and psychosocial problems (such as gender assignment at birth) be referred to mental health staff with specialized expertise in managing such problems [13]. ⊕⊕◯◯ We propose consideration of male assignment for these 46, XX patients who have fully developed male genitalia based on available outcome data[14].	We suggest that for severely virilized (Prader stage 3) females, clitoral and perineal reconstruction be considered in infancy and performed by an experienced surgeon in a center with similarly experienced pediatric endocrinologists, mental health professionals, and social work services [13]. ⊕⊕◯◯
2018	For individuals with congenital adrenal hyperplasia and their parents, we recommend behavioral/mental health consultation and evaluation to address any concerns related to congenital adrenal hyperplasia[2]. ⊕⊕◯◯	In all pediatric patients with congenital adrenal hyperplasia, particularly minimally virilized girls, we advise that parents be informed about surgical options, including delaying surgery and/or observation until the child is older. (*Ungraded Good Practice Statement*). In severely virilized females, we advise discussion about early surgery to repair the urogenital sinus (*Ungraded Good Practice Statement*). In the treatment of minors with congenital adrenal hyperplasia, we advise that all surgical decisions remain the prerogative of families (i.e., parents Speiser et al Guidelines on Congenital Adrenal Hyperplasia and assent from older children) in joint decision-making with experienced surgical consultants (*Ungraded Good Practice Statement*).

Legend: The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) directs authors of guidelines to assess the quality of evidence behind each recommendation[42]: recommendations are classified as very low (⊕◯◯◯), low (⊕⊕◯◯), moderate (⊕⊕⊕◯) and strong (⊕⊕⊕⊕).

[a] This is not a clinical practice guideline but an authoritative review article describing CAH and its clinical management in 2003.

2010 and 2020, respectively (**Appendix A**, Participants [https://dx.doi.org/10.7302/6647]). The total number of eligible health providers who participated was n = 432 (PES: 300; SPU: 132) at T1; 441 (PES: 323; SPU: 118) at T2; and 272 (PES: 118; SPU: 154) at T3. Participation rates in T1, T2, and T3 were 58.1%, 41.6%, and 27.2% for PES members and 69.5%, 54.1% and 54.8% for SPU members. Of the total sample, 86 respondents participated at all timepoints.

Materials

Survey development: Provisional survey items were generated based on a literature review and focus groups conducted by conference call. Focus groups were convened to identify themes pertinent to the investigation and canvass opinion regarding optimal survey administration format. Focus group participants included 16 junior and senior PES and SPU members nominated for participation by colleagues who thought their opinions would be particularly informative; a geographically diverse sample was sought. Web-based administration to facilitate recruitment was the consensus of focus group participants. A preliminary survey was pilot tested with a subgroup of focus group participants with others checking for comprehensiveness of content coverage and survey response options. As such, focus group members were not eligible to participate in the actual survey. The final version of the survey comprised five sections: 1) *Demographics,* 2) *Clinical Case Presentations*, 3) *Factors Affecting Life Satisfaction*, 4) *Surgical Informed Consent*, and 5) *Mental Health Services and the DSD Team* (**Appendix A**: Survey Development). Data from sections 1 and 2 are presented in this report.

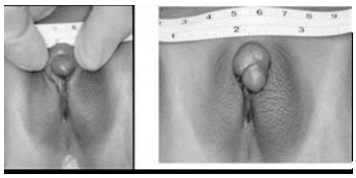
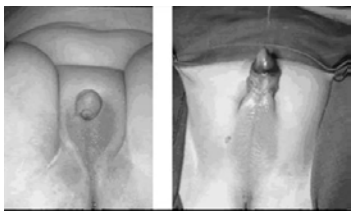
Demographics: This section focused on the participants' personal (gender: male / female / other; birth year) and professional (number of DSD cases seen annually and over one's entire career; specialty: endocrinology / urology; practice location: United States / Canada / Mexico / Other; and practice setting: solo or two-physician practice / group practice / HMO / medical school or hospital-based / other patient care employment / other non-patient care employment).

CASE PRESENTATIONS

This section comprised clinical vignettes, the first two of which involved 46, XX classic CAH: one with mild/moderate virilization and second with severe virilization (Table 2 and **Appendix A**: Survey Items). Main outcomes assessed include recommended gender of rearing, surgical decision-maker (parent or patient), genital surgery timing, and age at which to disclosure surgical history and karyotype to the patient.

Each case description was accompanied by color photos illustrating the degree of external genital virilization and followed by a series of multiple-choice questions asking for

Table 2: Clinician survey content overview.

Section	Survey Contents: Major Components	
Introduction	Overview of survey and eligibility screener[a]	
Demographics	Clinical practice and demographic characteristics	
Clinical Case Presentations	Cases:[b]	• Mild/Moderate CAH • Severe CAH
	Decisions:	• Gender of rearing[c] o *In your professional judgment, which sex assignment/gender of rearing would result in the best long-term quality of life outcome ['sex assignment' does NOT necessarily imply genital surgery]?* • Surgical decision maker o *Who should decide whether genital surgery (hypospadias repair) should be performed?* • Timing of surgery (lists case-specific procedures) o *In your professional judgment, when should genital surgery be performed?* • Timing of disclosing surgical history to patient o *Genital surgery is sometimes completed at an early age such that the boy will have no memory of the procedure. If surgery had been performed at such an age in the case of this particular patient, do you think that information regarding the details of the surgery or karyotype should be disclosed to the patient? If so, when?*
Cases[b]	**Clinical Case Presentations**	
Mild / Moderate CAH		Newborn with ambiguous genitalia identified by newborn screen and diagnosis of 21-hydroxylase congenital adrenal hyperplasia confirmed by Day 4. The clitoris was enlarged both in length (2 cm) and diameter, and there was partial posterior labioscrotal fusion.
Severe CAH		The child, announced as a boy at birth, is first referred to you at 3 weeks of age with a salt-wasting crisis. The phallic structure measured 3.5 cm with fusion of the labial-urethral folds to the distal shaft (i.e., distal hypospadias). The labio-scrotal folds were fused and "scrotalized" so that complete scrotal development was present. Workup reveals 46, XX 21-hydroxylase congenital adrenal hyperplasia.

