Growing up with clitoromegaly: experiences of North American women with congenital adrenal hyperplasia

Konrad M. Szymanski,[1] MD MPH, Paul Kokorowski,[2] MD MPH, Luis H. Braga,[3] MD PhD, Heather Frady,[1] RN, BSN, Benjamin Whittam,[1] MD MS, Devon J. Hensel,[4] MS PhD, on behalf of Life with Congenital Adrenal Hyperplasia Study Group, on behalf of the Life with Congenital Adrenal Hyperplasia Study Group

[1]Division of Pediatric Urology, Riley Hospital for Children at IU Health, Indianapolis, IN

[2]Division of Pediatric Urology, Children's Hospital Los Angeles, Keck School of Medicine, University of Southern California, Los Angeles, CA

[3]Division of Pediatric Urology, McMaster Children's Hospital, McMaster University, Hamilton, ON

[4]Division of Adolescent Medicine, Department of Pediatrics, Indiana University School of Medicine and Department of Sociology, Indiana University Purdue University Indianapolis, Indianapolis, Indiana

Short title suggestion: Growing up with clitoromegaly: experiences of North American women with CAH

Corresponding author:
Konrad M. Szymanski, MD MPH
Division of Pediatric Urology
Riley Hospital for Children at IU Health
705 Riley Hospital Dr., Suite 4230
Indianapolis, IN 46202, USA
Tel: (317) 944-7446
Fax: (317) 944-7481
Email: szymanko@iupui.edu

Acknowledgments: The many patients and parents for their support of and participation in the study. CARES Foundation for support of this project.

Steering Committee of the Life with Congenital Adrenal Hyperplasia Study Group: Paul Kokorowski, MD MPH, Division of Urology, Children's Hospital Los Angeles and Institute of Urology, Keck School of Medicine, University of Southern California, Los Angeles, CA; Dix P. Poppas, MD, Institute for Pediatric Urology, Department of Urology, Komansky Children's Hospital, New York Presbyterian Hospital, Weill Cornell Medicine, New York, NY; Richard C. Rink, MD, Division of Pediatric Urology, Riley Hospital for Children at Indiana University Health, Indianapolis, IN; Jonathan C. Routh, MD MPH, Division of Urology, Duke University School of Medicine, Durham, NC; Phyllis W. Speiser, MD, Division of Pediatric Endocrinology, Cohen Children's Medical Center of New York and Zucker School of Medicine at Hofstra/Northwell, Lake Success, NY; Konrad M. Szymanski, MD MPH, Division of Pediatric Urology, Riley Hospital for Children at Indiana University Health, Indianapolis, IN

Members of the Life with Congenital Adrenal Hyperplasia Study Group: Luis H. Braga, MD PhD, Division of Pediatric Urology, McMaster Children's Hospital, McMaster University, Hamilton, ON, Canada; Kelly L. Donahue, PhD, Division of Endocrinology and Division of

This is the author's manuscript of the article published in final edited form as:

Szymanski, K. M., Kokorowski, P., Braga, L. H., Frady, H., Whittam, B., Hensel, D. J., & Life with Congenital Adrenal Hyperplasia Study Group. (2022). Growing up with clitoromegaly: Experiences of North American women with congenital adrenal hyperplasia. Journal of Pediatric Urology, 18(6), 775–783. https://doi.org/10.1016/j.jpurol.2022.05.016

Adolescent Medicine, Department of Pediatrics, Indiana University School of Medicine and Riley Hospital for Children at Indiana University Health, Indianapolis, IN; Erica A. Eugster, MD, Division of Endocrinology, Department of Pediatrics, Indiana University School of Medicine and Riley Hospital for Children at Indiana University Health, Indianapolis, IN; Louise K. Fleming, PhD MSN-Ed RN, University of North Carolina Chapel Hill School of Nursing, Chapel Hill, NC; Heather M. Frady, RN BSN, Division of Pediatric Urology, Riley Hospital for Children at Indiana University Health, Indianapolis, IN; John S. Fuqua, MD, Division of Endocrinology, Department of Pediatrics, Indiana University School of Medicine and Riley Hospital for Children at Indiana University Health, Indianapolis, IN; Mitchell E. Geffner, MD, Center for Endocrinology, Diabetes & Metabolism, Children's Hospital Los Angeles and Keck School of Medicine, University of Southern California, Los Angeles, CA; Devon J. Hensel, MS PhD FASHM, Division of Adolescent Medicine, Department of Pediatrics, Indiana University School of Medicine and Department of Sociology, Indiana University Purdue University Indianapolis, Indianapolis, IN; Mimi S. Kim, MD MSc, Center for Endocrinology, Diabetes & Metabolism, Children's Hospital Los Angeles and Keck School of Medicine, University of Southern California, Los Angeles, CA; Oksana Lekarev, DO, Division of Pediatric Endocrinology, Department of Pediatrics, Komansky Children's Hospital, New York Presbyterian Hospital, Weill Cornell Medicine, New York, NY; Brian D. Leland, MD, Division of Pediatric Critical Care Medicine, Department of Pediatrics, Indiana University School of Medicine, Riley Hospital for Children at Indiana University Health, Charles Warren Fairbanks Center for Medical Ethics, Indianapolis, IN; Karen Lin-Su, MD, Division of Endocrinology, Department of Pediatrics, Komansky Children's Hospital, New York Presbyterian Hospital, Weill Cornell Medicine, New York, NY; Heino F. L. Meyer-Bahlburg, Dr. rer. nat., New York State Psychiatric Institute and Vagelos College of Physicians and Surgeons of Columbia University, New York, NY; Todd D. Nebesio, MD, Division of Endocrinology, Department of Pediatrics, Indiana University School of Medicine and Riley Hospital for Children at Indiana University Health, Indianapolis, IN; Rashida Talib, MBBS MPH, Division of Pediatric Endocrinology, Cohen Children's Medical Center of New York, Lake Success, NY; Benjamin Whittam, MD MSc, Division of Pediatric Urology, Riley Hospital for Children at Indiana University Health, Indianapolis, IN; Patrice M. Yasuda, PhD, Center for Endocrinology, Diabetes & Metabolism, Children's Hospital Los Angeles and Keck School of Medicine, University of Southern California, Los Angeles, CA

