

Breast development and satisfaction in women with disorders/differences of sex development

Tim C. van de Grift^{1,2,3}, Baudewijntje P.C. Kreukels^{2,3}, and on behalf of dsd-LIFE

¹Department of Plastic Reconstructive and Hand Surgery, Amsterdam UMC (VU University Medical Center), Amsterdam, the Netherlands
²Department of Medical Psychology (Gender and Sexology), Amsterdam UMC (VU University Medical Center), Amsterdam, the Netherlands
³Amsterdam Public Health Institute, Amsterdam, the Netherlands

*Correspondence address. De Boelelaan 1117, 1081 HV Amsterdam, the Netherlands. Tel: +31 20 4443520;
E-mail: t.vandegrift@amsterdamumc.nl

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STUDY QUESTION: What are the levels of breast development and satisfaction in women with a Disorder/Difference of Sex Development (DSD)?

SUMMARY ANSWER: Compared with normative data, women with DSD reached lower Tanner stages and reported less breast satisfaction.

WHAT IS KNOWN ALREADY: Women with DSD may have chromosomal and hormonal variations that can impact typical breast development. While much emphasis is placed on genital development in this group, little is known about breast development, satisfaction and their association.

STUDY DESIGN, SIZE, DURATION: Data collection was part of the cross-sectional European multicenter dsd-LIFE study. Fourteen recruiting sites included 1040 participants between February 2014 and September 2015.

PARTICIPANTS/MATERIALS, SETTING, METHODS: A total of 695 female-identifying participants were included (Turner $n = 332$, 46,XY DSD $n = 141$ and congenital adrenal hyperplasia $n = 222$), with a median age of 28 years. Clinical (i.e. history of hormone and surgical treatments, Tanner breast examination) and patient-reported (i.e. breast satisfaction, relationship status, sexual satisfaction and experienced femininity) data was collected by independent trained research staff. The relationship between breast development, satisfaction and femininity was assessed. Control data on breast development and satisfaction in women without DSD was retrieved from the literature.

MAIN RESULTS AND THE ROLE OF CHANCE: Of the 695 participants, 61% had received estrogen replacement and 51% puberty induction therapy, whereas 2% had received breast augmentation surgery. Approximately 65% of participants had reached Tanner breast stage 5, which is substantially less than the general population (90%). Breast satisfaction was lower than normative data as well ($P < 0.001$, Cohen's $d = 0.45$). Breast size and breast satisfaction were associated with feelings of femininity.

LIMITATIONS, REASONS FOR CAUTION: Limitations include the sample representativeness (e.g. regarding the clinical heterogeneity) and the limited in-depth knowledge on (prior) hormonal regimens. Furthermore, no (matched) control data was collected as part of this study.

WIDER IMPLICATIONS OF THE FINDINGS: In order to support the psychosexual well-being of women with DSD, enhancing breast development by sufficient hormone replacement and possible augmentation surgery is advocated. The scope of DSD management should be beyond genital development only and consider breasts as well.

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Key words: disorders of sex development / Turner syndrome / congenital adrenal hyperplasia / breast growth / body image / sexuality

Introduction

Disorders (or Differences) of Sex Development (DSD) concerns a group of chromosomal and hormonal conditions resulting in a variation of sexual development. DSD diagnoses in individuals living in the female gender encompass Turner syndrome (TS; 45,XO and mosaic), congenital adrenal hyperplasia (CAH; 46,XX and androgen excess) and multiple conditions with 46,XY karyotype (e.g. androgen insensitivity syndrome, gonadal dysgenesis (GD)). While much clinical and scientific emphasis is put on genital anatomy and (outcomes of) genital surgeries, little is known of breast development and (outcomes of) breast surgeries in these groups.