Abbreviations: CAH = Congenital Adrenal Hyperplasia

[a] Survey overview and instructions were included in all years; Eligibility screen included at T3 (2020) only

[b] Labels "Mild/Moderate CAH" and "Severe CAH" are used here as shorthand to describe virilization; these were not displayed in surveys materials seen by participants

[c] Gender of rearing recommendations were asked for the Mild/Moderate CAH case at T3 (2020) and for Severe CAH in all years

recommendations regarding: gender of rearing (boy / girl / other); who should decide whether genital surgery should be performed (parents in conjunction with physician / patient, likely during adolescence); timing of genital surgery (before 6 months / before 1 year / before school entry / during pre-adolescence: ages 6-10 years / adolescence: 11 years or older / I would recommend against surgery); and the age at which to disclose surgical details if surgery had been performed at so early age that the patient would not have a memory of the procedure and the age at which to disclose karyotype to the patient (before school entry: 5 years / during middle childhood: 6-10 years / during adolescence: 11-17 years / during adulthood: 18 years or older / I would recommend against disclosure).

The survey was designed with automated conditional branching and skip patterns (**Appendix A**: Survey Components, Figure 2). Accordingly, responses to stem questions determined follow-up questions relevant to that choice alone: for example, those who chose "girl" option in response to "which sex assignment/gender of rearing would result in the best long-term quality of life outcome?" would only be presented with questions on how to manage a girl with CAH, and those who choosing the "patient" option in response to "who should decide whether genital surgery should be performed?" would not receive questions on timing of surgery, because including patients in the decision-making would necessitate a later timing of surgery. Although this branching and skip format more faithfully reflected actual clinical decision-making, it necessarily reduced the sample size for data analysis of particular items.

Across the three survey timepoints, limited changes were made to the case vignette response options for the gender of rearing question. For the mild/moderate CAH case, gender of rearing was not asked in 2003 nor 2010; follow-up questions regarding genital surgery and disclosure of presumed rearing as a girl. It was asked in 2020 for the mild/moderate case and

in all years for the severe case. In 2020, "other" was added as a response option alongside "girl" and "boy" for both cases. Those who chose "other" were not presented follow-up questions regarding genital surgery and disclosure.

Procedure

Invitation letters that included an explanation of the study and survey login instructions were sent to PES and SPU members in 2003-04, 2010-11, and 2020. Participants were also offered a paper-and-pencil version. To optimize recruitment, eligible respondents received up to three contacts follow-up requests to participate. After rates of survey completion dropped to minimal levels for several weeks, final requests for participation to non-responders took the form of a single-page letter encouraging participation or otherwise provide a reason for declining to participate. Through this process, it was learned that non-responders were frequently either retired, not in clinical practice, were exclusively involved in research, or were not providing care to patients with a DSD. Participants were promised confidentially of their responses; procedures were approved by Institutional Review Boards of the University at Buffalo School of Medicine and Biomedical Sciences and subsequently at the University of Michigan Medical School.

Data Analysis Plan

Participant demographic characteristics and responses to case vignette clinical management recommendations are summarized using descriptive statistics. Trends in recommendations and associations with the two main variables of interest (year of administration and provider specialty) and other participant characteristics (gender, age, clinical experience as measured by the number of cases per career, and practice setting), were examined using Generalized Estimating Equations (GEE). Accounting the correlation between multiple responses from the same respondent (clustering by respondent), GEE has been recommended as a method for modeling longitudinal and categorical data [25]. In the case of the gender of rearing question, the "other" option was added in 2020: to accommodate this change, gender assignment is dichotomized as "girl" vs. "not girl." Continuous data (e.g., physician age, and number of cases seen over the career) were dichotomized using a median split to address outliers and categorized as "younger vs. older" (cut point: the birthyear 1952) and "less vs. more experienced" (cut point: 50 cases).

Options for the timing of surgery were classified into three categories: "early" (within the first year), "late" (after the first year), and a recommendation against surgery. The timing of disclosure options was similarly classified into three categories: "early" (before 18 years), "late" (after 18 years), and a recommendation against disclosure. Practice setting comprised "medical school or hospital-based" vs. "other." For each item, the first model includes the predictor variables of survey timepoints, age, gender, specialty, practice setting, and clinical experience, and the second model includes the previous predictors in addition to the interaction between timepoints and specialty and timepoints. All analyses were conducted using the Statistical Package for the Social Sciences (SPSS) for Windows software, Version 28.0.

RESULTS

Demographic characteristics of participants

At all three time points, the majority of survey participants were male; this varied over time (Wald χ^2 = 13.180, p = 0.001; male percentage: T1: 71.3%, T2: 61.7%, T3: 69.1%). At timepoints 1 and 2, more participants were PES members; at timepoint 3, more were SPU members (Wald χ^2 (2) = 70.932, p < 0.001; PES percentage T1: 69.4%, T2: 73.2% and T3: 43.4%) (see Participants for the explanation of reduced recruitment of PES members in 2020). The majority reported their practice setting as medical school or hospital-based with no significant change in time (Wald χ^2 (2) = 5.357, p = 0.069; T1: 67.1%, T2: 73.5%, and T3: 77.9%). The mean age of participants at the time of participation increased in the 3rd survey (T1: 51.9 years; T2: 51.1; T3: 56.3). A significant interaction between the time and specialty was found (Wald χ^2 = 64.222, p < 0.001) in age, where urologists (T1: 51.5; T2: 54.3; T3: 54.1) were younger in T2 but older in T3 compared to endocrinologists (T1: 52.1; T2: 50; T3: 59.3). Participants' clinical experience, as measured by the number of patients seen during their career, was slightly less during the T2 survey (T1: 50; T2: 42.5; T3: 50; Wald χ^2 = 9.623, p = 0.008) with urologists reporting more experience with DSD than endocrinologists (Table 3).

