Title Declining Rate of Clitoroplasty in 46,XX Patients with Congenital Adrenal Hyperplasia: A Retrospective Chart Review

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Key Points

Question Did a 2006 consensus statement for surgical management of intersex infants, developed with input from a patient advocacy group, influence clinical practice?
Findings Retrospective chart review of 60 46,XX infants with congenital adrenal hyperplasia born between 1979-2013 showed a linear decline in patients treated with clitoroplasty.
Meaning Guidelines developed with input from patients can successfully change surgical practices.

Abstract

Importance Prior to the 1990s, most 46,XX infants with clitoromegaly secondary to congenital adrenal hyperplasia were treated with feminizing genitoplasty to make their cosmetic appearance congruent with their genotypic sex. In the mid-1990s, adult females who were unsatisfied with the results of their infant genital surgery used the internet to their advantage. They found each other and gained a voice to advocate for change in the surgical management of virilized female infants. A 2006 consensus statement for management of intersex disorders accepted input from patient advocates and did not support purely cosmetic surgery for clitoromegaly. This study examines the extent to which the desired change was implemented in practice.

Objective To compare the percentage of 46,XX infants with virilizing congenital adrenal hyperplasia who received genitoplasty surgery prior to and subsequent to the publication of the 2006 consensus statement for management of intersex disorders.

Design Case series generated by retrospective electronic chart review of subjects born between 1979 and 2013 and seen since 1995.

Setting Single Midwestern tertiary care academic medical center.

Participants All 46,XX patients with documented diagnosis of congenital adrenal hyperplasia and at least one visit with pediatric endocrinology, gynecology, or urology service in the medical record.

Exposure Genital surgery

Main Outcome Measure(s) Presence of genito-urinary abnormalities, performance of genital surgery, need for additional surgeries, complications

Results Of the 45 virilized patients, 40 had clitoromegaly and 39 had a urogenital sinus or posterior labial fusion. Twenty-seven patients (67.5%) underwent clitoroplasty and 33 (84.6%) underwent perineoplasty (including vaginoplasty, urethroplasty, imperforate vagina repair, and/or posterior labial fusion repair). We observed a linear decline in the rates of clitoroplasty for patients born in 1979 through 2013.

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Conclusions and Relevance
The percentage of virilized female infants with CAH who received clitoroplasty declined steadily between 1979 and 2013. This change demonstrates the adoption of updated clinical practice recommendations that were developed with input from former patients. Our data represents an early example of the influence of patient advocacy to improve clinical practice.

Introduction

Classical congenital adrenal hyperplasia (CAH) is an autosomal recessive enzymatic disorder that leads to adrenal insufficiency in approximately 1:15,000 of the population. More than 95% of cases are caused by 21-hydroxylase deficiency, which is characterized by defective mineralocorticoid and glucocorticoid synthesis.[1] Precursors to cortisol and aldosterone accumulate and are shunted toward androgen production, starting in fetal life. The prenatal excess of androgens results in the virilization of 46,XX infants.

Historically, 90% of 46,XX patients who presented with ambiguous genitalia due to various etiologies were all treated with feminizing genitoplasty.[2] Surgical management of this population was guided for decades by a theory published by John Money in 1955, who proposed that infants are sexually neutral until they reach 2 years old. Thus, early feminizing surgery along with enculturation into a female gender role by the parents was thought to *create* a female gender identity.[3] In the case of virilized 46,XX infants with CAH, this practice did not likely influence their gender identity. This is because despite the exposure of the fetal brain to high levels of testosterone, studies show that these infants demonstrate a female gender identity in 95% of cases, even where there is significant virilization.[4,5] Feminizing genitoplasty, which is still practiced today, makes the genital appearance cosmetically more like unaffected female infants. There can be significant problems after genitoplasty, however, most prominently the loss of normal innervation of the clitoris and perineum. Attention was brought to this issue in the early 1990s when protests to Money's theory gained momentum. The movement was catalyzed and predominantly led by Cheryl Chase.[6]

Chase was born in 1956 as Charlie Sullivan, a baby with ambiguous genitalia. She underwent feminizing genitoplasty and clitorectomy at 18 months old. Her family spoke of it to no one, including Chase. At age 21, after years of anorgasmia, shame, secrecy, and lies by her family, physicians, and therapists, she finally gained access to her own medical records to learn about her birth and surgical history. She endured years of emotional distress and deep depression due to the surgeon who had "mutilated" her without her consent.[2]