In girls/women with DSD, breast development may be limited, when compared with women without DSD, due to lower estrogen production and/or effects. Over the years, a few studies on breast development have been published considering women with TS (Pertzelan *et al.*, 1982; Bannink *et al.*, 2009; Bartolin *et al.*, 2012; Labarta *et al.*, 2012; Ankarberg-Lindgren *et al.*, 2014; Sas *et al.*, 2014; Tanaka *et al.*, 2015; Wu and Li, 2019), CAH (Ning *et al.*, 2008; Völkl *et al.*, 2011; Kulshreshtha *et al.*, 2012) and 46,XY (Pertzelan *et al.*, 1982; Nihoul-Fékété *et al.*, 2006). Among women with TS, 36% had spontaneous breast development (Tanaka *et al.*, 2015). Breast development was more frequently observed in those with genetic mosaicism and those who had received estrogen (Ankarberg-Lindgren *et al.*, 2014) or growth hormone treatments (Tanaka *et al.*, 2015), while additional oxandrolone treatment was shown to delay breast development (Sas *et al.*, 2014). Estrogen replacement therapy aims to support female-typical hormonal levels and subsequent bone mass, body composition and breast development. While research showed that in the general population 90% of females reach the maximum of Tanner breast stage 5 (B5; and most others stage B4) (Mul *et al.*, 2001), a maximum of 50% of women with TS was likely to reach B5 (Pertzelan *et al.*, 1982; Bannink *et al.*, 2009; Labarta *et al.*, 2012). In addition, a wider chest (Wu and Li, 2019) but no major differences in breast morphology (Bartolin *et al.*, 2012) were observed, when compared with controls.

Studies in women with CAH showed varying levels of breast development (Ning *et al.*, 2008; Völkl *et al.*, 2011; Kulshreshtha *et al.*, 2012). Breast development differed according to deficiency variant and onset of treatment. One study reported that girls with CAH, aged 13 years on average, had a mean Tanner breast stage of 2.5 (3.2 in clinical controls) (Ning *et al.*, 2008), implying lesser/delayed breast development. Yet, another study reported earlier or similar breast development compared with controls (Völkl *et al.*, 2011). In the Völkl *et al.* (2011) study, patients received early diagnosis and treatment, while in another study (Kulshreshtha *et al.*, 2012) where limited breast development was observed, the majority of patients only received adequate treatment after the age of 8 years. The scarce literature on female individuals with 46,XY DSD showed frequent under- or atypically developed breasts (Pertzelan *et al.*, 1982; Nihoul-Fékété *et al.*, 2006).

With regard to breast satisfaction, even fewer studies have been published (Migeon *et al.*, 2002; Bannink *et al.*, 2006; Bartolin *et al.*, 2012; Kulshreshtha *et al.*, 2012; Ediati *et al.*, 2015; Kanhere *et al.*, 2015; van de Grift *et al.*, 2018). In both males and females with DSD, breast satisfaction has been observed to be lower than control values (Ediati *et al.*, 2015). Around three-quarters of control women were (very) satisfied with their breasts, yet no breast development data has been

collected among controls (van de Grift *et al.*, 2018). A higher BMI, body embarrassment and mental health problems were associated with more breast dissatisfaction (van de Grift *et al.*, 2018). In women with TS, one study reported breast satisfaction in 58% (Bannink *et al.*, 2006), similar to another study reporting relatively low satisfaction (Bartolin *et al.*, 2012). Although no reference data is provided in the aforementioned studies, other authors found satisfaction in around 80% of women without DSD (van de Grift *et al.*, 2016). The lowered satisfaction was mostly attributed to low breast volume. In one study, women with CAH expressed complaints about lack of breast development (Kulshreshtha *et al.*, 2012), albeit in a sample with significant delay of adequate treatment, and in another study 35% of women reported they wanted larger breasts (which was more frequently reported than dissatisfaction with genital appearance; 26%) (Kanhere *et al.*, 2015). One-third of the women surveyed with CAH and 46,XY karyotype reported breast dissatisfaction, which was more prevalent than in the matched controlled sample (Ediati *et al.*, 2015). Lastly, a study by Migeon *et al.* (2002) showed that while women with 46,XY DSD generally had small breasts, only a few had received breast augmentation surgery (Migeon *et al.*, 2002).

Study objectives

The aims of the present study are to investigate the stages of breast development and levels of satisfaction with breasts in a large sample of females with DSD and to study differences between diagnostic groups. Secondly, the study aims to quantify the number of women that received breast augmentation surgery and describe how this has impacted their lives. A last study objective is to examine the relationship between breast development, moderating factors (BMI, Tanner stage, relationship status, sexual satisfaction and experienced femininity) and breast satisfaction.