Gender of Rearing Recommendations: Boy vs Girl vs Other(Figure 1)

Mild/Moderate CAH: Recommended gender assignment for this case was only asked in 2020. The majority (94%) recommended rearing the child as a "girl," 1% as a "boy," and 4% as "Other (e.g., Intersex, non-binary)." None of the predictor variables were statistically significant.

Severe CAH: Across study time points, most providers recommended rearing the child as a girl (T1: 85%; T2: 82%; T3: 66%), however, a statistically significant shift in time was evident toward recommending a gender other than girl (Wald's χ^2 (2) = 30.98, p < 0.001). The likelihood of recommending girl as a gender of rearing in 2003 was 2.7 times higher compared to 2020 (95% C: 1.86 to 4.07, p < 0.001), and in 2010 was 2.13 times higher compared to 2020 (95% CI: 1.54 to 2.94, p < 0.001). There was no significant difference between 2003 and 2010. No other predictor was statistically significant (Supplementary Table 1, https://dx.doi.org/10.7302/6647).

Surgical Decision-Making: Parents or Patients (Figure 2)

Mild/Moderate CAH:

Recommending rearing as girl: Although most recommended parents are responsible for decision-making at all three timepoints (T1: 87.5%; T2: 79%; T3: 67%), a statistically significant trend toward involving the patient was evident (Wald's χ^2 (2) = 50.79, p < 0.001). The likelihood of recommending including patient in decision making in 2020 was 2.61 times higher than in 2010 (95% CI: 1.85 to 3.7, p < 0.001) and 4.05 times higher than in 2003 (95% CI: 2.72 to 5.99, p < 0.001), and in 2010 was 1.54 times higher than in 2003 (95% CI: 1.11 to 2.16, p < 0.001). At all three timepoints, endocrinologists (T1: 16.3%;

Table 3: Participant demographic and professional characteristics at each survey time point.

		2003 (n=432)			2010 (n=441)			2020 (n=272)	
		n	%		n	%		n	%
Specialty	PES	300	69.4%		323	73.2%		118	43.4%
	SPU	132	30.6%		118	26.8%		154	56.6%
Gender	Male	308	71.3%		272	61.7%		188	69.1%
	Female	124	28.7%		169	38.3%		83	30.5%
	Other[a]	--	--		--	--		1	0.4%
Practice setting	Medical school or hospital	290	67.1%		324	73.5%		212	77.9%
	Other	142	32.9%		117	26.5%		60	22.1%
Practice country	United States	407	94.2%		417	94.6%		256	94.1%
	Canada	25	5.8%		24	5.4%		16	5.9%
		Mean	SD		Mean	SD		Mean	SD
Birth Year		1951.1	9		1958.9	10		1963.7	10
Clinical experience (DSD cases/career)		50	100		43	167		50	337

Abbreviations: PES = Pediatric Endocrine Society; SPU = Societies for Pediatric Urology; DSD = Differences/disorders of sex development; SD = Standard deviation

[a] "Other" was added as a response option in 2020

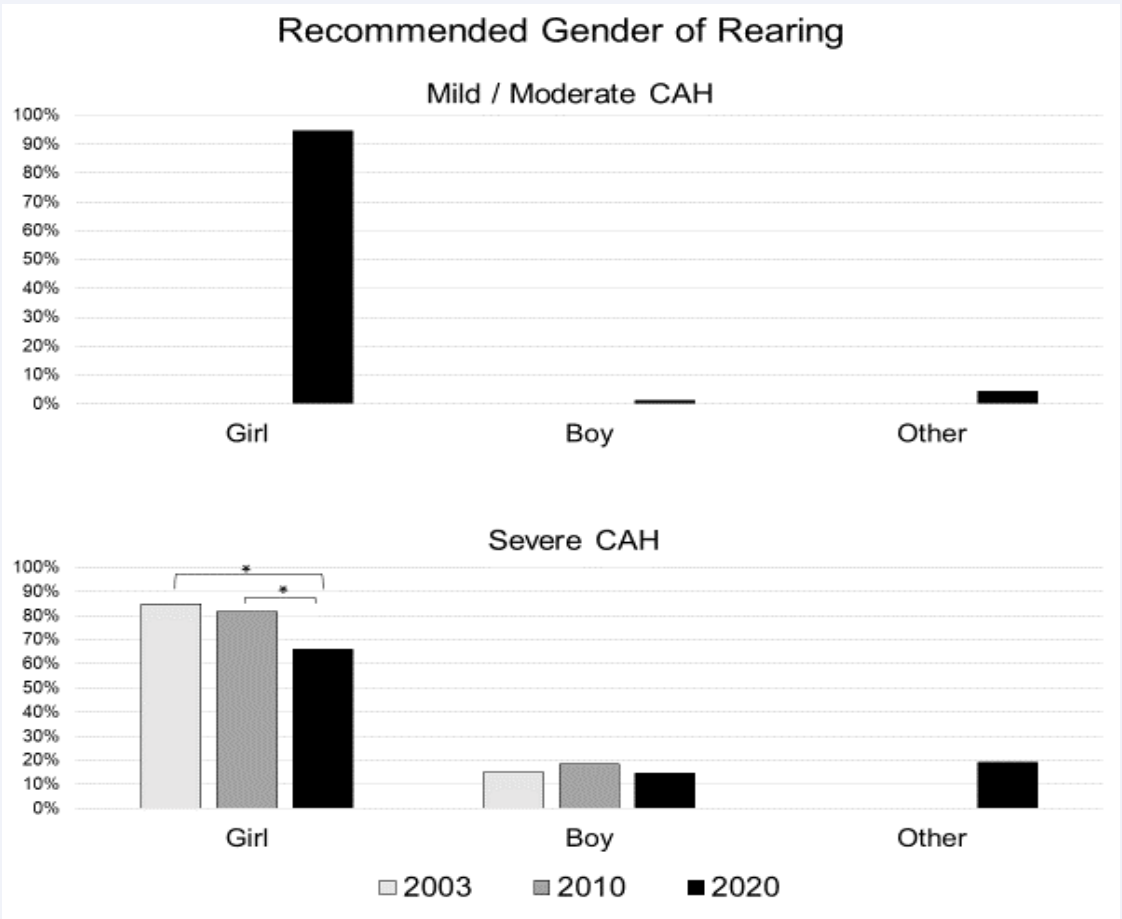


Figure 1. Recommended gender of rearing for CAH with mild / moderate and severe virilization. Gender of rearing was assessed in 2020 only for mild / moderate CAH; "Other" was added as an option in 2020 only for both cases; * Statistically significant between-group differences, $p<.001$