Potential conflicts of interest: Authors: Devon Hensel, MS PhD: consults for For Goodness Sake, LLC; none. Study Group Members: Louise Fleming, PhD RN: Chair of the CARES Foundation (volunteer position); Mitchell E. Gaffner, MD: consulted/consults for Adrenas, Millendo, Neurocrine Biosciences, Pfizer, and Spruce Biosciences, served on data safety monitoring board for Millendo, receives royalties from McGraw-Hill and UpToDate; Karen Lin-Su, MD: Medical Director of CARES Foundation; Dix P. Poppas, MD: Member of CARES Foundation Scientific Advisory Board (volunteer position); Phyllis W. Speiser, MD: Medical Advisor for National Adrenal Diseases Foundation (volunteer position) and Member of CARES Foundation Scientific Advisory Board (volunteer position); others: none

Funding: Departmental research fund

Abbreviations: CAH: congenital adrenal hyperplasia, IQR: interquartile range, DSD: differences of sex development

Keywords: adrenal hyperplasia, congenital; differences of sex development; patient reported outcome measures

Internal review board approval: Indiana University: 1903250601, Children's Hospital of Los Angeles: CHLA-19-00463, Weill Cornell: 1706018326

Growing up with clitoromegaly: experiences of North American women with congenital adrenal hyperplasia

Introduction: To describe experiences of clitoromegaly in women with congenial adrenal hyperplasia (CAH).

Methods: CAH females (46XX, >=16 years old) from the United States and Canada were eligible for a cross-sectional online survey (2019-2020) if reporting clitoromegaly (life-long: "growing up with a larger than average clitoris," secondary: "clitoris grew over weeks or months"). A multidisciplinary team and women with CAH drafted questions assessing net effects of clitoromegaly on 10 activities and 10 life domains. Fisher's exact test was used to compare net effect (positive-negative) vs. no effect (Bonferroni p=0.05/10=0.005).

Results: Of 97 women with CAH enrolled, 53 women (55%, median age: 36 years, advocacy group recruitment: 81%) reported recognizing clitoromegaly at median 11-13 years old, with 21% identifying it in adulthood. There was no difference in self-reported timing or clitoral shape between life-long or secondary clitoromegaly (p>=0.06). There were no net positive effects of clitoromegaly. Rather, clitoromegaly had net negative effects on 7/10 activities (p<=0.003) and no net effect (neutral) on 3 (**Table**). Women were less likely to wear tight clothing, change clothes in public locker rooms and play group sports. Women reported net negative effects for most romantic activities (dating, any sexual activity, pain-free sexual activity, having a partner see their genitalia, p=<0.003), but did not report a net effect on pleasurable sexual activity (p=0.12).

Clitoromegaly had net negative effects in 9/10 life domains (p<0.001) and neutral on job self-perception (p=0.25). Few women reported any positive impact (2-6%). However, 49-59% of women experienced poor self-esteem, anxiety, gender self-perception and body image, while 36% felt "down or depressed." A 21-23% experienced negative self-perception as friends and parents, 42-47% reported negative effects on plans for romantic and sexual relationships. Responses did not differ with advocacy group membership (p>=0.02).

Discussion: Our findings support qualitative and case series evidence that clitoromegaly has a negative psychological outcome on women with CAH. Clitoromegaly may add to the burden of living with a chronic endocrine disease. Women with positive and negative experiences had the same opportunity to participate. Since we could not assess objective clitoral size, baseline virilization and exact nature of any childhood clitoral procedures, these data cannot be used to estimate the impact of specific clitoral size or effectiveness of early clitoral treatments.

Conclusions: Clitoromegaly appears to be common among women with CAH. While experiences of clitoromegaly vary between women, the overall experience is negative in multiple social, romantic, and emotional activities and domains.

Introduction

Females (46XX) with congenital adrenal hyperplasia (CAH) represent half of newborns born with atypical genitalia[1, 2] and 9 out of 10 of these infants with a 46XX karyotype.[1] Qualitative studies indicate that negative, and even traumatic, experiences of stigma are common among women with CAH and relate to different aspects of CAH, but particularly to atypical genitalia, especially clitoromegaly.[3, 4] While these in-depth studies enrolled women seeking counselling, women with CAH have not been surveyed about clitoromegaly. The potential positive and negative effects of having atypical genitalia is particularly important in the CAH population. This is because compared to the general female population, women with CAH are already at a higher risk of sexual dysfunction,[5, 6] infertility, metabolic syndrome, osteoporosis,[7] depression and premature mortality.[8] Therefore, clitoromegaly can be a potentially alleviating or aggravating factor for women with CAH already living with a chronic endocrine disease.

Legal moratoria on genital surgery in childhood disproportionately affect females with CAH, who are at a particular risk of clitoromegaly. Proposed[9-13] and enacted[14, 15] legislative bans on genital surgery imply that growing up with atypical genitalia has insignificant negative impact on children. To the best of our knowledge, no group of individuals born with atypical genitalia has been systematically surveyed about the impact that atypical genitalia, particularly clitoromegaly, have had on their lives.

Limited scientific evidence exists in the field of CAH. As a result, patients and parents often relying on anecdotes and strongly held views of multiple stakeholders, including patients, families, healthcare professionals, advocates and politicians. It is in this evidence-poor setting that legislative moratoria have been proposed and enacted. This underlines the absolute need to carefully examine the impact that clitoromegaly may have on health and well-being of women with CAH. We therefore took a patient-centered approach to engage the very people potentially most affected by such measures in this research.

The impact of clitoromegaly is challenging to assess given the low incidence of CAH and potential measurement biases. For instance, a study of clitoromegaly may be self-fulfilling, as women who characterize their clitoris as large may be more likely to report negative effects. At the same time, if the counterarguments are true, the impact of a larger clitoris may be positive, or neutral. Additionally, any study of patient-reported outcomes without access to medical records or objective direct genital examination has its own significant limitations and cannot be used to estimate effectiveness of early treatments on clitoral size.