Materials and Methods

Procedure and participants

Data was collected as part of the dsd-LIFE study, a pan-European study including 14 academic clinics specialized in DSD care and research (Röhle *et al.*, 2018). The overarching objectives of dsd-LIFE were to comprehensively study the health and patient-reported outcomes of healthcare across the DSD conditions. Participants would be eligible to participate if they were at least 16 years old with a clinically confirmed DSD diagnosis (46,XY DSD, CAH, Klinefelter syndrome or TS). The study received ethical approval at all participating sites. The following institutions issued ethical approval: in France, the Université Claude Bernard Lyon, Le Centre Hospitalier Universitaire de Montpellier, Assistance Publique—Hôpitaux de Paris and Le Centre Hospitalier Universitaire de Toulouse; in Germany, Charité – Universitaetsmedizin Berlin, Ludwig-Maximilians-Universitaet, Munich, University of Luebeck, Universitaetsmedizin Goettingen and Westfaelische Wilhelms Universitaet Muenster; in Poland, Medical University of Lodz and Children's Memorial Health Institute, Warsaw; in Sweden: the Karolinska Institutet, Stockholm; in UK, University of Birmingham; and in The Netherlands, VU University Medical Center, Amsterdam, and Radboud University Nijmegen Medical Center, Nijmegen. This trial was registered in the German Clinical Trials Register: Registration

identification number: DRKS00006072, date of registration 17 April 2014. DRKS00006072.

Between February 2014 and September 2015, eligible individuals were identified through clinical records and invited to participate through a telephone call and/or mail. Additionally, support group members were invited in each country. An approximate number of over 3100 people was invited, of whom 1040 took part in the study (36%). After providing written informed consent, data collection included digital questionnaires, medical interviewing, physical examination and/or additional blood and bone tests. All anonymized clinical data was reviewed centrally for accuracy. For an extensive description of the study protocol, readers are referred to Röhle *et al.* (2018).

For the present study objective, data was included of the female-identifying participants. One transgender woman with Klinefelter syndrome was excluded from analyses due to her prior male-typical physical development. Control data on breast development and satisfaction was retrieved from the literature (Mul *et al.*, 2001; van de Grift *et al.*, 2016).

Measures

Clinical data

Clinical data was collected on standardized case report forms by independent trained research staff at each site. This included clinical diagnosis and age at diagnosis (in years). Clinical and patient-reported data was collected for information on prior puberty induction, (prior) estrogen replacement treatments, gonadectomy and breast augmentation performed. For those participants that provided consent, additional physical examination included measurement of height and weight to calculate BMI and assessment of Tanner breast stage.

Patient-reported data

Participants self-reported their current age, highest education according to the European Social Survey (recoded into lower, intermediate and higher) and relationship status on standardized scoring forms. Single items were used to question sexual satisfaction ('How satisfied are you with your sex life?', 1 = very dissatisfied to 5 = very satisfied; World Health Organization Quality of Life, abbreviated [WHO QOL-BREF; Whoqol Group, 1998]), experienced femininity ('In the last 12 months, how have you felt psychologically/emotionally?', 0 = not feminine at all to 10 = extremely feminine; self-constructed) and breast satisfaction ('How satisfied are you with your breasts?', 1 = very dissatisfied to 5 = very satisfied; body image scale [Lindgren and Pauly, 1975]). Lastly, a question asked for the experienced effects of surgery: 'Overall, how do you think that breast enlargement has affected your life?' (1 = very negative to 5 = very positive).

Analyses

The primary analyses included participant data regardless of the DSD subtype. Based on specific phenotype and hormone regimens, additional diagnosis-specific analyses were conducted. The sample demographics were presented as frequencies, means and medians depending on the distribution of data. Data on breast development, breast satisfaction and experienced femininity was analyzed by diagnostic subgroup (TS and mosaics, 46,XY DSD variants and CAH). Differences between diagnostic groups in the prevalence of Tanner stage and

levels of satisfaction were calculated using chi-squared tests, whereas diagnostic subgroup differences were calculated as means and independent sample Student's *t* tests or one-way ANOVA. Normative data on breast development and breast satisfaction in adult women without DSD was retrieved from the literature (Mul *et al.*, 2001; van de Grift *et al.*, 2016). Data on the prevalence and experienced effects of breast augmentation was analyzed as frequencies (i.e. the number of (dis)satisfied participants). Women with breast augmentation were included in the analyses of breast development and associations. Explorative bivariate associations were analyzed to test a relationship between Tanner stage, breast satisfaction and experienced femininity. Lastly, the association between breast satisfaction (dependent variable) and possible contributing factors was tested through multinomial logistic regression including BMI, Tanner stage, relationship status, sexual satisfaction and experienced femininity as independent variables (based on previous research and clinical expertise). Analyses were performed using SPSS Statistics (IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY, USA: IBM Corp.).