Figure 1

T2: 25.1%; T3: 50%) were more likely than urologists (T1: 3.8%; T2: 10.2%; T3: 20.1%) to recommend that patient should make surgical decisions (OR = 3.06, 95% CI: 1.96 to 4.78, Wald's χ^2 (1) = 24.11, $p < 0.001$) (Supplementary Table 2, https://dx.doi.org/10.7302/6647).

Recommending rearing as boy: Only 3 participants recommended this option: all recommended that parents in conjunction with physician specialists should make decisions.

Severe CAH:

Recommending rearing as girl: Most recommended that parents should make decisions at all timepoints (T1: 96%; T2: 89%; T3: 82%), but an increase in likelihood of including the patient in the decision-making process was also evident (Wald's χ^2 (2) = 24.90, $p < 0.001$). The likelihood of recommending including patient in decision making in 2020 was 2.11 times higher than in 2010 (95% CI: 1.26 to 3.57, $p = 0.005$) and 5.04 times higher than in 2003 (95% CI: 2.67 to 9.51, $p < 0.001$), and in 2010 was 2.37 times higher than in 2003 (95% CI: 1.36 to 4.14, $p = 0.002$). No other significant effects were detected.

Recommending rearing as boy: Most recommended that parents should make decisions about genital surgeries at each timepoint without any statistically significant change over time (T1: 75%; T2: 65%; T3: 51%). Compared to urologists (T1: 10%; T2: 36.4%; T3: 23.5%), endocrinologists (T1: 31.1%; T2: 34.5%; T3: 68.2%) were more likely to prioritize patients in decision-making (OR=2.67, 95% CI: 1.16 to 6.16, Wald's χ^2 (1) = 5.35, p = .021).

Surgical Timing Recommendations: Before or after one year of age (Figure 3)

Mild/Moderate CAH:

Recommending rearing as girl: At each timepoint, most recommended performing early genitoplasty/clitoroplasty (T1: 81%; T2: 79%; T3: 64%), although, a statistically significant decline was observed between T2 and T3 (Wald's χ^2 (2) = 13.45, $p = 0.001$). No other significant effects were detected. In contrast, when vaginoplasty was the surgical focus, an increasing percentage recommended early surgery (T1: 38%; T2: 49%; T3: 59%), although this change was not statistically significant.

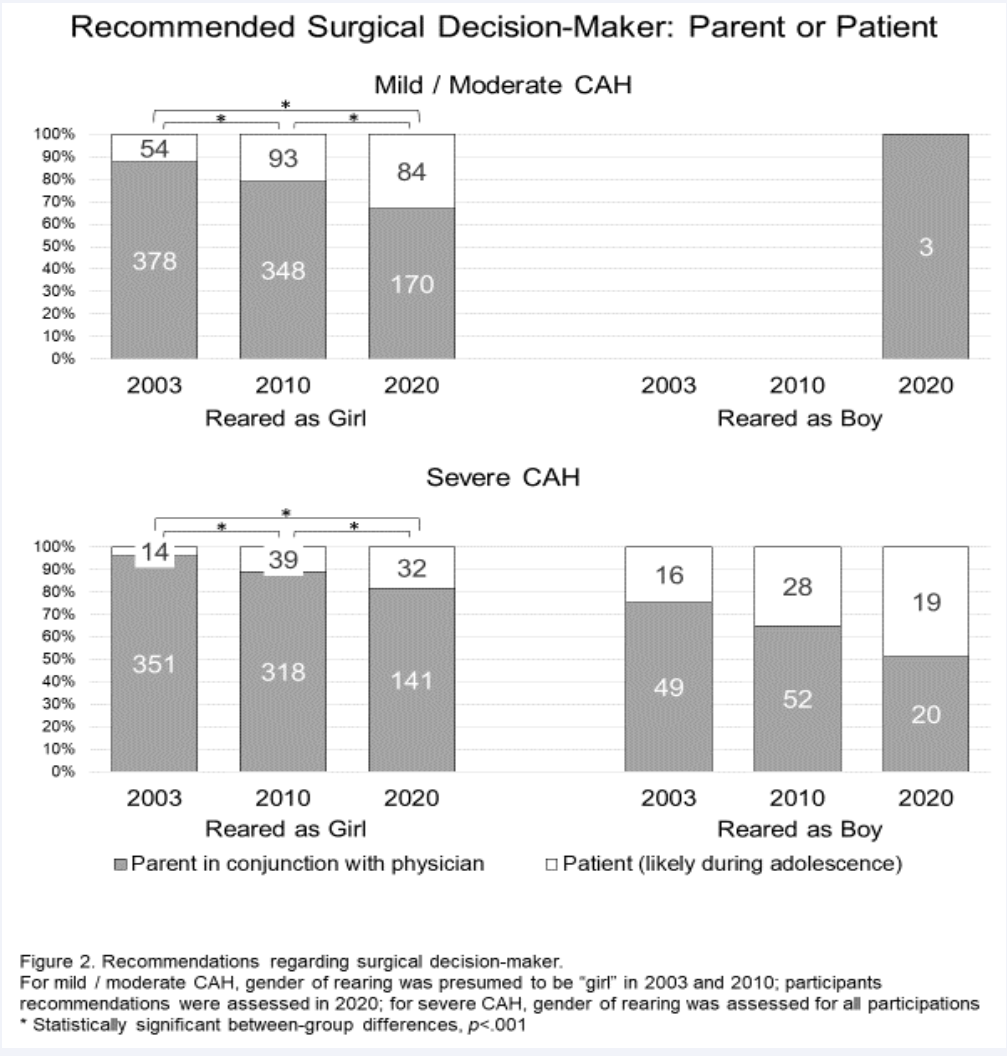


Figure 2. Recommendations regarding surgical decision-maker.
For mild / moderate CAH, gender of rearing was presumed to be "girl" in 2003 and 2010; participants recommendations were assessed in 2020; for severe CAH, gender of rearing was assessed for all participations
* Statistically significant between-group differences, $p<.001$