We aimed to conduct a cross-sectional self-reported survey of women with CAH to better characterize the epidemiology and clinical manifestations of clitoromegaly, and the effects of clitoromegaly on women. We hypothesized that few women with CAH would report clitoromegaly and, when present, its overall impact was neutral.

Methods

We conducted an IRB-approved anonymous, Qualtrics-based cross-sectional online survey of women with CAH (46XX, ≥16 years old) living in the United States and Canada (2019-2020).[16, 17] Given that research questions referred to experiencing clitoromegaly, no controls were enrolled, since they did not share this experience. The study aim was one of several identified by focus groups of CAH females, and parents of CAH females, as an important research topic deserving further investigation (unpublished). Study questions were generated and reformatted by a multidisciplinary international team of an ethicist, psychologist, sociologist, endocrinologists, urologists and nurses involved in CAH care (see **Acknowledgements**). Face validity was supported by pretesting (3 women with CAH) and post-study participant feedback (data not shown).

Questionnaire administration and security

The study was advertised through email at four multidisciplinary CAH clinics (Canada, Midwest, East and West coasts of the United States) and the CARES Foundation, allowing participation regardless of advocacy group affiliation. CARES Foundation is the world's largest patient and family advocacy group for people affected by CAH. Design, administration and analysis safeguards protected study integrity.[10] Participants received no incentive payments, questions were used to detect automatic data entry and the questionnaire was lengthy (response rate: 34.9%, completion rate: 79.3%, median completion: 24 minutes). Each group was recruited 1-2 months apart with unique secure links. No repeating IP addresses/answers were detected. We classified as classical CAH females diagnosed in the first 5 years of life by atypical genitalia or adrenal crisis, and those diagnosed later (or for different reasons) and taking salt or fludrocortisone. Discrepancies were resolved by consensus among endocrinologists (4 records reviewed, 2 excluded due to inconsistent history/medications listed).

Questionnaire content

Clitoromegaly was elicited with two questions: "Did you grow up with a clitoris that was larger than average" (primary, life-long clitoromegaly) and "Did you ever notice your clitoris grew over a short period of time (weeks or months)?" (secondary clitoromegaly) (see **Supplementary Data** online for complete question list).

Effects of clitoromegaly were assessed on ten activities: four social, five romantic and one medical. Participants were asked "After you noticed this difference (primary) / change (secondary) in your clitoris, how likely were you to do the following activities?" (stopped doing this, less, same, more, not sure/not applicable/prefer not to answer). One activity was "being sexually active," without specifying types of behavior or intercourse. Effects were also assessed on ten life domains: five emotional, three social and two romantic. Participants were asked "What impact did having a larger clitoris have on the following?" (negative, no impact, positive, not sure/not applicable/prefer not to answer).

Sensitivity analyses

We performed one primary and three secondary (exploratory) sensitivity analyses to determine whether net effects varied between subgroups. The primary sensitivity analysis compared those with and without advocacy group affiliation, since some,[18] but not all studies,[16, 17] suggest

their responses may differ. Secondary analyses included clitoromegaly type (primary vs. life-long), age when clitoromegaly was noted (<=13 vs. >13 years old, based on median age) and appearance (protrusion vs. not). Choosing an alternative age categorization of <11 vs. >=11 years old yielded similar results (data not shown). A sensitivity analysis between CAH forms was not performed due to small numbers of patients in the non-classical group and potential misclassification.

Statistics

Due to demographic similarities and that <10% of participants being recruited from Canada, the study sample was only compared to the United States female population based on 2018 census data.[19] Fisher's exact and Wilcoxon rank sum tests were used. Since the study aim was to assess overall net effect of clitoromegaly (positive, neutral or negative), we calculated the net effect for each activity and life domain. The numerator was calculated by subtracting the number of participants reporting negative effects from those reporting positive effects. The denominator included all 53 women reporting clitoromegaly. For each question, Fisher's exact test was conducted between the net effect observed (x/53) and the null hypothesis of no net effect (0/53). Due to multiple statistical comparisons being performed, we used a Bonferroni-corrected critical p-value of p=0.005 (0.05/10) to minimize detecting spurious associations (Stata, StataCorp, College Station, TX, USA).

Results

A total of 97 women with CAH participated at a median age 39 years old (86% white, 93% from United States, **Table 1**). Those from the United States lived in 32 states (36% resided in California, Texas, Florida, New York, and Pennsylvania, mirroring national census data, p=0.83). Among females >=25 years old, 75.0% had a post-secondary degree (above national values, p<0.001). Median annual household income approximated the national average ($60,000-79,999, p=0.60). Participants were recruited through the CARES Foundation (85%) and clinics (14.7%). Sixty-three women (66.3%) were diagnosed with CAH in the first year of life and 80% provided diagnostic/medication history consistent with classical CAH.

Women with clitoromegaly

Fifty-three women (56%) reported experiencing clitoromegaly (median age: 36 years old). Thirty-five (66%) of them reported undergoing genital surgery in the first 4 years of life. In the absence of surgical documentation, the exact nature of these early procedures, whether they involved the labia, vagina and/or clitoris, could not be reliably determined based on patient reports alone. Age, race, country/state of residence, income, education, advocacy group affiliation and timing of CAH diagnosis were similar between women with and without clitoromegaly (p>=0.07, **Table 1**). While women with presumed classical CAH reported clitoromegaly more often, this did not meet statistical significance (89% vs. 69%, p=0.02).

Timing of clitoromegaly

Women recalled first noticing clitoromegaly at median age of 11-13 years, although ages ranged from <=6 years old to adulthood (**Table 2**). Thirty-one women (59%) reported life-long clitoromegaly (no change noted) and 22 (42%) reported secondary clitoromegaly (growth over weeks-

months). Women in the two groups had similar distributions of ages, residence, CAH forms, when they noted clitoromegaly and its appearance (p>=0.06). Most commonly, the clitoris was described as longer and more protruding, with or without being wider/thicker at the tip (64%).

