ORIGINAL RESEARCH—TRANSGENDER AND GENDER NONCONFORMANCE

Clinical Review: Breast Development in Trans Women Receiving Cross-Sex Hormones

Katrien Wierckx, MD,* Louis Gooren, MD, PhD,† and Guy T'Sjoen, MD, PhD*‡

*Department of Endocrinology, Ghent University Hospital, Ghent, Belgium; †AndroConsult, ChiangMai, Thailand; ‡Department of Sexology and Gender Problems, Ghent University Hospital, Ghent, Belgium

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ABSTRACT

Introduction. In trans women (male-to-female transsexual persons), cross-sex hormone therapy is administered to induce feminization. Breast development is an important part of feminization for most trans women.

Aim. The aim of this study is to assess the effect of cross-sex hormone therapy on breast development in adult trans women. Additionally, we aimed to investigate the benefit or harm of administration of progestogens on breast development.

Methods. A review of the literature in Embase, Medline, The Cochrane Library, PsycINFO databases, PubMed, and Web of Knowledge until January 2014.

Main Outcome Measures. Effects of cross-sex hormone therapy and progestogens on breast development in trans women.

Results. Only few studies with low quality of evidence addressed these topics. The available evidence suggests that breast development is insufficient for the majority of trans women and that type and dosage of hormonal therapy seem not to have an important role on final breast size.

Conclusions. Our knowledge concerning the natural history and effects of different cross-sex hormone therapies on breast development in trans women is extremely sparse and based on low quality of evidence. Current evidence does not provide evidence that progestogens enhance breast development in trans women. Neither do they prove the absence of such an effect. This prevents us from drawing any firm conclusion at this moment and demonstrates the need for further research to clarify these important clinical questions. **Wierckx K, Gooren L, and T'Sjoen G. Clinical review: Breast development in trans women receiving cross-sex hormones. J Sex Med 2014;11:1240–1247.**

Key Words. Transsexualism; Progesterone; Breast; Side Effects; Breast Cancer

Introduction

The current treatment regimens of most trans women (male-to-female trans persons) involve hormonal therapy as well as sex reassignment surgery (SRS). The aims of hormonal treatment are mainly to induce feminization which consists of breast formation, reduction of masculine hair growth, and a more female fat distribution [1]. In addition to inducing physical changes, the act of using cross-sex hormones is itself an affirmation of gender identity in many trans persons.

With regard to the hormonal impact on female breast development, the classic view is that estrogens induce proliferation, whereas progestins cause differentiation in female breast development [2,3]. It is widely assumed that progestins have no significant role in the formation of the volume of the breasts, the reason why it is not included in endocrine treatment of girls with Turner and juvenile trans women persons [1]. The first physical sign of puberty in girls is usually a firm, tender lump under the center of the areola of one or both breasts. By the widely used Tanner staging of

puberty, this is stage 2 of breast development (stage 1 is a flat, prepubertal breast). Within 6–12 months, the swelling has clearly begun in both sides, softened, and can be felt and seen extending beyond the edges of the areolae, described as stage 3 of breast development. By another 12 months (stage 4), the breasts are approaching mature size and shape, with areolae and nipples forming a secondary mound. In most young women, this mound disappears into the contour of the mature breast (stage 5), although there is so much variation in sizes and shapes of adult breasts that stages 4 and 5 are not always separately identifiable [2,4].

A number of studies have demonstrated the efficacy of several hormonal preparations to induce feminization in trans persons, but these observations are rather of a subjective than of an objective nature, in the sense that the feminization has not been quantified [5–8]. These treatment regimes mostly combine estrogen treatment with anti-androgen and/or gonadal axis suppressing medication. In Europe, cyproterone acetate, a progestational agent with androgen receptor-blocking properties, is commonly used before SRS, usually preceding or in combination with estrogens [8,9]. Thus, most trans women in Europe receive in fact a compound with progestational properties before SRS, though cyproterone acetate is not administered for its progestational properties but for its efficacy as an oral anti-androgen. As there is no FDA approval of cyproterone acetate, many centers in the United States use spironolactone, a diuretic with mainly anti-androgen but also a weak estrogenic [10] and progestational activity [11]. Other agents with anti-androgenic properties used are nonsteroidal androgen receptor blockers, such as flutamide and bicalutamide or 5-alpha reductase inhibitors such as finasteride and dutasteride. Several centers use gonadotropin-releasing hormone (GnRH) analogs to suppress androgen production [12,13], but the use of GnRH analogs is limited mainly because of its high costs [13]. Some clinicians also prescribe progestogens to decrease the doses of estrogens required for complete suppression of testosterone levels [14].