Results

Study sample

A total of 695 female-identifying individuals participated (TS $n = 332$, 46,XY DSD $n = 141$ and CAH $n = 222$) in the study. Participants were on average 28 years old and frequently single (Table I). The majority of participants had received puberty induction or/and estrogen replacement therapy.

Breast augmentation and effects on life

Eleven participants (4%) had received breast augmentation surgery. Women who received breast augmentation were diagnosed with TS ($n = 4$), GD [complete ($n = 2$) and partial ($n = 1$)], complete androgen insensitivity syndrome ($n = 2$), partial androgen insensitivity syndrome (PAIS) ($n = 1$) and CAH ($n = 1$). In all participants, surgery was performed between ages of 16 and 25 years. Most participants who had received breast augmentation were younger than 30 years at time of study participation, implying that this surgery was mostly performed recently. Of the participants who had received a breast augmentation, nine reported that the surgery has had a (very) positive effect on their lives, one reported no effect whereas one reported a negative effect.

Breast development, satisfaction and associations

Data on Tanner stage were available for 69% (46,XY) and 84% (TS) of the participant groups while data on breast satisfaction was available for 87% (TS) and 95% (46,XY) of the participant groups. Minor differences in participation rate for the breast examination by study site are described in Röhle *et al.* (2018). The majority of the women had Tanner stage B5 (TS 62%, 46,XY 60% and CAH 68%), and the ones who did not generally had B4 (Table II). For the sample as a whole, a negative association was observed between age of diagnosis and Tanner stage at follow-up (a later diagnosis was associated with lesser breast development; $r[494] = -.152$, $P = 0.001$). Within the 46,XY DSD group, participants with complete GD ($M = 3.7$ [1.2]) and PAIS ($M = 4.1$ [.86]) had on average lower Tanner breast

Table I Characteristics of the sample in a study of breast development in women with disorders/differences of sex development.

	n (%)*
N = 695	
Diagnosis	
Turner syndrome (incl. mosaic)	332 (48)
46,XY DSD	141 (20)
CAIS/PAIS	69/17
Gonadal dysgenesis (complete/partial)	20/12
Other [^]	23
Congenital adrenal hyperplasia	222 (32)
Median age at diagnosis (in years; Q1–Q3)	7 (0–14)
Median age at study participation (years; Q1–Q3)	28 (21–39)
Education level	
Lower	108 (17)
Intermediate	303 (49)
Higher	208 (34)
Relationship status	
Single	423 (64)
In a relationship	241 (36)
Sexual satisfaction	
(Very) satisfied	241 (37)
Neither satisfied nor dissatisfied	235 (36)
(Very) dissatisfied	172 (27)
Puberty induction received	327 (51)
Estrogen treatments received (ever)	351 (61)
Gonadectomy performed	156 (48)
Breast augmentation performed	11 (4)
Mean BMI (kg/m ² ; SD)	26 (6)

CAIS = complete androgen insensitivity syndrome, DSD = differences/disorders of sex development, PAIS = partial androgen insensitivity syndrome

*Percentages calculated over the available data

[^]Including ovotesticular DSD, steroid metabolism disorders

stages than the other 46,XY subgroups as well as the participants with TS and CAH. No such difference was observed between the CAH subgroups. Those with spontaneous puberty had a higher mean Tanner breast stage ($M = 4.5$ [.91]) compared with those without spontaneous puberty ($M = 4.3$ [.99]; $t[524] = -2.1$, $P = 0.04$, Cohen's $d = 0.19$), while no such difference was observed for those who had or had not received estrogen therapy. No difference between 'estrogen only' treatment and 'combined estrogen/progesterone' treatment was observed on breast growth and satisfaction. As mentioned earlier, reference data state that in females without DSD, around 90% reaches B5 at the age of 19 years, while the others reach B4 (Mul *et al.*, 2001). All women who had received breast augmentation had B5 after surgery.