When women with secondary clitoromegaly first noticed clitoral growth, 32% recalled taking less glucocorticoid steroids than usual (23% none, 9% less), 41% same, 5% more and 23% were not sure. Unfortunately, this question asked about taking medications "when" clitoromegaly was noted, leaving it unclear how many women interpreted this to mean "before," rather than "after, or as a result of" noting clitoromegaly.

Effects of clitoromegaly on activities

Clitoromegaly was not associated with increased net participation in any activities. Instead, a statistically significant negative net effect was noted for 7 of 10 activities and a neutral effect on 3 activities (**Table 2**). After noting clitoromegaly, women were less likely to change in public locker rooms (26% less vs. 0% more), wear tight clothing or a swimsuit (25% vs. 4%) and exercise in a group (17% vs. 2%, all p<=0.003), but not exercise alone (13% vs. 4%, p=0.03).

Women reported net negative effects for 4 of 5 romantic activities (p=<0.003). Almost half of the women (45%) allowed their sexual partner view their genitalia less frequently (17% stopped, 8% did so more frequently). A quarter of women went on fewer dates (23% less [2% stopped] vs. 4% more), engaged in less sexual activity (26% less [8% stopped] vs. 11% more) and had more painful sexual activity (23% more painful vs. 6% less painful). Overall, increased romantic and sexual activity after noting clitoromegaly were modest (4-11%). Similar proportions of women reported more and less pleasurable sex, with no net effect (p=0.12).

While 21% of women accessed gynecological care less frequently (8% stopped), 9% did so more often, leading to a neutral net effect (p=0.013).

Not all women reported positive or negative effects, but this varied by activity. Half noted no change in social interactions, dating and getting regular gynecological exam. Only a third noted no change in sexual activities.

Effects of clitoromegaly on life domains

Clitoromegaly had significant net negative effects in 9 of 10 life domains (p<0.001) and a neutral effect on how women viewed themselves in their job (p=0.25, the actual job was not ascertained) (**Table 2**). Clitoromegaly had no net positive effects. Few women (2-6%) reported any positive impact across life domains.

After noticing clitoromegaly, half of women (49-58%) reported experiencing poor self-esteem, anxiety, gender self-perception ("How I viewed myself as a woman") and body image ("How I viewed my body [self-image]"). A third endorsed feeling "down or depressed." A quarter experienced negative effects when considering themselves as parents and being uncomfortable around friends. Negative effects on their plans for romantic and sexual relationships were reported by 42-47%.

Sensitivity analyses

Regardless of advocacy group affiliation, women reported similar net effects on activities ($p>=0.02$) and life domains ($p>=0.08$) (**eTable 1)**. On secondary (exploratory) sensitivity analyses, women tended to provide similar responses regardless of whether clitoromegaly was primary vs. life-long, age when it was first noted and clitoral shape (no statistically significant differences for 57/60 comparisons, 95.0%).

Discussion

Clitoromegaly is common among women with CAH, occurring from childhood into adulthood. Such experiences were predominantly associated with net negative effects across multiple activities and life domains. While clitoromegaly had a net neutral effect in a few areas, there were no net positive effects of clitoromegaly. Effects of clitoromegaly vary between individuals. For instance, a significant number of women reported neither negative nor positive effects of clitoromegaly for several areas. Not surprisingly, our findings also indicate that clitoromegaly has more profound negative effects on some areas of life, especially sexual and mental health. The potential traumatic intensity of this effect is particularly clear when one notes that some women stopped certain activities altogether due to clitoromegaly. Indeed, 8% of women stopped participating in group sports, sexual activity and getting regular Pap smears. A quarter (23%) of women had more painful sexual activity and one in six women (17%) stopped allowing her sexual partner view her genitalia.

Our findings are consistent with qualitative and case series evidence indicating that clitoromegaly is associated with negative psychological outcomes among women with CAH. Work by Meyer-Bahlburg *et al.* indicates that women with CAH and clitoromegaly avoid peer activities, changing in front of others,[3] dating, sexual intimacy or having a partner look at her genitals.[4] Compared to women without CAH, women with CAH report higher levels of anxiety about romantic partnerships, sexual contacts, feeling less accepted, attractive, feminine, sensual, romantic and sexually active.[20]

Considering the health of women with CAH, our findings suggest that, for some, clitoromegaly may add to the burden of living with a chronic endocrine disease. Compared to the general population, women with CAH are at a higher risk of multiple health problems, including hypercholesterolemia, insulin resistance, obesity, osteopenia, osteoporosis, infertility,[7] sexual dysfunction,[5, 6] depression and premature mortality.[8] Clitoromegaly may further add to stigma, or "undesired differentness," that 40-67% of women with CAH experience.[3, 4] Combining social and romantic withdrawal due to clitoromegaly with multiple comorbid conditions and stigma can further aggravate the physical and mental health in an already vulnerable population of women with CAH.

Clitoromegaly and its impact on female development, health and well-being is likely the most controversial and least studied aspects of CAH. Acknowledging that the appearance of labia, introitus and vagina may be important to some women, it is the clitoris which may protrude and be visible, or palpable, for a woman with CAH. Clearly, women's body image and sense of femininity are impacted by multiple factors not captured in our study. This is particularly pertinent to CAH females, who are at risk of menstrual irregularities, infertility, hirsutism and

obesity.[3, 7] Indeed, the fact that other factors, including medical hormonal control and levels of hyperandrogenism, play a significant part is underlined by a report that women with non-classical CAH may be more likely to report poor sexual function, desire and performance than those with classical CAH.[5] In such cases, delayed diagnosis and less severe salt-wasting may potentially contribute to less stringent cortisol control and higher levels of androgens.

