CONGENITAL adrenal hyperplasia is the most common diagnosis in virilized infants with 46,XX DSD.\(^1\) Even so it is a rare diagnosis, occurring in approximately 1/5,000 to 20,000 individuals.\(^2\) Surgical aims for virilized girls with CAH are to create cosmetic and functional external genitalia from a sexual, reproductive and urinary standpoint.\(^3\)

Concerns remain as to the potential need for additional procedures, long-term effects on psychosocial and sexual function, and cosmetic and
functional outcomes. The 2006 statement of the International Consensus Conference on Intersex recommended a multidisciplinary approach with centralized surgical care. Feminizing genitoplasty was only recommended in cases of severe virilization. It was also recommended that children with an inadequate vagina should undergo repair in adolescence. Knowledge of practice patterns remains limited to physician surveys and retrospective series from high volume centers. At the Fourth World Congress of the International Society of Hypospadias and Disorders of Sex Development 48 of the 61 surgeons (78%) surveyed preferred to perform feminizing genitoplasty before age 2 years. A study from the largest DSD referral center in the United Kingdom between 2001 and 2012 showed a minimal decrease in clitoroplasty or overall surgical reconstruction rates in infancy or early childhood. This study was encouraging since it demonstrated improved cosmetic outcomes and a decreased need for secondary procedures.

Given the lack of large-scale data on current surgical practice, our primary objective was to evaluate current practice patterns at academic centers in the United States, including the prevalence of children proceeding to surgical procedures, patient age at surgery and type of reconstructive procedures performed in girls with a diagnosis of CAH. As secondary outcome measures we evaluated the degree of centralization of care in an analysis of surgeon and hospital volume, and whether volume was associated with the timing of reconstruction.

METHODS
We queried Faculty Practice Solutions Center, a national billing database, to identify all patient encounters for females younger than 18 years with a diagnosis of an adrenogenital disorder (ICD-9 255.2). Data were obtained from more than 90 academic centers in the United States from January 1, 2009 to December 31, 2012. We further analyzed incidence of diagnosis by patient date of birth during this 4-year period.

To capture all relevant procedures we compiled all urological, gynecologic and gastrointestinal CPT codes (40000 to 50000) billed for these patients. After analyzing these codes for relevance to a genitourinary reconstructive procedure we selected some of them as index feminizing genitoplasty procedures, including clitoroplasty (56805), repair of introitus (56800) and 2 additional codes for vaginal surgery (57291 and 57335). Other relevant codes, including perineoplasty (56810), reconstruction of urethra (53430), lysis of labial adhesions (56441), dilation of vagina (57400) or unspecified genital procedure (58999), were termed other reconstructive procedures. We analyzed the occurrence of any of these codes or combination of codes to determine the first and subsequent reconstructive procedures during the 4-year period by patient age at the time of these procedures.

We further used evaluation and management inpatient and outpatient consultation CPT billing codes (99221 to 99226, 99251 to 99255, 99201 to 99205 and 99241 to 99245) to evaluate the timing of initial evaluation by a urologist or an endocrinologist and the time that elapsed after the consultation until surgical intervention. A pediatric urologist designation was made by self-identification as a urologist who also performed at least 1 hypospadias or orchiopexy during the study period in a patient younger than 12 years or a surgeon who lacked self-identification but completed a minimum of 6 annual orchiopexies (54640) and 6 annual hypospadias repairs (54322 to 54326) in patients younger than 12 years. Pediatric endocrinologists were defined as those who evaluated at least 6 patients younger than 12 years with a diagnosis of short stature (783.43) and diabetes (250) annually, and were self-identified in the database as having an endocrine specialty.

A linear mixed effects model was used to compare mean time from consultation to surgery between surgeon volume groups. The model included a random effect for surgeon to adjust for within surgeon correlations. Time was log transformed before analysis.

Cohort Incidence Analysis
Consultation to surgery. To more accurately determine the timing of initial procedures in infants and young children we performed subgroup analysis of infants with an initial consultation before age 12 months with either specialist between January 1, 2009 and December 31, 2011. Procedures performed in these patients through December 31, 2012 were evaluated to enable a minimum of 1 year of followup. The proportion of patients who proceeded to surgery after consultation with either specialist as well as time from consultation to surgery were evaluated in this cohort. The indication for this analysis was to further determine whether consultation timing, institution volume or surgeon volume was associated with surgery timing. Additionally, to provide a minimum estimate of the percent of patients who proceeded to early surgery we evaluated procedures performed in all patients younger than 2 years at the time of the procedure regardless of consultation status.

Virilization. Since we found a lower than anticipated proportion of females proceeding to surgical reconstruction and many individuals with CAH have nonclassic forms without virilization, we identified the diagnosis of virilization and analyzed its association with patient age and timing of surgery. We included patients with a CAH diagnosis as well as a second ICD-9 code of 752.x, indicative of congenital anomaly of genital organs.