After SRS which involves orchidectomy, penectomy, and vaginoplasty, estrogen therapy is to be continued alone, and many centers discontinue agents blocking testosterone action or reducing testosterone levels and generally do not prescribe progestogens after SRS [8,9].

Postpubertal women show a large degree in size and shape of breast development [2]. Trans women are primarily interested in a sufficient degree of breast development confirming the gender role of a woman to themselves and to the outside world. Although there is undeniably a role of progesterone in breast development and lactation, it is uncertain whether the treatment of progestogens adds much to the volume of the breasts, the concern of trans women.

This review will discuss the current knowledge on breast development during cross-sex hormone treatment. The second aim of this literature review is to investigate whether there is a specific role of progestogens relevant to breast development of trans women. In the medical profession and even more in the transsexual community, there has been an ongoing debate for many years on the potential benefit of adding progestogens to estrogen use in trans women's hormonal treatment, especially concerning its role in the volume/size breast development and maintenance. Progestagen treatment is also often requested by trans women themselves as it is their perception that their treatment should closely mimic hormonal treatment of hypogonadal women requiring hormone treatment. However, for the latter group, addition of progestogens has a different relevance, specifically the modifying estrogen effects on the uterus potentially inducing cancerous development.

Methods

We searched through the following electronic databases up to January 2014: Embase, Medline, The Cochrane Library, PsycINFO databases, PubMed, and Web of Knowledge. Search terms included "breast" and "trans," and "transsexual" or "transgender." We also searched on "cross-sex hormone therapy," "hormone therapy," "estrogen," "progestins," "progestogens," "progesterone" and "trans," and "transsexual" or "transgender" as some papers on endocrine treatment of trans persons included a section on breast development. English language articles in peer-reviewed medical journals concerning the effects of cross-sex hormone therapy and progestogens in adult trans women on breast size and breast growth were retrieved and reviewed for content. Also, the references of these papers were used to identify other literature of interest. Articles addressing surgical techniques or surgical complications and histological findings were excluded.

Results

The development of breasts in pubertal girls has been described in the Introduction highlighting

Table 1 Studies concerning the effect of cross-sex hormone treatment on breast size in trans women

Center	Study design	Hormone treatment	N	Outcome
Department of Dermatology, New York University, New York [15]	Case reports	Various estrogen treatments	5	Breast development
Gender Clinic, University of Texas, Medical Branch, Galveston, Texas [16]	Cross- sectional	EE 0.05–10 mg OD or conjugated equine estrogens (1.25–5 mg OD)	38	Effect of EE vs. conjugated equine estrogens on breast hemicircumference Effect of estrogen dose on breast hemicircumference
Gender Clinic, University of Texas, Medical Branch, Galveston, Texas [17]	Prospective	EE 0.05–10 mg OD or conjugated equine estrogens (1.25–10 mg OD) 15% oral progestin (mostly MPA 10 mg OD)	60	Time course of breast growth (breast hemicircumference) Effect of ethinyl estradiol vs. conjugated equine estrogens on breast hemicircumference Effect of estrogen dose on breast hemicircumference Effect of progestin on breast hemicircumference
Department of Endocrinology, University of Britisch Columbia, Vancouver, Britisch Columbia, Canada [18]	Prospective (12 months)	Conjugated equine estrogen 0.625 OD up to 5 g OD Spironolactone 100–200 mg OD MPA 10 mg OD if needed	50	Cup size
Department of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand [19]	Cross sectional	Various cross-sex hormone treatments	28	Tanner stage
Department of Plastic and Reconstructive Surgery, Academic Hospital Vrije Universiteit, Amsterdam, Netherlands [20]	Prospective	EE 100 μg OD and CPA 100 mg OD	120	Effects of cross-sex hormone treatment on thorax circumference
Department of Plastic and Reconstructive Surgery, Academic Hospital Vrije Universiteit, Amsterdam, Netherlands [21]	Retrospective	EE 100 μg OD and CPA 100 mg OD	359	Percentage of trans persons that underwent augmentation mammoplasty
Department of Medicine University of Seville Seville, Spain	Cross sectional	Various cross-sex hormone treatments	27	Tanner stage
Department of Obstetrics and Gynaecology, Erlangen University Hospital, Germany [22]	Prospective (24 months)	Subcutaneous injection of GnRH every 4 weeks and estradiol valerate 6 mg OD	60	Cup size Percentage of trans persons that planned to undergo augmentation mammoplasty
Department of Sexology and Gender Problems, University Hospital Ghent, Belgium [23]	Cross-sectional	CPA 50–100 mg OD; various estrogen treatments	32	Percentage of trans persons that underwent augmentation mammoplasty
Department of Medicine, St George's hospital, London, United Kingdom [13]	Retrospective	Various estrogen and anti-androgen treatments	165	Predictive markers for mammoplasty Type of estrogen and type of anti-androgen