Although experiences of clitoromegaly may be different for women with CAH living in other parts of the world, our results are likely generalizable to the female CAH population in North America. This is supported by multiple participant characteristics reflecting the general population, recruitment involving different social clusters, women with positive and negative experiences of clitoromegaly having the same opportunity to participate, responses not varying with advocacy group affiliation and participants reporting heterogenous outcomes. Since 20% of clitoromegaly was noted in adulthood and participants' ages varied, some younger women may have not yet recognized life-long clitoromegaly or experienced secondary growth. Since the average participant was in her thirties, we suspect this number to be small.

This anonymous cross-sectional study has several limitations. Rather than assessing a comprehensive list of activities and domains, we focused on areas deemed relevant by women with CAH and healthcare professionals experienced in CAH care. We did not assess potentially changing cultural attitudes about genital appearance, or capture whether and how clitoromegaly was subsequently treated. The study focused on the previously unexplored experiences of clitoromegaly, rather than how clitoromegaly could be mitigated, including the effects of poor hormonal control and any surgical procedures.

Since we did not assess objective measures of clitoral size, these data cannot be used to predict the impact of specific clitoral size. Nonetheless, we consider the data very important, since the controversy and uncertainty surrounding the management of children born with atypical genitalia center around personal experiences. Since no validated questionnaires specific about clitoromegaly exist, we acknowledge the possibility that some phrasing of the non-validated questionnaire may be prone to bias. Importantly, we took care to establish face validity of the questions used (substantiating that the questions used indeed asked what we thought they asked) based on pilot and post-study feedback by women with CAH.

Our goal was not to dwell on differences between women with primary and secondary clitoromegaly, since the distinction may be inaccurate when ascertained solely based on patient reporting. Secondary clitoromegaly that was not noticed as it occurred, especially at a younger age, could be reported as primary clitoromegaly. Conversely, primary clitoromegaly noticed with arousal during adolescence could be reported as secondary.

The anonymous and self-reported nature of the study implied an inability to verify medical records, baseline virilization levels and the exact nature of any childhood clitoral procedures. Moreover, females born with more virilized genitalia due to more severe endocrine disease are more likely to undergo early genital surgery, may be at an increased risk of developing secondary clitoromegaly and, as a result, have different experiences related to clitoromegaly. Missing accurate data on baseline virilization and surgery, we could not define two groups clearly and reliably: the women who did not undergo early clitoroplasty and the women with the same baseline

level of virilization who did. We were therefore unable to compare women who did and did not undergo clitoral surgery in childhood without risking a significantly biased (confounded) analysis. For these reasons, these data cannot be used to extrapolate the effectiveness of early clitoral treatments.

Conclusions

Clitoromegaly appears to be common among women with CAH. While experiences of clitoromegaly vary between women, the overall experience is negative in multiple social, romantic, and emotional activities and domains.

References

[1] Finlayson C, Rosoklija I, Aston CE, Austin P, Bakula D, Baskin L, et al. Baseline Characteristics of Infants With Atypical Genital Development: Phenotypes, Diagnoses, and Sex of Rearing. J Endocr Soc. 2019;3:264-72. https://doi.org/10.1210/js.2018-00316

[2] Rohle R, Gehrmann K, Szarras-Czapnik M, Claahsen-van der Grinten H, Pienkowski C, Bouvattier C, et al. Participation of adults with disorders/differences of sex development (DSD) in the clinical study dsd-LIFE: design, methodology, recruitment, data quality and study population. BMC Endocr Disord. 2017;17:52. https://doi.org/10.1186/s12902-017-0198-y

[3] Meyer-Bahlburg HF, Reyes-Portillo JA, Khuri J, Ehrhardt AA, New MI. Syndrome-Related Stigma in the General Social Environment as Reported by Women with Classical Congenital Adrenal Hyperplasia. Arch Sex Behav. 2017;46:341-51. https://doi.org/10.1007/s10508-016-0862-8

[4] Meyer-Bahlburg HFL, Khuri J, Reyes-Portillo J, Ehrhardt AA, New MI. Stigma Associated with Classical Congenital Adrenal Hyperplasia in Women's Sexual Lives. Arch Sex Behav. 2018;47:943-51. https://doi.org/10.1007/s10508-017-1003-8

[5] Schernthaner-Reiter MH, Baumgartner-Parzer S, Egarter HC, Krebs M, Kautzky-Willer A, Kirchheiner K, et al. Influence of Genotype and Hyperandrogenism on Sexual Function in Women With Congenital Adrenal Hyperplasia. J Sex Med. 2019;16:1529-40. https://doi.org/10.1016/j.jsxm.2019.07.009

[6] Nordenskjold A, Holmdahl G, Frisen L, Falhammar H, Filipsson H, Thoren M, et al. Type of mutation and surgical procedure affect long-term quality of life for women with congenital adrenal hyperplasia. J Clin Endocrinol Metab. 2008;93:380-6. https://doi.org/10.1210/jc.2007-0556

[7] Arlt W, Willis DS, Wild SH, Krone N, Doherty EJ, Hahner S, et al. Health status of adults with congenital adrenal hyperplasia: a cohort study of 203 patients. J Clin Endocrinol Metab. 2010;95:5110-21. https://doi.org/10.1210/jc.2010-0917

[8] Jenkins-Jones S, Parviainen L, Porter J, Withe M, Whitaker MJ, Holden SE, et al. Poor compliance and increased mortality, depression and healthcare costs in patients with congenital adrenal hyperplasia. Eur J Endocrinol. 2018;178:309-20. https://doi.org/10.1530/EJE-17-0895

[9] SB 201 California: Medical procedures: treatment or intervention: sex characteristics of a minor. 2019-2020 ed2020.