Figure 2

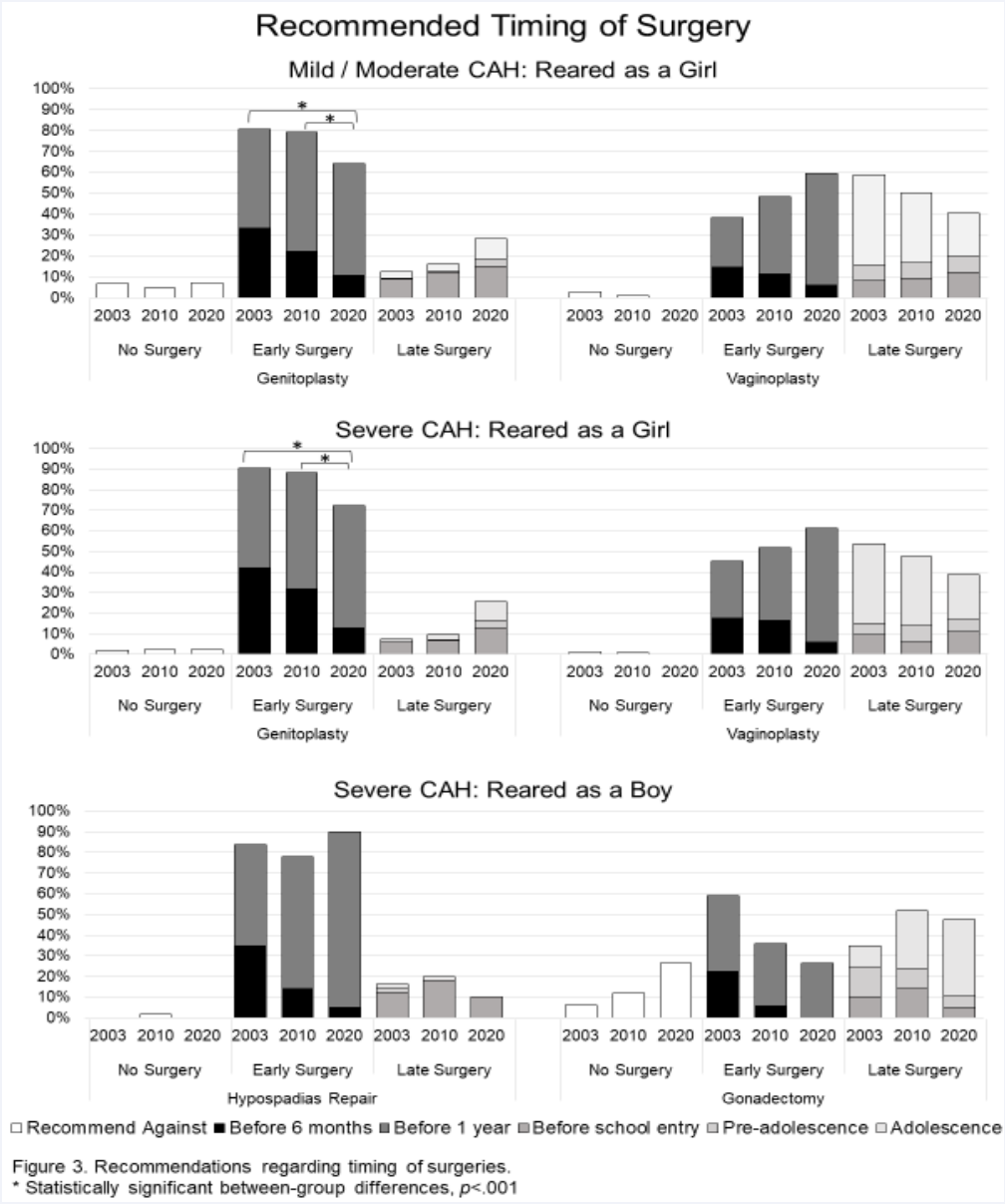


Figure 3

Urologists at each timepoint (T1: 61.4%; T2: 64.8%; T3: 65.5%) were more likely to recommend early vaginoplasty than endocrinologists (T1: 26.5%; T2: 41.5%; T3: 46.2%; Wald's χ^2 (1) = 17.21, $p < 0.001$).

Recommending rearing as boy: Among the three participants who recommended rearing this case as a boy, one recommended against any surgery and two recommended surgeries before one year.

Severe CAH:

Recommending rearing as girl: Most recommended early genitoplasty/clitoroplasty (T1: 90.6%; T2: 88.3%; T3: 72.1%); however, a statistically significant decline for this recommendation occurred over time (Wald's χ^2 (2) = 18.65, $p < 0.001$). No other predictors yielded statistically significant effects. In the case of vaginoplasty, early surgery trended toward being more frequently recommended over time (T1: 45.30%; T2: 52.10%; T3: 61.30%), although the increase was not statistically significant. Urologists (T1: 60.2%; T2: 65.5%; T3: 64.0%) were more likely than endocrinologists (T1: 38.6%; T2: 47.2%; T3: 56.9%) to recommend early vaginoplasty (Wald's χ^2 (1) = 6.52, p = .011). Similarly, male respondents (T1: 47.8%; T2: 57.1%; T3: 61.5%) were more likely than female respondents to recommend early vaginoplasty (T1: 38.3%; T2: 43.7%; T3: 60.6%; Wald's χ^2 (1) = 4.51, p = .034; Wald's χ^2 (1) = 6.63, p = .01).