In 1993, Chase established the Intersex Society of North America (ISNA) and became an active advocate for the elimination of infant genital surgery.[6] Views on intersexuality that she was combating at that time were very different from what they are now. Intersexuality was considered "a treatable condition of one's genitals, one that needed to be resolved expeditiously."[7] A major focus of treatment was commonly to alleviate the parental distress of dealing with a child with ambiguous genitalia, without thorough consideration of the long-term outcome of the infant.[7] In 2008, ISNA was dissolved and the current organization fulfilling the advocacy needs for people with DSDs is the Accord Alliance.[8]

In 1995, Chase created a website that brought members of this rare population together.[6] The Internet gave the intersex population, previously an underrepresented group in the medical literature, a voice for change in the surgical management of their conditions. Throughout the late 1990s and early 2000s, Chase and ISNA advocated for decreased performance of infant genitoplasty by creating educational videos, picketing outside of hospitals, and giving presentations at medical symposiums.[2,9] Their personal testimonies and strong advocacy culminated in a change in the established surgical guidelines.

In 2006, in response to ISNA raising awareness of the potential late morbidities from

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feminizing genitoplasty, the former Lawson Wilkins Pediatric Endocrine Society (LWPES), now known as the Pediatric Endocrine Society (PES), and the European Society for Paediatric Endocrinology (ESPE) jointly published a consensus statement. They recommended against infant clitoroplasty in girls with CAH, unless they were severely virilized (Prader 3 or greater). Emphasis was placed on avoiding any genital surgery in 46,XX infants for purely cosmetic reasons in favor of maximizing sensation and erectile function.[10]

The new guidelines make it clear that ISNA has influenced the opinions of medical experts regarding considerations for care of infants with ambiguous genitalia as well as their surgical management. However, the extent of the impact of this patient advocacy has not been measured since before the 2006 consensus statement.[11] We hypothesized that the rates of infant clitoroplasty would have begun to decrease in the 1990s, preceding this consensus statement as the views of ISNA became known to the medical community and would have decreased further as a result of its publication. In this study, we examined the data from 1979 to 2013 to see if the recommendations were indeed implemented and to what extent performance of clitoroplasty was decreased.

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Methods

The subjects in this study were identified via ICD 9 or ICD 10 code. They represent all 46,XX infants with CAH due to either 21-hydroxylase (21OH) deficiency or 11β-hydroxylase (11OH) deficiency who were treated at Washington University Medical Center since 1995 and were born between 1979 and 2013. A retrospective chart review was performed, collecting the birthdate, demographic data, age at follow-ups, degree and type of virilization, as well as the dates, types, and complications of surgery.

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A subject was classified as virilized if she presented in infancy with ambiguous genitalia including clitoromegaly, a perineal anomaly, or both. A subject was considered to have a perineal anomaly if she had a persistent urogenital (UG) sinus, a posterior labial fusion, or both. Lesser genital anomalies that were also quantified included hyperpigmented and rugated labia.

The records of virilized subjects were examined for genitoplasty, including clitoroplasty and perineoplasty. Clitoroplasty included clitoral reduction and recession. Perineoplasty indicated the performance of a vaginoplasty, urethroplasty, imperforate vagina repair, or posterior labial fusion repair.

The outcomes after perineoplasties were grouped both by age at first surgery and by whether the initial surgery required revision(s). For classification into these groups, strict adherence to the contents of the medical record was used. Additionally, we quantified the occurrence of urinary tract infections (UTIs) in subjects with a UG sinus.

We entered these data into a database and managed it using REDCap electronic data capture tools.[12] This study was approved by the Human Research Protection Office of Washington University School of Medicine.

Statistical analysis:

For the analysis of the declining rates of clitoroplasty, Fisher’s exact test and Kendall’s tau (rank correlation coefficient) were used. Two-tailed p-values were calculated and considered significant if < 0.05. For the comparisons of clitoral measurements, a student’s t-test was used.