[10] SB 408 Nevada: An act relating to health care; establishing conditions for the performance on a child of any surgical procedure to assign anatomical sex; providing for disciplinary action

against certain providers of health care for any violation of those conditions; and providing other matters properly relating thereto. 2017 ed2017.
[11] Bill 388 Connecticut: An act concerning a person's intersex status or characteristics. 2019.
[12] Parliamentary.Assembly.of.the.Council.of.Europe. Promoting the human rights of and eliminating discrimination against intersex people. 2017.
[13] United.Nations.Human.Rights.Office. United Nations for Intersex Awareness: Intersex babies are perfect just as they are. 2020.
[14] Government.of.Malta. Gender identity, Gender Expression and Sex Characteristics Act.
[15] Guilbert K. Portugal approves law to boost transgender rights, protect intersex infants. 2018.
[16] Szymanski KM, Braga LH, Whittam B, Kokorowski P, Leland BD. What Do Patients and Parents Say About Parents' Ability to Choose Early Genital Surgery for Girls with Congenital Adrenal Hyperplasia? J Urol. 2021;205:1770-7. https://doi.org/10.1097/JU.0000000000001573
[17] Szymanski KM, Rink RC, Whittam B, Hensel DJ, Life with Congenital Adrenal Hyperplasia Study G. Majority of females with a life-long experience of CAH and parents do not consider females with CAH to be intersex. J Pediatr Urol. 2021;17:210 e1- e9. https://doi.org/10.1016/j.jpurol.2020.09.009
[18] D'Oro A, Rosoklija I, Jacobson DL, Finlayson C, Chen D, Tu DD, et al. Patient and Caregiver Attitudes toward Disorders of Sex Development Nomenclature. The Journal of urology. 2020:101097JU0000000000001076. https://doi.org/10.1097/JU.0000000000001076
[19] UnitedStatesCensusBureau. United States Census Bureau. https://www.census.gov/en.html. 2020.
[20] Kuhnle U, Bullinger M, Schwarz HP, Knorr D. Partnership and sexuality in adult female patients with congenital adrenal hyperplasia. First results of a cross-sectional quality-of-life evaluation. J Steroid Biochem Mol Biol. 1993;45:123-6. https://doi.org/10.1016/0960-0760(93)90131-f

Acknowledgments: The many patients and parents for their support of and participation in the study. CARES Foundation for support of this project.

Steering Committee of the Life with Congenital Adrenal Hyperplasia Study Group: Paul Kokorowski, MD MPH, Division of Urology, Children's Hospital Los Angeles and Institute of Urology, Keck School of Medicine, University of Southern California, Los Angeles, CA; Dix P. Poppas, MD, Institute for Pediatric Urology, Department of Urology, Komansky Children's Hospital, New York Presbyterian Hospital, Weill Cornell Medicine, New York, NY; Richard C. Rink, MD, Division of Pediatric Urology, Riley Hospital for Children at Indiana University Health, Indianapolis, IN; Jonathan C. Routh, MD MPH, Division of Urology, Duke University School of Medicine, Durham, NC; Phyllis W. Speiser, MD, Division of Pediatric Endocrinology, Cohen Children's Medical Center of New York and Zucker School of Medicine at Hofstra/Northwell, Lake Success, NY; Konrad M. Szymanski, MD MPH, Division of Pediatric Urology, Riley Hospital for Children at Indiana University Health, Indianapolis, IN

Members of the Life with Congenital Adrenal Hyperplasia Study Group: Luis H. Braga, MD PhD, Division of Pediatric Urology, McMaster Children's Hospital, McMaster University, Hamilton, ON, Canada; Kelly L. Donahue, PhD, Division of Endocrinology and Division of Adolescent Medicine, Department of Pediatrics, Indiana University School of Medicine and Riley Hospital for Children at Indiana University Health, Indianapolis, IN; Erica A. Eugster, MD, Division

of Endocrinology, Department of Pediatrics, Indiana University School of Medicine and Riley Hospital for Children at Indiana University Health, Indianapolis, IN; Louise K. Fleming, PhD MSN-Ed RN, University of North Carolina Chapel Hill School of Nursing, Chapel Hill, NC; Heather M. Frady, RN BSN, Division of Pediatric Urology, Riley Hospital for Children at Indiana University Health, Indianapolis, IN; John S. Fuqua, MD, Division of Endocrinology, Department of Pediatrics, Indiana University School of Medicine and Riley Hospital for Children at Indiana University Health, Indianapolis, IN; Mitchell E. Geffner, MD, Center for Endocrinology, Diabetes & Metabolism, Children's Hospital Los Angeles and Keck School of Medicine, University of Southern California, Los Angeles, CA; Devon J. Hensel, MS PhD FASHM, Division of Adolescent Medicine, Department of Pediatrics, Indiana University School of Medicine and Department of Sociology, Indiana University Purdue University Indianapolis, Indianapolis, IN; Mimi S. Kim, MD MSc, Center for Endocrinology, Diabetes & Metabolism, Children's Hospital Los Angeles and Keck School of Medicine, University of Southern California, Los Angeles, CA; Oksana Lekarev, DO, Division of Pediatric Endocrinology, Department of Pediatrics, Komansky Children's Hospital, New York Presbyterian Hospital, Weill Cornell Medicine, New York, NY; Brian D. Leland, MD, Division of Pediatric Critical Care Medicine, Department of Pediatrics, Indiana University School of Medicine, Riley Hospital for Children at Indiana University Health, Charles Warren Fairbanks Center for Medical Ethics, Indianapolis, IN; Karen Lin-Su, MD, Division of Endocrinology, Department of Pediatrics, Komansky Children's Hospital, New York Presbyterian Hospital, Weill Cornell Medicine, New York, NY; Heino F. L. Meyer-Bahlburg, Dr. rer. nat., New York State Psychiatric Institute and Vagelos College of Physicians and Surgeons of Columbia University, New York, NY; Todd D. Nebesio, MD, Division of Endocrinology, Department of Pediatrics, Indiana University School of Medicine and Riley Hospital for Children at Indiana University Health, Indianapolis, IN; Rashida Talib, MBBS MPH, Division of Pediatric Endocrinology, Cohen Children's Medical Center of New York, Lake Success, NY; Benjamin Whittam, MD MSc, Division of Pediatric Urology, Riley Hospital for Children at Indiana University Health, Indianapolis, IN; Patrice M. Yasuda, PhD, Center for Endocrinology, Diabetes & Metabolism, Children's Hospital Los Angeles and Keck School of Medicine, University of Southern California, Los Angeles, CA