Roughly half of the participants in each diagnostic group was (very) satisfied with their breasts (TS 48%, 46,XY 50% and CAH 54%), while around 30% was (very) dissatisfied. No statistically significant differences between the three major diagnostic groups were observed. When compared with female BIS reference values ($M = 2.2$ [.78])

(van de Grift *et al.*, 2016), participants with DSD were significantly less satisfied with their breasts ($M = 2.7$ [1.2]; $t[626] = 11.4$, $P < 0.001$, Cohen's $d = 0.45$). Females with complete GD reported lowest breast satisfaction on average ($M = 3.1$ [1.5]), although the sample sizes were too small to perform reliable statistics. Participants of all clinical groups reported moderate feelings of femininity (around 7/10). Both a lower Tanner stage and more breast dissatisfaction were associated with lower feelings of femininity (Tanner: $r[492] = 0.10$, $P = 0.02$; BIS: $r[597] = -.21$ $P < 0.001$).

Factors associated with breast satisfaction

No statistically significant relationship between breast satisfaction and BMI, Tanner stage of the breasts and relationship status was observed (Table III). Breast satisfaction was significantly associated with sexual satisfaction and feelings of femininity, implying a positive relationship between breast and sexual satisfaction and feelings of femininity.

Table II Breast development and satisfaction by diagnostic subgroup.

	Turner syndrome (n = 332)**	46,XY DSD (n = 141)##	Congenital adrenal hyperplasia (n = 222)§§	Test statistics
Tanner stage breasts				$\chi^2(8,549) = 23, P = 0.004$
1	8 (3)	3 (3)	8 (5)	
2	2 (1)*	3 (3)	5 (3)	
3	18 (7)	12 (12)*	1 (1)*	
4	77 (28)	21 (21)	42 (24)	
5	173 (62)	58 (60)	118 (68)	
Mean Tanner (SD)	4.5 (.88)	4.3 (1.0)	4.5 (1.0)	
Breast satisfaction (BIS)				$\chi^2(8,627) = 12, P = 0.171$
Very satisfied	33 (12)	28 (21)	37 (18)	
Satisfied	104 (36)	39 (29)	73 (36)	
Neutral	65 (23)	24 (18)	36 (18)	
Dissatisfied	64 (22)	30 (22)	38 (19)	
Very dissatisfied	22 (8)	13 (10)	21 (10)	
Mean satisfaction (SD)#	2.8 (1.1)	2.7 (1.3)	2.7 (1.3)	
Mean feelings of femininity (SD)§	7.0 (2.2)	7.4 (2.3)	7.1 (2.3)	$F(2,617) = 1.6, P = 0.198$

Data: n (%), percentages calculated over the available data

BIS = body image scale

*Value different compared to expected in post hoc testing (possible statistically significant differences), #higher implies less satisfied (1 to 5). §0 = not feminine at all, 10 = extremely feminine

** $n_{\text{Tanner}} = 278$ and $n_{\text{satisfaction}} = 288$, ## $n_{\text{Tanner}} = 97$ and $n_{\text{satisfaction}} = 134$, §§ $n_{\text{Tanner}} = 174$ and $n_{\text{satisfaction}} = 205$

Norm value of BIS = 2.18 (.78), 77% (very) satisfied, 14% neutral, 9% dissatisfied in female controls (van de Grift et al., 2016)

Data includes women who had had breast augmentation

Table III Multinomial logistic regression of factors predicting breast satisfaction (BIS).

	B (SE)	OR (95% CI)	P
(Very) satisfied versus neutral			
Intercept	-.62 (1.02)		.54
BMI	<.01 (.02)	1.00 (.96–1.05)	.85
Tanner stage	.14 (.14)	1.15 (.87–1.52)	.34
Relationship status	-.34 (.28)	.71 (.41–1.23)	.22
Sexual satisfaction	-.13 (.06)	.88 (.78–.98)	.03
Femininity feelings	.12 (.13)	1.12 (.87–1.15)	.37
(Very) satisfied versus (very) dissatisfied			
Intercept	1.81 (.82)		.03
BMI	<.01 (.02)	1.00 (.97–1.04)	.85
Tanner stage	-.01 (.11)	.99 (.80–1.23)	.93
Relationship status	-.08 (.24)	.92 (.58–1.46)	.73
Sexual satisfaction	-.19 (.05)	.83 (.75–.91)	<.001
Femininity feelings	-.27 (.10)	.77 (.62–.95)	.01