Insurance, Race and Region
Patient demographics were obtained, including region, race and insurance type, for all with a diagnosis of CAH. We performed multivariate analysis using a mixed effects model with random effect for surgeon and time log transformed to evaluate the effects of these factors in association with time from consultation to surgery and patient age at surgical reconstruction.
Surgeon and Hospital Volume
Surgeon and hospital volume was divided into 3 cohorts for analysis. Fewer than 4 cases, 4 to 10 and greater than 10 in 4 years were considered low, medium and high volume, respectively. This was consistent with the ESPE (European Society for Paediatric Endocrinology) recommendation for treatment to be performed at high volume surgical centers.7 If multiple surgeons were associated with a procedure, the highest volume surgeon was counted as the surgeon for analysis.

RESULTS
We identified 2,614 female patients who had a diagnosis of CAH, of whom 1,104 had an initial recorded consultation with a urologist or an endocrinologist. When analyzing only those born during the 4-year study period, 573 patients were identified with a date of birth of between January 1, 2009 and December 31, 2012 for a mean of 143 births per year.

A total of 260 feminizing genitoplasty procedures were performed in 219 patients. These operations were done at a total of 60 hospitals by 66 urologists and 20 other surgeons (pediatric general surgery and gynecology). Multiple surgeons were involved during several procedures. During the study period 219 first, 32 secondary and 9 tertiary procedures were performed (see table).

Procedures at All Ages
Primary. Of the total number of first recorded procedures per patient 110 were combined clitoroplasty and vaginoplasty, 56 were vaginoplasty alone, 21 were clitoroplasty alone and another 32 reconstructive procedures were also performed (see table). Median patient age was the least (11.3 months) at the first procedure in the combined genitoplasty cohort while 74% of the total combined procedures were performed at ages less than 2 years. Vaginoplasty alone and clitoroplasty alone were done at older median ages of 53 and 70 months, respectively. The histogram plots of all surgeries performed and the timing of each procedure showed bimodal peaks for infants and adolescents for clitoroplasty alone or vaginoplasty alone as well as skewing toward infancy for combined procedures (figs. 1 to 3). Of all first procedures in patients younger than 2 years 89% of operations included vaginoplasty and 73% included clitoroplasty. Of patients treated with surgery a combined procedure, clitoroplasty alone and vaginoplasty alone were done in 68%, 5% and 21%, respectively.

Secondary. Within the 4-year window the secondary procedures were primarily in the other reconstructive procedure category with only 1 recorded combined vaginoplasty and clitoroplasty (see table). Tertiary procedures followed the same pattern, that is 1 vaginoplasty and 8 other reconstructive procedures were performed.

Cohort Incidence Analysis
Consultation to surgery. Of the 577 infants who were younger than 12 months during the first 3 years of the study period 106 (18%) underwent a reconstructive procedure during the 1 to 4-year followup. Of these patients 347 were evaluated by an endocrinologist, of whom 82 (24%) proceeded to surgery. Of the 186 patients evaluated by a urologist 91 (49%) proceeded to surgery (fig. 4). Of the total of 106 procedures performed in this cohort 70% were a combined reconstructive procedure. Only 4% of the total number of procedures were coded as clitoroplasty alone while 22% represented vaginoplasty alone.

Virilization. Of the 412 patients born during the first 3 years of the study who were followed a minimum of 1 year 181 had recorded diagnostic codes 255.2 (CAH) plus 752.X (congenital anomaly of genital organs). A procedure was done during the study period in 80 of these patients (44.2%), of whom 57 (71.2%) underwent combined vaginoplasty and clitoroplasty.

Insurance, Race and Region
On multivariate analysis of patients who were 0 to 12 months old at consultation Medicaid insurance (estimated age difference 2.9 months, 95% CI 0.4–5.4, p = 0.02) or self-pay status (age difference

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6.3 months, 95% CI 0.4–12.1, p = 0.04) was significantly associated with increased age at surgery compared to those with private insurance. No association was found between race or region and age at surgery. However, there was a significantly longer time from consultation to surgery in children with self-pay vs commercial insurance (geometric mean ratio 3.6, 95% CI 1.8–7.3, p = 0.001).

Volume Surgeon. Of all surgeons who performed reconstructive procedures there were 70 low, 14 medium (4 to 10 cases per 4 years) and 2 high volume (11 or more cases per 4 years) surgeons. Analysis of surgeon case volume by highest volume surgeon listed in a case showed that 32% of reconstructive procedures included a medium volume surgeon and 31% of cases included a high volume surgeon. Only 2 surgeons, who performed 27 and 34 procedures, respectively, were high volume surgeons. Time to surgery was shorter in patients seen by a high volume surgeon at a median of 1.1 months from consultation (range 0 to 19, IQR 4.1) vs a medium volume surgeon at 6.6 months (range 0 to 44.1, IQR 7.9) or a low volume surgeon at 6.9 months (range 0.7 to 19.1, IQR 5.9) after consultation. This did not translate to a difference in patient age at reconstruction (p = 0.96). There was no significant difference in time to surgery between medium and low volume surgeons (p = 0.97).
Hospital. At 3 high volume institutions 14, 27 and 34 cases, respectively, were performed during the 4-year period. At the remaining hospitals 10 or fewer such procedures were performed during the 4-year period. Patients seen at high volume institutions were almost 3 times more likely to have a consultation with an endocrinologist as well as a urologist at the same institution (23% vs 8%). Those seen at high volume institutions by an endocrinologist as well as a urologist were almost twice as likely to undergo reconstruction than if evaluated at an institution where 1 to 10 reconstructive procedures were done in the 4-year period (73.9% vs 40.2%).