Potential conflicts of interest: Authors: Devon Hensel, MS PhD: consults for For Goodness Sake, LLC; none. Study Group Members: Louise Fleming, PhD RN: Chair of the CARES Foundation (volunteer position); Mitchell E. Gaffner, MD: consulted/consults for Adrenas, Millendo, Neurocrine Biosciences, Pfizer, and Spruce Biosciences, served on data safety monitoring board for Millendo, receives royalties from McGraw-Hill and UpToDate; Karen Lin-Su, MD: Medical Director of CARES Foundation; Dix P. Poppas, MD: Member of CARES Foundation Scientific Advisory Board (volunteer position); Phyllis W. Speiser, MD: Medical Advisor for National Adrenal Diseases Foundation (volunteer position) and Member of CARES Foundation Scientific Advisory Board (volunteer position); others: none

Funding: Departmental research fund

Abbreviations: CAH: congenital adrenal hyperplasia, IQR: interquartile range, DSD: differences of sex development

Keywords: adrenal hyperplasia, congenital; differences of sex development; patient reported

559 outcome measures
560
561 **Internal review board approval:** Indiana University: 1903250601, Children's Hospital of Los
562 Angeles: CHLA-19-00463, Weill Cornell: 1706018326
563

564 **Table.** Effect of clitoromegaly on different activities and life domains among 53 women with
565 congenital adrenal hyperplasia.
566

Activity	**Overall net effect**	**Less frequent (stopped doing this)**	**More frequent**	**No change**	**Not sure, not applicable, prefer not to answer**
Social interactions					
Wear tight clothing or a swimsuit	-21% (p<0.001*)	25% (2%)	4%	53%	19%
Play ports, workout, jog or walk around by myself	-9% (p=0.03)	13% (6%)	4%	66%	17%
Play ports, workout, jog or walk around with others (like in gym class or on a sports team)	-15% (p=0.003*)	17% (8%)	2%	64%	17%
Change clothes in a public locker room	-26% (p<0.001*)	26% (6%)	0%	51%	23%
Romantic and sexual interactions					
Go on dates	-19% (p=0.001*)	23% (2%)	4%	51%	23%
Be sexually active	-15% (p=0.003*)	26% (8%)	11%	38%	25%
Have pleasure from sexual activity	-6% (p=0.12)	28% (2%)	23%	34%	15%
Be sexually active without pain	-17% (p=0.001*)	23% (4%)	6%	38%	34%
Have my sexual partner look at my genitalia	-38% (p<0.001*)	45% (17%)	8%	28%	19%
Medical interactions					
Get regular gynecological checkups (like Pap smears)	-11% (p=0.013)	21% (8%)	9%	49%	21%
Life domain	**Overall net impact**	**Negative impact**	**Positive impact**	**No impact**	**Not sure, not applicable, prefer not to answer**
Emotional					
My self-esteem	-53% (p<0.001*)	55%	2%	32%	11%
Feeling down or depressed	-36% (p<0.001*)	38%	2%	43%	17%
Feeling anxious	-43% (p<0.001*)	49%	6%	34%	11%
How I viewed myself as a woman	-51% (p<0.001*)	57%	6%	30%	8%
How I viewed my body (self-image)	-54% (p<0.001*)	58%	4%	30%	8%
Social					
How I viewed myself in my job	-4% (p=0.25)	8%	4%	70%	19%
Being comfortable around my friends	-21% (p<0.001*)	25%	4%	62%	9%
How I viewed myself as a current (or future) parent	-23% (p<0.001*)	26%	4%	51%	19%
Romantic					
My plan or hopes to be in a romantic relationship	-36% (p<0.001*)	42%	6%	38%	15%
My plans or hopes to be sexually active	-42% (p<0.001*)	47%	6%	34%	13%

567
568
569

570 **Table 1.** Participant characteristics.

Variable	Overall (n=95)	No clitor-omegaly (n=42)	Clitoromeg-aly (n=53)	p-value
Age (median, IQR, years)	39 (29-48)	41.5 (37-52)	36 (27-45)	0.07
Race				
White	82 (86%)	37 (88%)	45 (85%)	0.13
Black or African American	2 (2%)	0 (0%)	2 (4%)	
Asian	1 (1%)	0 (0%)	1 (2%)	
Native Hawaiian or Pacific Islander	2 (2%)	0 (0%)	2 (4%)	
More than one race	4 (4%)	3 (7%)	1 (2%)	
Other	2 (2%)	0 (0%)	2 (4%)	
Prefer not to answer	2 (2%)	2 (5%)	0 (0%)	
Hispanic/Latino	9 (10%)	2 (5%)	7 (13%)	0.29
Primary language at home other than English	3 (3%)	1 (3%)	2 (4%)	0.33
Living in the United States	88 (93%)	38 (91%)	50 (94%)	0.70
State of residence (n=88)				
California	14 (16%)	5 (13%)	9 (18%)	0.17
Texas	4 (5%)	2 (5%)	2 (4%)	
Florida	7 (8%)	0 (0%)	7 (14%)	
Pennsylvania	5 (6%)	3 (8%)	2 (4%)	
New York	4 (5%)	2 (5%)	2 (4%)	
Alabama, Arizona, Colorado, Connecticut, Georgia, Illinois, Indiana, Iowa, Kansas, Kentucky, Maryland, Massachusetts, Michigan, Minnesota, Missouri, Nebraska, New Jersey, North Carolina, Ohio, Oklahoma, Oregon, Tennessee, Utah, Vermont, Virginia, Washington, West Virginia	54 (61%)	26 (68%)	28 (56%)	
Median annual household income	60,000-79,000	80,000-99,000	60,000-79,000	0.28
Educational level among those 25 years old or older (n=84)				
High school or equivalent	2 (2%)	0 (0%)	2 (4%)	0.26
Some college	16 (19%)	8 (21%)	8 (17%)	
Associate degree	13 (16%)	6 (16%)	7 (15%)	
Bachelor degree	30 (36%)	10 (26%	20 (44%)	
Graduate degree	22 (26%)	13 (34%)	9 (20%)	
Currently studying	1 (1%)	1 (3%)	0 (0%)	
Recruited through advocacy group	81 (85%)	38 (91%)	43 (81%)	0.25
Diagnosed with CAH in the first year of life	63 (66%)	26 (62%)	37 (70%)	0.51
Classical CAH	76 (80%)	29 (69%)	47 (89%)	0.02

571 Note: Percentages may not add to 100% due to rounding.
572

573 **Table 2.** Characteristics of 53 women with CAH reporting clitoromegaly.