CPA = cyproterone acetate; EE = ethinyl estradiol; MPA = medroxyprogesterone acetate; OD = once daily

the relevance of estrogens with a much less significant role of progesterone in formation and size of pubertal breast development [3,4]. Our literature search on the effects of cross-sex hormone treatment in trans women on breast development is shown in Table 1, listed by the year of publication.

Few studies have investigated the effects of cross-sex hormone treatment on breast volume. Meyer et al. [17] investigated breast growth in 52 trans women during cross-sex hormone treatment. Notably, 41 trans women received cross-sex hormone treatment with a median of 26.4 months before inclusion in the study. Different estrogen regimes (ethinyl estradiol [EE], conjugated estrogen, or both) were analyzed, and 15 trans women of their sample (28%) additionally received a progestational agent. No difference in breast size was observed between trans women who received progestogens compared with the others. Use of different formulations of estrogens as well as the fact that many trans women had already received cross-sex hormone treatment hampered good comparison, although prior estrogen treatment and type of estrogen were not found to affect final breast size.

The authors observed that the increase in breast size usually begins within 2–3 months after the start of cross-sex hormone treatment and progresses over 2 years. Final breast size was not dif-

ferent in relation to which type of estrogen had been used (conjugated estrogens or EE) or to the dose of EE. The latter was in contrast with their previous cross-sectional study in 38 trans women whose breast size, measured by the maximal breast tissue circumference, differed according to the dose of estrogen therapy: trans women using EE 0.05 mg daily and those using conjugated equine estrogens 5 mg daily had a higher maximal breast circumference compared with respectively those using EE 0.01 mg daily and those using conjugated equine estrogens 1–2.5 mg daily [16]. Orentrich et al. [15] neither found a clear association between final breast size and dose of estrogen in four case reports. Seal et al. [13] neither observed a difference in type of estrogen treatment between trans women who underwent augmentation mammoplasty compared with those who did not.

Kanhai et al. [20] investigated the effect of cross-sex hormone therapy, consisting of cyproterone acetate 100 mg (an anti-androgen with progestational properties) and EE 100 μg daily, on thorax circumference at the nipple. They observed that the circumference at the nipple increased from a mean of 91–93 cm during the first 18 months of cross-sex hormone treatment. Kanhai et al. [21] also explored how many of their post-SRS sample of trans women underwent augmentation mammoplasty after cross-sex hormone treatment and concluded that almost 70% of trans women did so.

Similar results were observed by others [22,23]. De Cuypere and colleagues [23] found that 66% (N = 21) of their sample underwent augmentation mammoplasty after treatment with cyproterone acetate 50–100 mg daily and estrogens aiming at female physiological levels. In the study of Dittrich et al. [22], 60 trans women were treated with GnRH analogs and estradiol valerate 6 mg daily. Seventy percent of them wished to undergo augmentation mammoplasty as they found their breast size too small after 24 months of hormonal therapy. Only 35 percent of trans women in their group had a B cup (mean difference of 14–16 cm between circumference at the nipple and circumference just below the breast) or more, 35% had an A cup (mean difference of 12–14 cm), and 30% had less than an A cup after 2 years of cross-sex hormone therapy. The authors concluded that this treatment regime, not including a drug with progestational properties, had a similar efficacy compared with prior reported treatment regimes using cyproterone acetate and EE [21] and thus questioned the use of progestogens as part of the endocrine treatment of trans persons in order to enhance breast growth.

Prior et al. [18] also observed that most trans women developed an A cup. They explored the effects of 12-month administration of spironolactone 100–200 mg in combination with conjugated equine estrogen 0.625 daily up to 5 g daily on feminization in 50 trans women. In spite of this modest breast development, few trans women in their group sought augmentation surgery afterwards. Reutrakul and colleagues as well as Sosa and colleagues reported that all trans women developed tanner stage 2 or 3, unless they underwent augmentation mammoplasty [19,24].