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Results

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Description of cohort (Figure 1)

There were 60 46,XX subjects with CAH. Birth years ranged from 1979-2013. Forty-seven (78%) presented with classic CAH, indicating diagnosis in early infancy, and thirteen (22%)

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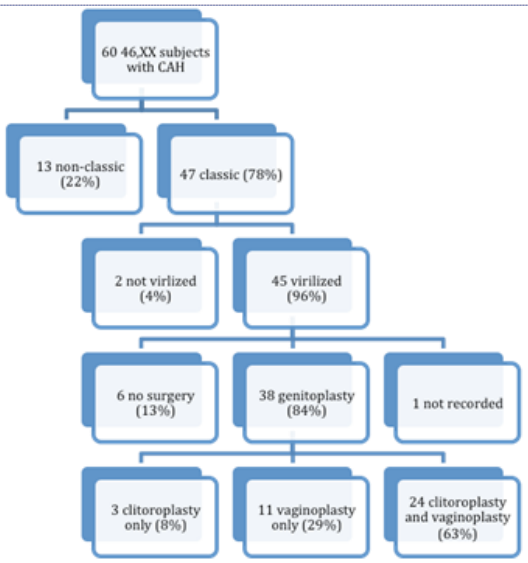
presented with non-classic CAH (see table 1). Among those with classic CAH, 45 were virilized at birth. Forty-two virilized subjects (93%) had 21-OH deficiency and three had 11-OH deficiency. Thirty-eight of 42 patients with 21-OH deficiency (90%) had salt-losing CAH, and 4 had simple virilizing CAH. Of the 45 CAH patients who were virilized, 36 (80%) presented with both clitoromegaly and a perineal anomaly. Three had clitoromegaly only, and three had a perineal anomaly only. An additional three were not fully classified (one had a UG sinus but unknown clitoral size, one had clitoromegaly but unknown perineal anatomy, and one had insufficient description of anatomy for classification). Of the 39 with a UG sinus, 14 (36%) had an additional perineal anomaly: five had hyperpigmented labia, two had rugated labia, and seven had both.

Figure 1. Classification of our CAH population based on type, virilization, and surgery



Clitoroplasty

Clitoromegaly was described in 40 of the 45 virilized patients; and 27 had a clitoroplasty performed (67.5%). The age at clitoroplasty ranged from one week old to 11 years old, with a median age of 7 months. Five subjects had clitoroplasty at >1 year of age, and surgery was performed at 1.5, 1.5, 2, 3, and 11 years old.

The patients were grouped by birth year and evaluated for the occurrence of clitoroplasty (Table 2). The groups did not differ in the number of subjects included. We found a significant decrease in the number of clitoroplasties performed in the later cohort as compared to the earlier one (Fisher's exact p-value = 0.035).

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Table 2. Rates of clitoroplasty for the early and late cohorts, p = 0.035

	Clitoroplasty	No Clitoroplasty	Total
Birth years 1979 – 1998	17	3	**20**
Birth years 1999 – 2013	10	10	**20**
Total	**27**	**13**	**40**

Using the five cohorts based on birth year, we observed a linear decline in performance of clitoroplasty. The decrease is approximately two-fold over the course of 35 years, starting from nearly 100% in the early 1980s and falling to < 50% in the past decade (see Figure 2).

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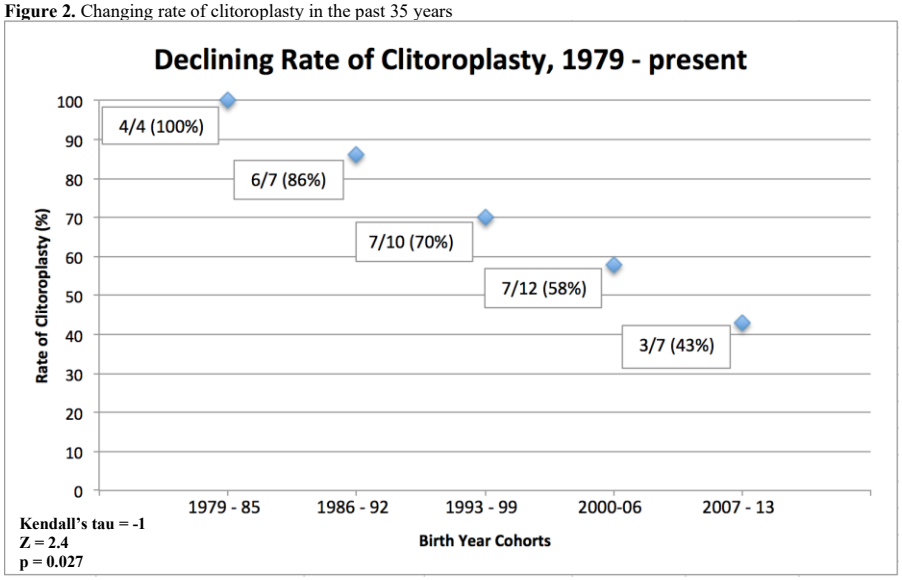
Figure 2. Changing rate of clitoroplasty in the past 35 years