Recommending rearing as boy: The majority recommended early hypospadias repair surgery with no statistically significant change over time (T1: 84%; T2: 78%; T3: 90%). Male respondents (T1: 88.2%; T2: 82.8%; T3: 93.3%) were more likely than female respondents to recommend early surgery (T1: 73.3%; T2: 71.4%;

T3: 80%) at each timepoint (Wald's χ^2 (1) = 6.06, p = .014). No other significant differences were detected.

Regarding gonadectomy, there was a decrease in the proportion of those recommending early gonadectomy (T1: 59%; T2: 36%; T3: 26%), but this apparent trend was not statistically significant. Male respondents (T1: 61.8%; T2: 42.9%; T3: 35.7%) were more likely than females to recommend early gonadectomy (T1: 53.3%; T2: 27.3%; T3: 0%) (Wald's χ^2 (1) = 4.23, p = .04). No other significant effects were found.

Disclosing Early Surgery and Discordant Karyotype (Figure 4)

Mild/Moderate CAH

Recommended rearing as girl: At each timepoint, most respondents recommended disclosure before the patient reaches 18 years old (T1: 88%; T2: 94%; T3: 96%) with a significant increase over time (Wald's χ^2 (2) = 6.41, p = .041). No other statistically significant effects were detected.

Recommending rearing as boy: All three participants recommending male gender assignment also recommended disclosing the karyotype and history of early surgical procedures to the patient before 18 years of age.

Severe CAH:

Recommended rearing as girl: At each timepoint most respondents recommended early disclosure of surgeries (T1: 88%; T2: 95%; T3: 97%) with a statistically significant increase across survey waves (Wald's χ2 (2) = 16.84, p < 0.001). No other significant effects were found.

Recommending rearing as boy: At each timepoint, most respondents recommended early disclosure (before 18 years of age) of early surgeries (T1: 88%; T2: 96%; T3: 97%) and the patient's chromosomal sex (T1: 68%; T2: 86%; T3: 90%). No other statistically significant effects were detected.

Sub-sample participating in all three surveys

Eighty-six participants participated in all three surveys. The median birth year of these participants was 1957, 55.8% were members of PES and, 75.6% identified as men. In brief, there was a decline in recommending a female gender assignment for Case #2, severe CAH (T1: 84.9%; T2: 75%; T3: 68.2%; Wald's χ^2 (2) = 6.939, p = .031); an increase in involving the patient in decision-

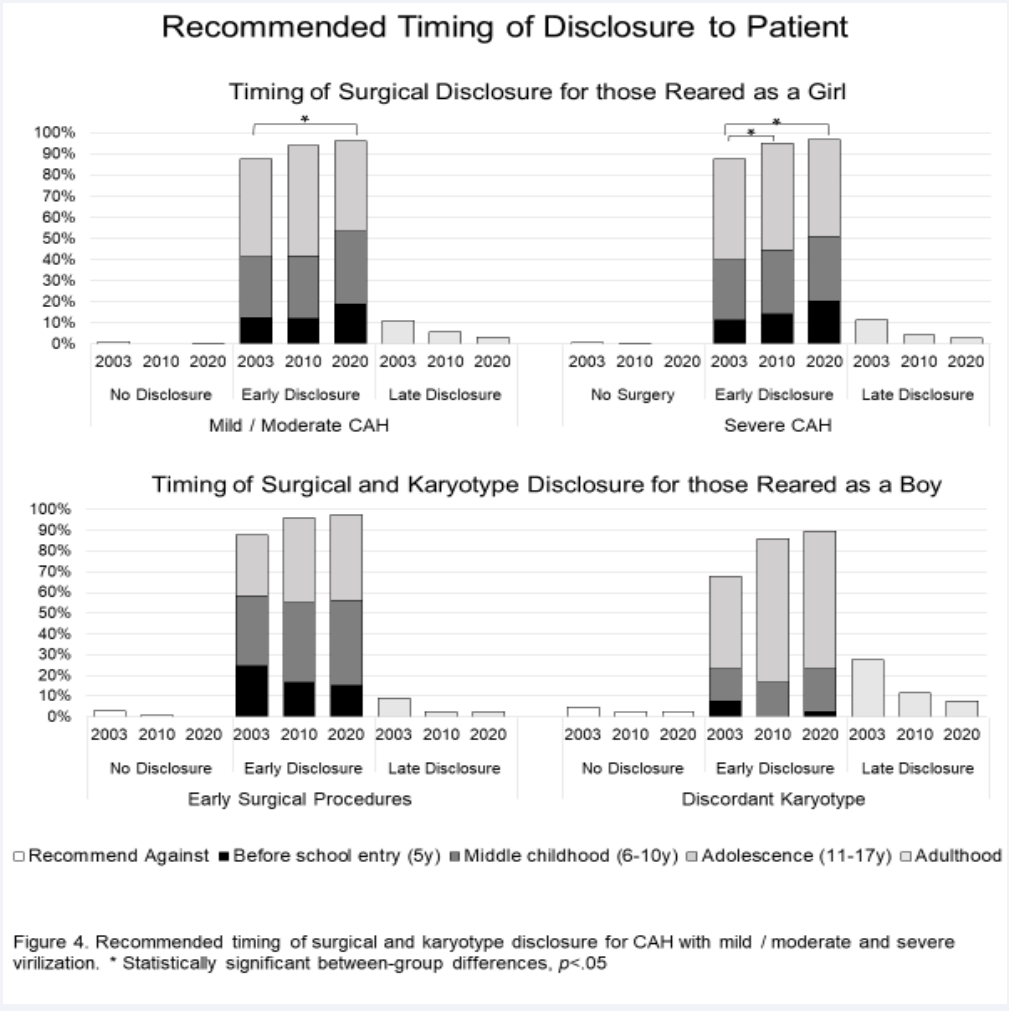


Figure 4. Recommended timing of surgical and karyotype disclosure for CAH with mild / moderate and severe virilization. * Statistically significant between-group differences, p<.05