Variable	Overall	Primary (life-long) (n=31)	Secondary (n=22)	p-value
Age (median, IQR)	36 (27-45)	34 (27-42)	42.5 (27-58)	0.13
Living in the United States	50 (96%)	29 (94%)	21 (96%)	0.99
Classic CAH	47 (89%)	28 (90%)	19 (86%)	0.68
Age at onset or notice (years)				
6 or younger (before elementary school)	7 (13%)	7 (23%)	0 (0%)	0.06
7-10 (elementary school)	7 (13%)	5 (16%)	2 (9%)	
11-13 (middle school)	16 (30%)	8 (26%)	8 (36%)	
14-17 (high school)	12 (23%)	5 (16%)	7 (32%)	
18 or older	11 (22%)	6 (19%)	5 (23%)	
Clitoral shape				
Longer, more protruding	17 (32%)	9 (29%)	8 (36%)	0.87
Wider, thicker at the tip	12 (23%)	8 (26%)	4 (18%)	
Both	17 (32%)	10 (32%)	7 (32%)	
Neither	1 (2%)	1 (3%)	0 (0%)	
Not sure	6 (11%)	3 (10%)	3 (14%)	

574 Note: Percentages may not add to 100% due to rounding.

eTable 1. Sensitivity analysis of responses by 53 women with CAH and clitoromegaly.

	Primary	Secondary (exploratory)		
Activity	**Advocacy group affiliation (p-value)**	**Primary vs. secondary clitoromegaly (p-value)**	**Clitoromegaly noted <=13 vs. >13 years old (p-value)**	**Protrusive shape of clitoris vs. not (p-value)**
Social interactions				
Wear tight clothing or a swimsuit	0.13	0.004 (-6% vs. -41%)	0.31	0.29
Play ports, workout, jog or walk around by myself	0.02	0.001 (+3% vs. -27%)	0.64	0.64
Play ports, workout, jog or walk around with others (like in gym class or on a sports team)	0.24	0.05	0.99	0.23
Change clothes in a public locker room	0.26	0.21	0.23	0.06
Romantic interactions				
Go on dates	0.99	0.99	0.99	0.30
Be sexually active	0.16	0.44	0.07	0.70
Have pleasure from sexual activity	0.08	0.07	0.99	0.55
Be sexually active without pain	0.48	0.40	0.78	0.25
Have my sexual partner look at my genitalia	0.99	0.27	0.72	0.13
Medical interactions				
Get regular gynecological checkups (like Pap smears)	0.99	0.02	0.22	0.66
Life domain				
Emotional				
My self-esteem	0.99	0.09	0.99	0.27
Feeling down or depressed	0.08	0.57	0.57	0.14
Feeling anxious	0.48	0.26	0.28	0.57
How I viewed myself as a woman	0.99	0.41	0.99	0.40
How I viewed my body (self-image)	0.99	0.57	0.99	0.57
Social				
How I viewed myself in my job	0.99	0.99	0.50	0.04
Being comfortable around my friends	0.99	0.99	0.02	0.001 (+5% vs. -35%)

Online appendix

Life with CAH Study

Clitoromegaly questions

Some women with CAH have told us that they noticed their clitoris became larger when they were older. Other women with CAH have mentioned they can always remember their clitoris being larger. We are trying to find out what impact this has on women with CAH. Please choose the answer that best describes you. You may choose to skip any question that makes you feel uncomfortable by clicking on prefer not to answer.

Did you ever notice your clitoris grew over a short period of time (weeks or months)?
Yes / No / Not sure / Prefer not to answer

If: No / Not sure / Prefer not to answer, then:

Did you grow up with a clitoris that was larger than average?
Yes / No / Not sure / Prefer not to answer

How old were you when this happened?
6 years old or younger (before elementary school)
7-10 years old (elementary school)
11-13 years old (middle school)
14-17 years old (high school)
18 years old or older
Prefer not to answer

When this happened, how did you take your steroid medications (glucocorticoids)?
I did not take any
I took less than usual
I took same as usual
I took more than usual
Not sure
Prefer not to answer

How would you describe your clitoris at that time?
Longer/more protuberant
Wider/thicker at the tip of the clitoris
Both
Neither
Not sure
Prefer not to answer

After you noticed this difference in your clitoris, how likely were you to do the following activities?
OR
After you noticed this change in your clitoris, how likely were you to do the following activities?
Stopped doing this / Less / Same / More / Not sure / Does not apply / Prefer not to answer

Wear tight clothing or a swimsuit
Play sports, workout, jog or walk around by myself
Play sports, workout, jog or walk around with others (like in gym class or on a sports team)
Change clothes in a public locker room
Go on dates
Be sexually active
Have pleasure from sexual activity
Be sexually active without pain
Have your sexual partner look at your genitalia
Get regular gynecological checkups (like a Pap smear)

What IMPACT did having a larger clitoris have on the following?
Negative impact / No impact / Positive impact / Not sure / Does not apply / Prefer not to answer

My self- esteem
Feeling down or depressed
Feeling anxious
How I viewed myself as a woman
How I viewed my body (self-image)
How I viewed myself in my job
Being comfortable around my friends
How I viewed myself as a current (or future) parent
My plans or hopes to be in a romantic relationship
My plans or hopes to be sexually active