Clitoral size was recorded in 21 virilized subjects. Clitoral length was reported in 20 and width was reported in 11. Nineteen of the 20 length measurements were used for significance testing, and they ranged from 0.75 cm to 3.3 cm. One outlier length of 6 cm was not included in the calculations. Average clitoral length and width for the surgery group was 2.2 cm and 1.1 cm, respectively. For the no-surgery group, the measurements were 1.8 cm and 0.86 cm. There was no association between the size of the clitoris and whether or not the patient underwent clitoroplasty (p = 0.24 for length, p=0.12 for width). Pre- and post-operative clitoral measurements for individual subjects were not reported, so they could not be compared. There were 14 subjective reports of the results of clitoroplasty. Six subjects (43%) were described to have a cosmetically normal female appearance; two exhibited scarring; four were described to have persistent clitoromegaly, one of which underwent a second clitoroplasty; two presented with an absent clitoris, with one described to have an absent clitoral hood. Two nonsurgical virilized subjects had resolution of clitoromegaly with increased age and somatic growth.

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Perineoplasty

Perineal anomalies were observed in 39 of the 45 virilized patients; perineoplasty was performed in 33 of them (84.6%). The initial surgeries reported were 29 vaginoplasties, 2 posterior labial fusion repairs, 1 imperforate vagina repair, and urethroplasty. Table 3 shows the age at first perineoplasty, revision status, and vaginal stenosis rate.

Table 3. Age at first perineoplasty, revisions, and complications

	< 1yo		1-3yo		4-9yo	10-15yo	> 15yo	Totals
1. Perineoplasties	20		6		2	1	4	**33**
2. Revised	8		3		0	0	0	**11**
3. Post-pubertal follow up not available	12		1		0	1	0	**14**
4. Confirmed not revised	0		1		1	0	4	**6**
5. More surgery needed, but no f/u	Revised 3	Unrevised 3	Revised 1	Unrevised 1	Unrevised 1	Unrevised 1	0	**9**
6. Vaginal Stenosis	6		3		1	0	0	**10**

This chart shows that the majority of patients undergo perineoplasty early in life (a majority had their first surgery before their first birthday). The patients who are "too young to know or lost to follow-up" (line 3) were all 14 years old or younger when their chart records stopped. Several patients still required additional surgeries but had not yet gotten them. This happened in both patients who had previously been revised and in patients who were anticipating their first revision (see line 5).

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11 patients underwent revision of their genitoplasty. There were two groupings for the timing of their revision: one which had their second surgery within a year of the first (N=2), and another which waited for revision until the onset of puberty or later (N=9). In the latter group, ages of revision ranged from 11.5 years old to 22 years old. The mean and median ages were 16.3 and 16.75 years old, respectively.

The four surgeries in the >15 years old age group included two cut-back vaginoplasties, one repair of posterior labial fusion, and one vaginoplasty with creation of the labia minora. None of these required any revision.

The types of vaginoplasties performed on these patients included total and partial urogenital mobilization (TUM and PUM), cut-back, pull-through, and flap vaginoplasties. Data was insufficient to determine the complications or revision rate associated with the kind of vaginoplasty.

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Urinary Tract Infections

The most common comorbidity observed in the total cohort was recurrent UTIs. Four patients had UTIs in the presence of a UG sinus. Two were treated medically, and the other two were treated surgically. One surgical subject had post-operative eradication of the infection, and

the other continued to have UTIs after her vagina and urethra were separated. Five patients did not have recurrent UTIs preoperatively but developed them after perineoplasty.

Conclusions and Discussion

Our data confirm our hypothesis and show a downward trend in the rate of clitoroplasty both preceding and following the publication of the 2006 consensus statement. The very high rates of clitoroplasty that we observed in the early 1980s are consistent with previous reports.[13,14] Although this declining trend has been observed before in 2002,[11] we now know that rates continued to fall over the past decade, after the official recommendation against clitoroplasty.