Figure 4

making for both cases when the recommendation was to rear as a girl (mild/moderate: T1: 15.1%; T2: 18.6%; T3: 32.5%, Wald's χ^2 (2) = 13.103, p = 0.001; severe: T1: 4.1%; T2: 11.1%; T3: 15.8%; ns); a decrease in recommending early surgery for both cases when rearing as a girl was recommended (mild/moderate: T1: 89%; T2: 82.6%; T3: 62.3%, Wald's χ^2 (2) = 6.656, p = .036; severe: T1: 92.9%; T2: 92.9%; T3: 68.8%, Wald's χ^2 (2) = 10.813, p = .004); and an increase in recommending early disclosure for both cases reared as girls (mild/moderate: T1: 94.2%; T2: 92.9%; T3: 95.1%, ns; severe: T1: 94.5%; T2: 93.7%; T3: 96.5%, ns).

DISCUSSION

At three timepoints, spanning two decades, this survey focused on North American pediatric endocrinologists and urologists assessed clinical recommendations for two cases of 46, XX CAH – one with mild/moderate and the other with severe virilization of the external genitalia. For both cases, the substantial majority of participants recommended rearing as a girl. For the severely virilized case, there was a statistically significant increase over time in those recommending a gender other than girl. Regarding the contentious topic of elective genital surgery, the majority at all three timepoints, and for both the mild/moderate and severe cases, recommended that the parents arrive at a decision (in conjunction with the physician) and that early surgery is preferred; yet an increase over time was detected in the proportion of participants recommending that the patient be the one to decide on surgery rather than the parents and physicians. Moreover, a significant increase was observed in the proportion recommending that surgery occur at later ages. In addition to changes in time, urologists were more likely to recommend parent as decision maker, and an earlier time for vaginoplasty, compared to endocrinologists at each timepoints. These findings suggest that although most participants recommend actions that follow CPGs, there are growing trends either inconsistent or in opposition to those guidelines.

Gender assignment

A statistically significant increase in recommending a gender other than girl was observed across survey timepoints. Although only 5% of respondents in 2020 recommended rearing the child with mild/moderate virilization as "Other (e.g., Intersex, non-binary)," approximately 20% in 2020 recommended this option for the severely virilized case. To the best of our knowledge, there are no published studies on the long-term psychological adjustment of people reared as other than "boy" or "girl." If the findings from the survey are observed in actual clinical practice, then research should be undertaken to compare outcomes of patients with 46, XX CAH reared as girls, boys, or other gender (intersex or nonbinary). Because the gender of rearing option of "other" appeared only in the T3 survey, we can only speculate whether any participants would have recommended this option for either case in previous years. However, it would be a mistake to assume that it had been an oversight to not have included this option at the earlier timepoints. In fact, a prominent leader of the intersex advocacy movement stated in 2003 that "All children should be assigned as male or female, without surgery" [26], (p. 240) and the 2006 Consensus Statement on Management of Intersex [3], which included two members of the intersex advocacy community (one from the US and the other from Europe) made no mention of rearing a child with a DSD as other than male or female.

Surgical decision-making

The majority of survey participants recommended that parents should be the primary authority for surgical decision-making. Nevertheless, a trend was observed in recommending that this authority be transferred to the patient, when older. Also, endocrinologists were more likely than urologists, to recommend including patients in the decision-making. One important point to keep in mind is that including patients in decision-making inevitably means declining early surgery; accordingly, the reason for the respondents choosing parents instead of patients as the authority for decision-making may have more to do with claimed surgical outcome benefits of early surgery [27, 28.27, 28]. These patterns were also observed in the smaller sample of those participating in all three surveys.

White papers on pediatric decision-making published by the Council on Ethical and Judicial Affairs of the American Medical Association support the recommendation of the majority of our respondents regarding the authority of parents in making decisions on behalf of their young children [24, 29]. The Endocrine Society's most recent CAH CPGs [2], similarly recommended that "In the treatment of minors with congenital adrenal hyperplasia, we advise that all surgical decisions remain the prerogative of families (i.e., parents and assent from older children) in joint decision-making with experienced surgical consultants" (Recommendation 7.3). Although this recommendation was categorized as an "Ungraded Good Practice Statement" [15], it is clear that the type of studies required to settle the question of decision-making authority based on long-term health and quality of life outcomes –randomized clinical trials – are unlikely ever to be performed.

Surgical timing

According to the Endocrine Society's most recent CAH CPGs [2], "In all pediatric patients with congenital adrenal hyperplasia, particularly minimally virilized girls, we advise that parents be informed about surgical options, including delaying surgery and/or observation until the child is older. (Ungraded Good Practice Statement)" (Recommendation 7.1). Although in our sample, most recommended early genitoplasty for girls with CAH, a shift toward postponing genitoplasty/clitoroplasty was evident: in the mild/moderate case, 127 out of 432 (29.4%) in T1, 165 out of 441 (37.4%) in T2, and 143 out of 254 (56.3%) in T3 recommended either late surgery (including those recommending the patient as the decision maker) or were opposed to any surgery. In the severe case, out of those who had recommended a girl gender of rearing, 47 out of the 365 (13%) in T1, 76 out of 357 (21%) in T2, and 71 out of 178 (40%) in T3 recommended either late surgery (including those recommending the patient as the decision maker) or were opposed to any surgery. In contrast, the percentage of those recommending early vaginoplasty for both cases was increasing in time, although not statistically significant. It comports with the 2018 recommendation "In severely virilized females, we advise discussion about early surgery to repair the urogenital sinus. (Ungraded Good Practice Statement)" (Recommendation 7.2).