$R^2 = 0.08$; model $\chi^2(10,464) = 31.83, P < 0.001$

OR = odds ratio

Discussion

To our knowledge, the present study was the first of this scale to report on breast development, breast satisfaction and experienced femininity of women across the DSD spectrum. Main findings include

- the lower portion of women with DSD reaching Tanner breast stage 5
- (B5) and the lower portion of women being satisfied with their breasts,
- compared to control values (obtained from the literature). Objectified
- breast development and breast satisfaction were found to be associ-
- ated with experienced femininity. A small minority of women (n = 11)

had received breast augmentation surgery, while those who did generally reported a positive effect on their lives. These findings shed some light on the role of breasts in psychosexual development in DSD as well as the importance of adequate hormone replacement treatments and the possible role of breast surgery in the conduct of clinical care.

The present data indicate that 60–68% of the women in the diagnostic subgroups had reached Tanner B5 in adulthood. Normative data shows that this percentage is around 90% in women without DSD (Mul *et al.*, 2001). Available literature confirms the smaller likelihood of women with DSD to reach Tanner B5 (Pertzalan *et al.*, 1982; Nihoul-Fékété *et al.*, 2006; Bannink *et al.*, 2009; Labarta *et al.*, 2012), yet with varying percentages. These differing findings between the clinical studies on DSD may be explained by the sample sizes and by the changing regimen with early diagnosis and hormone replacement therapy. The present finding, negatively associating age of diagnosis with Tanner stage, is in line with this hypothesis. Early diagnosis and treatment enable (monitoring and possibly replacing) sufficient levels of circulating estrogens during the critical period of breast development, resulting in the development of more female-typical breast tissue (Ankarberg-Lindgren *et al.*, 2014).

Around 50% of the participants in the present study were satisfied with their breasts, with no differences between the diagnostic subgroups. The levels of breast dissatisfaction are largely in line with the existing literature (Bannink *et al.*, 2006; Bartolin *et al.*, 2012; Ediati *et al.*, 2015; van de Grift *et al.*, 2018). The lowered breast satisfaction is likely the result of the female-atypical breast size and/or morphology (Bartolin *et al.*, 2012; Wu and Li, 2019). Having smaller breasts may result in lower body image, lower self-esteem and feelings of being different. An earlier study pointed out that a significant portion of women with DSD mentioned they wanted larger breasts (Kanhere *et al.*, 2015). While genital appearance and interventions of genitalia generally receive much attention in DSD 'management', breasts are a less frequent a topic of discussion.

Besides early diagnosis and the subsequent early start of hormone replacement therapy, which should be the primary focus of clinical treatments, breast augmentation surgery may be a possible additional modality for women with DSD. Only recently have systematic registries on breast augmentation been developed, but older studies estimate a prevalence of breast augmentation in the general population of around 0.8% (Cook and Perkins, 1996). Among the present participants, only 2% ($n = 11$) had received breast augmentation surgery, while a much larger group could possibly qualify (60 women with Tanner stages 1 to 3, 140 women with Tanner stage 4). To our knowledge, little scientific evidence has been produced on the incidence of breast augmentation in DSD, while it appears to be marginally applied (Migeon *et al.*, 2002). In contrast with a number of genital surgical procedures, breast surgery is applied after individual request/informed consent. The fact that relatively few women with DSD had received breast augmentation surgery may be related to the fact that the topic is not included in most clinical guidelines and many patients and providers are not aware of the treatment options. The present finding that it was mostly younger participants that had received breast augmentation suggests that this treatment may become more conventional. In the current study, women reported that breast augmentation generally had a positive effect on their lives. This again may be associated with a more positive body image, higher self-esteem and more openness and support—factors that have previously been associated with devel-