Predictive markers for mammoplasty were examined by Seal et al. [13] in 156 trans women. They found that type of estrogen, duration of hormonal therapy, and age of initiation of cross-sex hormone treatment were no predictive markers for breast augmentation. Self-administration of estrogens and previous use of spironolactone were associated with a higher rate of augmentation mammoplasty. In addition, it appeared that besides serum estradiol levels, testosterone levels were also higher in those women who self-medicated their hormonal therapy and that the latter women underwent more often augmentation mammoplasty.

In summary, treatment protocols using medications with progestational properties [15,21,23] did not result in a difference in the request for mammoplasty in comparisons with treatment protocols that did not use progestins [18,19,22].

Discussion

To our knowledge, this is the first review addressing the effects of cross-sex hormone treatment on breast growth and whether the use of progestogens has an additive effect on breast size in trans women. Despite the fact that breast growth is a very important aspect of feminization, to which trans women themselves assign great importance, we detected only a few studies addressing this topic. This may also be related to the difficulty of assessing reliably and reproducibly breast growth upon cross-sex hormone treatment. Objective measurements of breast size as breast hemicircumference may not reflect the appearance as a whole as breasts in trans women are placed more laterally on the chest wall and appear smaller than the objectively same-sized breast in natal women [13]. However, the desire to undergo augmentation mammoplasty may not only

be dependent on final breast size but may also be associated with many other factors, for example body image perception and satisfaction and reimbursement practices. Studies comparing objective measurements as breast hemicircumference and clinical end points (breast augmentation surgery) are of interest.

Current evidence suggests that final breast size appears insufficient in the perception of the majority of trans women as 60–70% seeks surgical augmentation. However, as in cisgender women, many interindividual differences in breast size between trans women are present. In order to have realistic expectations when initiating hormone treatment, trans women should be counseled regarding the expected effects of current cross-sex hormone therapies on breast development. Some trans persons desperately seeking breast augmentation resort to quackery such as injection of silicone or petroleum jelly [25], with potentially important side effects [26–31].

Limited data are currently available on predictors of breast size. Meyer et al. [17] found that duration of hormonal therapy influences final breast size. Some authors suggest that depending on the age of trans women, other effects are to be expected and that breast growth in young trans women may be more pronounced compared with older women [25]. Additionally, individual breast tissue sensitivity and body weight are suggested as important determinants of breast size in trans women [15,32–34], although to our knowledge, these hypotheses are only experience based. In trans women, shoulder width may also be an important factor of perceived breast size and configuration [13].

The majority of current evidence suggests that neither type nor dosage of estrogen has an effect on final breast size [16,17]. Also, serum estradiol levels were found to be similar in trans women undergoing augmentation mammoplasty compared with those who did not [13]. In addition, the proportion of trans women seeking augmentation mammmoplasty was comparable among different types of estrogens [13] and between centers using different estrogen treatment regimes (cyproterone acetate/EE vs. GnRH-analogs and estradiol valerate) [21–23]. However, the retrospective nature of this study should be taken into account as baseline differences between those two groups of women cannot be ruled out. In addition, women who self-medicated may have other personality traits compared with those who did not, which may have affected surgical practices.

Overall, these findings may suggest that besides estrogen levels, the degree of testosterone suppression may also be an important factor regarding breast development in trans women. Androgen levels have indeed been found to inhibit breast tissue proliferation in vitro [35–37] in rodents [38] and monkeys [39,40]. However, in human clinical studies, the results are inconclusive as most [41,42] but not all studies [43,44] observed that higher total testosterone levels are associated with increased breast tissue proliferation in both pre and postmenopausal women.

Interestingly, Seal et al. [13] described that previous users of spironolactone more often underwent augmentation mammoplasty compared with users of other anti-androgens. The authors hypothesized that the agonistic estrogen effects of spironolactone could lead to an excessive estrogenic action and consequent poorer breast outcome as also seen in their group of trans women who self-medicated cross-sex hormonal therapy and had higher levels of estrogens. However, the potential androgen receptor agonistic effects may be another explanation. Indeed, spironolactone has been shown to induce cell growth in an in vitro study of androgen-sensitive murine mammary cancer cells [45]. Furthermore, it was found that spironolactone significantly activated both wild-type and mutant androgen receptors in prostate cancer cells [46].