A recent review of surveys among samples of patients with DSD regarding their opinions on the timing of genital surgery, demonstrates that banning genital surgery in early age is in sharp contrast with what the clear majority of patients actually prefer [30]. For instance, a survey of 14 DSD-specialized clinics in six European countries reported that 46% of the 173 participants with CAH believed that surgeries should be performed in infancy (before 6 months of age) and an additional 20% believed surgeries should be performed in childhood. Less than 10% stated that the surgeries should be done in "adulthood" (5%) or "at any age the patient decides" (4%) [31]. Emphasizing the preference for early surgery even further, 74% of 151 female participants with CAH who had received surgeries, disagreed with the sentence, "I think I would have been better off without any of the surgeries performed in my childhood/adolescence," and 51% of them disagreed with the sentence, "Any decision about surgical procedures should be postponed until the affected person reaches the age of legal responsibility" [31]. The contrast between emerging trends among clinicians and the findings from studies of adults who had received early genital surgery suggests that the shift in recommendations may be based more on the dissemination of intersex activist messages in various media and efforts at legislating bans on early elective genital surgery (for example, proposed California legislation [32]). Even if adults who had received such procedures express a preference for the procedures being performed before they could provide assent or legal consent, it may be understandable that clinicians are less likely to recommend an option which has been equated by the United Nations to "torture" [18-20].

Our findings, although based on surveys and hypothetical clinical cases, there is some limited evidence that a trend toward delaying genitoplasty is occurring in actual clinical practice: a chart review study at a single Midwestern tertiary care medical center found that, between 1979 and 2013, a linear decline in the rate of clitoroplasty in CAH patients which the authors attribute to the "power of patient advocacy" [33].

Disclosure

An area of tension voiced by intersex advocates concerns failures to fully share information with the patient. From the earliest stages of the intersex advocacy movement, "honest, complete disclosure" was recommended as a strategy to prevent the patient from experiencing their medical condition as shameful [26]. Because genital surgery is often completed at an early age such that children may have little memory of procedures, survey respondents were given the opportunity to recommend the age when information about genital surgery (genitoplasty/hypospadias repair or vaginoplasty) should be shared with the patient. In our study, regardless of condition severity and gender assignment, most recommended early disclosure at all three timepoints. Moreover, a significant increase in favor of earlier disclosure was detected for both cases such that by 2020, this recommendation was almost universal. In addition to the calls from intersex activists, empirical evidence supports the value of early disclosure: data from 903 individuals with DSD obtained from 14 DSD clinics in Europe demonstrated that openness about the condition is associated with better mental health, lower anxiety, and depression [34].

LIMITATIONS

The findings of this study need to be considered within the context of its limitations. One potential limitation to consider is the participation rates. At T1, 58% and 69% of the pediatric endocrinologists and urologists, respectively, participated. These proportions fell to 42% and 54% at T2, and 27% and 56% in T3. The relatively high percentage of non-responders may suggest the risk of non-response bias. Notwithstanding the substantially lower participation rate among endocrinologists in the T3, the proportion of eligible participants completing our surveys is actually higher than studies also targeting members of both the PES [35,36] and SPU [37]. Very few studies have reported higher participation rate (for example, [38]). A meta-analysis of surveys has shown that the mean participation rate in those using email is 33% and in those using traditional mail is 53%,[39] and according to a systematic review of response rates in patient and health care professional surveys in surgery, the average response in 1,746 surveys on clinicians was 53% [40].

As in any other survey study, there are also concerns that responses to vignette-based clinician surveys do not accurately reflect "real world" decision-making. A defense of this methodology goes beyond the scope of this report; however, as noted above, there is emerging evidence that trends observed in our survey are mirrored in studies suggesting similar changes in ongoing care. More generally, studies of clinician judgements and decision-making using vignettes have been shown to be generalizable [41].

CONCLUSION

Despite variability in the recommendations, the majority of expert responses follow CAH CPGs. However, there are growing trends for some decisions which are at odds with these. There is a slowly growing trend to recommend rearing a child with severe 46, XX CAH in a gender other than boy or girl, as well as to perform genital surgery later in life. Given that evidence or expert opinion is lacking regarding the wisdom of these trends, it remains to be seen whether these trends are evident in real life clinical management and, if so, whether they will result in better outcomes for patients compared with current standards of care.

ACKNOWLEDGMENTS

The authors would like to thank Dr. Leona Cuttler, who passed away in 2013, for her collaboration in authoring T1 survey components; providers who participated in focus groups and survey beta-testing, which informed initial survey development; John Roden for T1 survey programming; Lauren Zurenda for T1 recruitment and project management; Rachel Hatfield and Tola Oyesanya for T2 survey programming and recruitment; Kristina Suorsa-Johnson for T3 survey programming and recruitment; and Karl Bosse and Acham Gebremariam for statistical consultation.

FUNDING/SUPPORT

The (Lawson Wilkins) Pediatric Endocrine Society provided funding for the T1 survey. The T2 survey was partially funded by the Albany Medical Center Falk Family Endowment in Urology. Sandberg's efforts were also supported, in part, by grants R01 HD068138 and R01 HD093450 (the DSD-Translational Research

Network) from the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development.

ARTICLE SUMMARY

In 3 successive surveys targeting pediatric endocrinologists and urologists across two decades, this study explores changes in recommendations on how to manage controversial aspects of 46, XX congenital adrenal hyperplasia (CAH).

WHAT'S KNOWN ON THIS SUBJECT?

CAH clinical practice guidelines provide recommendations regarding gender of rearing and genital surgery. These recommendations are increasingly at odds with sociopolitical movements.

WHAT THIS STUDY ADDS

This study identifies trends in clinician's recommendations corresponding with ideological pressures that are only partially supported by expert opinion or clinical evidence.

DATA SHARING STATEMENT

DE identified individual participant data (including data dictionaries) will be available. The data will be made available upon publication to researchers who provide a methodologically sound proposal for use in achieving the goals of the approved proposal. Proposals should be submitted to dsandber@med.umich.edu.

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