Many adults who underwent infant genitoplasty feel damaged and mutilated.[15] Their infant surgeries have left them with decreased sensation of the clitoris, and some of them are anorgasmic. One study found the rate of anorgasmia to be as high as 40%.[16] However, their study population was born between 1972-88, which means they were subjected to surgical techniques that are no longer used. Nerve-sparing clitoroplasties have been increasingly implemented in the past two decades.[17, 18] In more recent studies on clitoral innervation after surgery, few report anorgasmia but almost all still report significantly reduced sensation.[19, 20, 21]

Our observed decrease in infant clitoroplasty reflects recognition of the recommendations of LWPES and ESPE Consensus Statement. Surgery for cosmetic reasons is no longer recommended; sensation is emphasized over appearance.[10] The ethics of allowing parents to consent for elective surgeries that could permanently impair the genital sensation of the child is problematic. Projected concern over appearance can be unnecessary. Cheryl Chase has reported instances of adults with hypertrophied clitorises who, along with their significant other, are happily unaware of their anatomical difference.[22] Additionally, the clitoromegaly of some CAH infants resolves over time with increased somatic growth and sexual maturation at puberty.[23] Women who do not have surgery have the opportunity to be satisfied with appearance, retain full sensation, and avoid surgery with its potential complications.

The timing of vaginoplasty for patients with CAH is another important area in need of further study. Whereas clitoroplasty is performed for cosmetic reasons, vaginoplasties can serve a functional and anatomical purpose. Commonly cited reasons for vaginoplasty include providing the capacity for sexual function and the ability to monitor the cervix by Pap screening, promoting normal psychosexual development, and preventing urological sequelae such as urinary reflux, urinary tract infections, and post-void dribbling.[24] However, infant genitoplasty almost always requires revision surgery at puberty (one study reported a 90% revision rate[25]). Thus, the major debate is not over whether to do them, but rather *when* to do them – in infancy or after puberty. Current endocrine guidelines recommend early single-stage repair.[1] A survey of urologists reports that this is what they prefer as well.[26] In the gynecology literature, the lack of follow-up data on outcomes for patients who have late feminizing surgery leaves the optimal timing of surgery as something to be determined by future studies,[27]but the data supports that most patients who have early surgery will need treatment in adolescence or early adulthood for vaginal or introital stenosis.[28] A survey of adult women with CAH shows a slight preference for early intervention.[29]

Complications from infant vaginoplasty like scarring, stenosis, and the requirement for further surgery lead some to conclude that waiting until puberty for the initial reconstruction is ideal. [30, 31] Although our study does not have many subjects, it supports this perspective. Our data show that the patients who had their first perineoplasty after puberty had good post-operative results with no need for revision. We found that surgery in infancy, however, was revised in all 8 cases in which post-pubertal follow up was available. Our results also revealed UTI as a significant complication of vaginoplasty.

One question our study was unable to answer was the effect of genitoplasty and/or vaginoplasty on the fertility of virilized 46,XX patients. One survey has found that only 15% of

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46,XX patients with CAH were able to conceive naturally[32] Any effect of genitoplasty and vaginoplasty on the fertility rates is likely to bear an influence on patient or parent preferences in regards to such surgeries. Efforts are currently underway to build registries of patients with CAH and other DSDs to facilitate research requiring large sample sizes of patients and longer duration of follow-up to answer such questions. The DSD-Life research collaborative and International-DSD (I-DSD) registry in Europe and the DSD-Translational Research Network (DSD-TRN) in the United States have all been founded within the last decade.[33] With approximately 300 patients enrolled in the DSD-TRN[34] and 2100 patients enrolled I-DSD/DSD-Life[35] registries and growing, future insights gained from these patients over longer periods of time may change the guidelines and recommendations on if and when to perform genital surgery on virilized 46,XX patients.

In conclusion, our data support that clitoroplasty for virilizing CAH has significantly declined in frequency over the past 35 years. This change reflects in part the acceptance of input from patient advocates to provide perspectives not available through traditional clinical studies. More long-term follow-up data must be sought to determine optimal treatments for virilized 46, XX patients with CAH.

Acknowledgements

We thank Dr. Jennifer Heeley for assisting in the creation of the REDCap database, as well as for her guidance throughout the research process.

Grant support

This research was supported by the OMSR and the NIDDK summer fellowship through the NIH.

The REDCap program is supported by Clinical and Translational Science Award (CTSA) Grant [UL1 TR000448] and Siteman Comprehensive Cancer Center and NCI Cancer Center Support Grant P30 CA091842

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