DISCUSSION

Controversies exist on the optimal timing, indications and techniques for feminizing genitoplasty procedures. Opponents of early surgery cite concerns regarding the frequent need for further reconstructive procedures, the lack of multinstitutional long-term data on function and cosmesis in adulthood, and the inability to obtain informed consent of the patient in infancy. Advocates of early surgery argue that there may be psychosocial benefits for patient and parent when there is consistency of anatomy with gender of rearing, potentially better quality of genital tissue with exposure to maternal estrogens in infancy and the relatively minor procedures anticipated later in life compared to initial reconstruction.¹ ⁵

These unanswered questions on the optimal management of CAH highlight the relevance of a study such as ours to inform the debate through a detailed assessment of current practice. To our knowledge this study is unique in its era and scope. It captures the breadth of surgical practices, including variations in timing and type of reconstructive procedures performed, and provides insight into centralization and surgeon experience with these procedures.

Despite the limitations imposed by a 4-year window this study allows for the observation that feminizing genitoplasty in infants with CAH continues to be performed and approximately 90% of the time it includes vaginoplasty as a portion of the procedure. In a comparable unpublished study DaJusta et al used the PHIS (Pediatric Health Information System) database to evaluate CAH genitoplasties between 2004 and 2008 at 42 hospitals, where a total of 187 procedures were performed.⁸ In this study 78% of all procedures performed in patients younger than 2 years included vaginoplasty compared to 89% in our series.

However, a unique finding of the current study is that many infants with CAH (up to 82%) did not proceed to early surgery (1 to 4-year followup). This may have been due to absent or mild virilization associated with nonclassic forms of CAH, surgery postponement or surgery performed elsewhere. A CAH diagnosis refers to the enzymatic defect in steroid synthesis pathways but varied phenotypic outcomes may be observed.⁹ A potential limitation in describing surgical practice patterns is the inability in this database to determine the degree of virilization. A manner in which this was addressed was by including the presence of a second ICD-9 code (752.x), which is used for congenital anomaly of genital organs, in an attempt to find virilized patients. When a patient had the 2 diagnoses during the first 3 years of the study and was followed a minimum of 1 year, 44% underwent a surgical procedure compared to 18% without the diagnosis. Additionally, although the code 255.2 is overall specific to CAH, it may include a few rare instances of other adrenogenital disorders, such as Achard-Thiers syndrome or virilization of a fetus due to maternal exposure through endogenous (eg adrenal tumor) or exogenous androgen sources. Although we attempted to avoid missing relevant procedural codes through a top-down approach of code identification, miscoding procedures is a possible means to underrepresent the cases completed.

Our results suggest that vaginoplasty combined with clitoroplasty is the most common procedure performed in infancy and early childhood, and it appears to be primarily restricted to this age range (fig. 3). In patients treated with surgery before age 2 years 89% of procedures included vaginoplasty.

Centralization of care has occurred to a certain extent with 63% of cases performed by medium and high volume surgeons. At high volume hospitals patients more commonly underwent evaluation by an endocrinologist and a urologist, followed by reconstruction, than those seen at low or medium volume hospitals.

CONCLUSIONS

Many patients with CAH did not proceed to early reconstructive surgery. Of those referred to surgeons, who were potentially the most virilized female patients, about half proceeded to early surgery and almost all underwent vaginoplasty as a component of surgery. About two-thirds of procedures were performed by medium or high volume surgeons, indicative of DSD surgical centralization.

ACKNOWLEDGMENTS

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REFERENCES


EDITORIAL COMMENT

The authors provide timely insight that may help frame the debate regarding the current state of feminizing genitoplasty for virilized female patients with CAH. Generating far-reaching conclusions based on billing data can be fraught with potential errors. However, even with such limitations the authors applied a thoughtful set of criteria to analyze the data and found a promising trend that has been advocated by several DSD consensus statements. Their findings seemed to indicate that almost 70% of feminizing genitoplasty procedures were performed as a combined procedure of vaginoplasty and clitoroplasty, presumably using the modern anatomical approach of urogenital sinus mobilization, at medium to high volume centers housing multidisciplinary DSD teams. It was also interesting and encouraging to note that a significant majority of patients with CAH did not undergo genitoplasty after the initial consultation. Although it could not be demonstrated using this approach, this suggests that the pros and cons of surgical intervention might be more carefully weighed before proceeding with surgery. At least these findings may be an indication that surgical decisions are being deferred to centers where multidisciplinary DSD care is delivered with a team approach. Obtaining meaningful, patient centered long-term data must remain the ultimate goal. Without a clear understanding of its outcome it is impossible to know the true impact of any surgical intervention and for that matter the effectiveness of surgical decision making in the context of multidisciplinary team function. I believe that integrating and centralizing DSD care, including that of CAH, with the primary focus on patient and family centered shared decision making partnership are the right way to proceed.

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