The hypothesis that excessive estrogenic action negatively affects breast development brings up the question whether a step-up dose of estrogens would be preferable to enhance breast development in trans women. To our knowledge, no data are available on the effects of this treatment on breast development of trans women. However, step-up dosages of unopposed estrogens are usually prescribed for puberty induction (e.g., in Turner girls). This therapy is mainly prescribed to avoid acceleration of bone maturity by high-dose estrogen treatment resulting in a reduced final height. However, beneficial effects on breast development have been suggested, although clinical rather than experience based [47].

The available evidence does not provide support for better effects on breast size of adding progestogens to cross-sex hormone administration in trans women as suggested by some authors [14,18,48–51]. However, it should be said that the quality and amount of available evidence are extremely poor and hamper any firm conclusion at this moment. Also, many centers use anti-androgens with some progestational action and

complicate the available evidence. In addition, some occasionally use progestins to lower testosterone levels after maximum estrogen levels when a patient cannot tolerate an estrogen-based regimen, abnormal psychological irritability, and mammary tenderness [52,53]. Furthermore, all progestogens by definition have some progestational activity, but they differ in chemical structure, metabolism, pharmacokinetics, affinity, potency, and efficacy via steroid receptors and intracellular action. All these differences can translate into very different biological and clinical effects and advocate the absence of a class effect of progestogens [54].

Nevertheless, breast development in trans women might be similar as in cisgender women indicating a major role for estrogen rather than progesterone in the early stages of breast development. The central role of estradiol in initiating breast growth at puberty is revealed by the poor-developed breast of estrogen receptor-alpha knockout mice [55], whereas progesterone knockout mice showed to have a morphologically indistinguishable ductal architecture from wild-type virgin mice [56]. Moreover, during pubertal induction in girls, early administration of progesterone is not recommended as premature initiation of progestin therapy can compromise ultimate breast growth [57]. It is however of note that progesterone is known to be an important determinant of the histology of the breast in cis women. When the mammary epithelial of the progesterone knockout mouse is transplanted into a wild-type parous mouse, the obligatory role of progesterone in acinar and lobular development is demonstrated [58,59]. Additionally, other theoretical advantages of progesterone administration might be the fact that breast epithelium exhibits maximal proliferation in the luteal phase of menstruation, when progesterone levels are at their highest [60] and increased mammographic breast density is observed when progestogens are administered [61]. However, importantly, there is no evidence that these histological and mammographic differences result in clinically significant breast size differences. Another consideration is that the increased breast density by progestogens rapidly decreases after hormone withdrawal [62], which raises the question how long progestogens then should be prescribed.

The results of this review mainly highlight the need for more research on pathophysiological mechanism, natural history, and predictors of breast development in trans women, especially considering its importance for trans women themselves. In addition, studies are needed to evaluate the benefit of one type and/or mode of cross-sex hormone therapy above the other. Also, well-designed studies should investigate the possible benefit or harm of different types of progestogens to the feminization process of trans women, particularly its role on breast development. In addition, to improve comparisons between studies, validated methods for assessing breast development are required.

Conclusion

Our knowledge concerning the natural history and effects of different cross-sex hormone therapies including progestogens on breast development in trans women is extremely sparse and based on low quality of evidence. This prevents us from drawing any firm conclusion at this moment and demonstrates the need for further research to clarify these important clinical questions.

Corresponding Author: Katrien Wierckx, MD, Department of Endocrinology, Ghent University Hospital, De Pintelaan 185 9000 Ghent, Belgium. Tel: 003293322137; Fax: 003293323897; E-mail: Katrien.wierckx@ugent.be

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Statement of Authorship

Category 1

(a) Conception and Design
Katrien Wierckx; Louis Gooren; Guy T'Sjoen

(b) Acquisition of Data
Katrien Wierckx; Louis Gooren; Guy T'Sjoen

(c) Analysis and Interpretation of Data
Katrien Wierckx; Louis Gooren; Guy T'Sjoen

Category 2

(a) Drafting the Article
Katrien Wierckx; Louis Gooren; Guy T'Sjoen

(b) Revising It for Intellectual Content
Katrien Wierckx; Louis Gooren; Guy T'Sjoen

Category 3

(a) Final Approval of the Completed Article
Katrien Wierckx; Louis Gooren; Guy T'Sjoen

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