opment of (secondary) sex characteristics in individuals with DSD (van de Grift *et al.*, 2018). Another reason breast augmentation is infrequently performed may be the fact that in many countries this procedure is considered solely as aesthetic surgery and therefore not reimbursed. Recently, the Dutch government has decided to reimburse breast augmentation for transgender women in case of an invisible inframammary fold and breast tissue smaller than 1 cm objectified by ultrasound (Ministry of Health, Welfare and Sport, 2017). Although not clearly marked, the inframammary fold may become visible at B4/B5, while the average glandular breast volume was measured to be 0 mL in B1, around 5 mL in B2, around 50 mL in B3 (with one-quarter below around 20 mL) and around 80 mL in B4/B5 (with one-quarter below around 60 mL) in peri-pubertal girls, using MRI scans (Fugl *et al.*, 2016). The rationale behind refunding breast augmentation surgery was that women in this group in which estrogen therapy does not result in sufficient breast tissue development can be hampered by lower feelings of femininity and be less socially emancipated. Additional analysis may be required to determine to what extent this line of reasoning could also apply to women with DSD (e.g. given the nature of gonadal dysfunction and lowered levels of estrogens during the timeframe of breast development), recognizing that sufficient hormone replacement therapy is the keystone of supporting female-typical breast development.

Although the cross-sectional design of the present study did not allow causal relationships to be determined, several factors were observed to be associated with breast development and breast satisfaction. Both Tanner stage and breast satisfaction were found to be associated with experienced feelings of femininity. Also, breast satisfaction was positively associated with sexual satisfaction. While little evidence on these topics is available for women with DSD, these findings are in line with studies in women without DSD (e.g. Woertman and van den Brink, 2012); it is known that body appearance and body satisfaction influence self-attitudes and sexual behavior. Lower body image can result in increased self-awareness during sexual activities, problems with initiating sexual contacts and a higher incidence of sexual dysfunction. The relationship between breast development and experienced femininity/sexual satisfaction may therefore be mediated by concepts such as body image and self-esteem (van de Grift *et al.*, 2018). This implies that breast development and breast satisfaction (as an outcome of adequate hormone treatment in some females with DSD) can impact multiple domains of psychosocial well-being. These domains have been described as being impaired in individuals with DSD, when compared with normative samples (e.g. Schützmann *et al.*, 2009). In addition, we observed no statistically significant associations between breast satisfaction and BMI or relationship status. Earlier literature did find an association between general body satisfaction and BMI (van de Grift *et al.*, 2018); yet, (over)weight is likely to influence other areas of appearance more than breasts specifically. With regard to relationship status, the quality of and support within one's relationship may be more influential for breast satisfaction than the relationship status as such. In conclusion, it is important for clinicians to be aware that breast development and satisfaction can be important subjects to discuss during treatment as they may impact different areas of psychosexual well-being.

Limitations

The present study has several methodological limitations. Regarding the sample, the representativeness may be limited by the relatively

low participation rate. While it is unclear whether participants and non-participants differed in major demographic characteristics (due to ethical restrictions no data on non-responders was collected [Röhle *et al.*, 2018]), participants may have been more motivated to participate in this extensive study, leaving more reluctant or less involved individuals out of scope. Furthermore, no (matched) control data has been collected as part of this study. Also, the heterogenic sample included women with a large variety of syndromic and genetic variances. Due to the small sample size for each condition and underlying genetic mutation, no in-depth analyses including these variables were possible. Similarly, little information was available on the specific hormone treatment regimens, leaving this important variable out of the scope of the study. Lastly, several psychometric biases may have been in place, including recall and confirmation biases, fostering the relationships between self-reported measures such as breast satisfaction, experienced femininity and sexual satisfaction. Future studies could focus on replicating the present findings or on hypothesis-generating designs such as explorative qualitative approaches (e.g. on the role of breast development in DSD, on experiences of women who had received breast augmentation).

Conclusion

The present study reports on an infrequently studied subject, namely breast development and satisfaction in women with DSD. Similarly as in other areas of physical development, the present findings underline the importance of early diagnosis and appropriate hormone treatment to support feminine-typical breast development. Women in the current sample had less breast development and lower breast satisfaction compared with control values obtained from the literature. In contrast with genitalia, the role of breasts and breast surgery has received little scientific and (most likely) clinical attention. While current guidelines on clinical management of individuals with DSD include little information on breast development, optimal hormone regimens to support breast development and possible augmentation, those women who did receive breast augmentation mostly reported positive effects on their life. Therefore, in order to support positive psychosexual development, more attention to this subject is recommended.

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Authors' roles

T.G and B.K. conceptualized, designed, and supervised the study. Data collection and statistical analyses were conducted by T.G and B.K. T.G.

wrote a first draft of the manuscript, which was entirely revised by T.G. and B.K., until full consensus was reached regarding the final version of the article. The final version of the article was approved by the dsd-LIFE consortium.

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Conflict of interest

None to declare.

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