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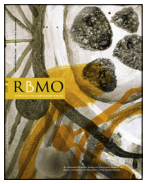

ARTICLE

Endometrial thickness assessed by transvaginal ultrasound in transmasculine people taking testosterone compared with cisgender women

BIOGRAPHY

Joyce Asseler is a PhD student at the Amsterdam UMC researching the safety of testosterone and fertility in gender diverse persons. Furthermore, she is MD at the Centre of Expertise on Gender Dysphoria at the Amsterdam UMC providing gynaecological care and fertility counselling for gender diverse persons.

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KEY MESSAGE

Transmasculine people with at least 1 year of gender affirming hormone therapy (testosterone), have a significantly thinner endometrium, as assessed by transvaginal ultrasound, compared with cisgender women. These results suggest an absence of endometrial proliferation by exogenous testosterone. Burdensome endometrial screening in asymptomatic transmasculine persons may, therefore, be unnecessary.

ABSTRACT

Research question: What is the endometrial thickness of endometrium exposed to testosterone in transmasculine people compared with unexposed endometrium in cisgender women as determined by transvaginal ultrasound (TVU)?

Design: Single centre, cross-sectional cohort study conducted the Centre of Expertise on Gender Dysphoria in Amsterdam. Between 2013 and 2015, transmasculine people scheduled for gender affirming surgery (GAS) were included in this study after they provided informed consent. They were undergoing gender affirming hormone therapy (testosterone) for at least 1 year. Endometrial thickness (mm) was measured by TVU in transmasculine people, immediately before their GAS while under general anaesthesia. Cisgender control women from the general population underwent the exact same TVU measurements in an outpatient clinical setting on cycle days 2–5.

Result: Fifty-one transmasculine people and 77 controls were included. The mean duration of testosterone use was 30.2 months (SD 8.8). Endometrial thickness was significantly lower in transmasculine people compared with cisgender women: median 3.9 mm (interquartile range [IQR] 2.8–5.1) and 4.9 mm (IQR 4.0–6.3), respectively ($P < 0.001$), after correcting for confounding factor (current gonadotrophin releasing hormone agonist use).

Conclusions: Endometrial thickness in transmasculine people exposed to testosterone is significantly lower compared with cisgender women without testosterone exposure. These results suggest an absence of endometrial proliferation by exogenous testosterone.

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KEYWORDS
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INTRODUCTION

Transgender individuals experience gender dysphoria. This refers to the discrepancy between a person's gender assigned at birth and their gender identity (*Coleman et al., 2012*). The term transmasculine people will be used throughout to describe individuals who were assigned female at birth but do not identify as female, including but not limited to transgender men, genderqueer and non-binary persons.

To transition to a more masculine physique, most transmasculine people seek medical treatment in the form of gender affirming hormone treatment (GAHT) with testosterone, gender affirming surgery (GAS), i.e. mastectomy (*Wiepjes et al., 2018*), or both. In 2014, transgender laws in the Netherlands were abolished and transgender people were no longer obligated to be sterile to change their gender in official documents (Dutch civil law, article 1:28). Since then, fewer transmasculine people desire a hysterectomy as part of their transition and choose to retain their reproductive organs, either now or indefinitely (*Grimstad et al., 2020*). Combined with a reported worldwide increase in gender dysphoria (*Wiepjes et al., 2018*), this will result in the endometrium of more transmasculine people being exposed to testosterone over a longer period of time.

Although testosterone therapy is generally considered safe, the question about risk of endometrial hyperplasia and endometrial cancer remains (*Allen et al., 2008*; *de Blok et al., 2019*). This is based on the following findings: first, in theory, the aromatization of testosterone to oestradiol may induce proliferation of the endometrium. Endometrial exposure to oestradiol, unopposed by progesterone, is a known risk factor for endometrial cancer (*Barry et al., 2014*; *Grimstad et al., 2019*). In cisgender (i.e. non transgender) women with anovulation, it is known that endometrial hyperplasia prevails in 41% (*Xue et al., 2021*). Studies indicate a two- to six-fold increased risk of endometrial cancer in women with polycystic ovary syndrome (PCOS), which often presents before menopause; however, absolute risk of endometrial cancer remains relatively low (*Teede, 2018*). Another study showed that women who had PCOS at reproductive age with a thick endometrium (>7 mm) had an 8.7% risk of having endometrial neoplasia (*Indhavivadhana et al., 2018*). Second, testosterone has been shown to be involved in the regulation of sex hormone receptor expression in the endometrium and may, therefore, influence endometrial proliferation and differentiation (*Zang et al., 2008*). Third, androgen receptors have also been detected in endometrial carcinomas (*Maia et al., 2001*).

Reassuringly, only one case of endometrial cancer (*Urban et al., 2011*) and one case of atypical endometrial hyperplasia, with small focus of adenocarcinoma (*Grynberg et al., 2010*) in transmasculine people using GAHT, have previously been reported. In addition, multiple studies examining histology of removed uteri during GAS did not describe endometrial malignancy (*Futterweit and Deligdisch, 1986*; *Miller, 1986*; *Perrone et al., 2009*; *Grynberg et al., 2010*; *Loverro et al., 2016*; *Grimstad et al., 2019*; *Khalifa et al., 2019*; *Ralph et al., 2019*; *Hawkins et al., 2021*).

The risk of (lifelong) GAHT on developing endometrial hyperplasia and cancer is not yet known; therefore, it is also unclear if a specific ultrasound strategy should be executed. In asymptomatic cisgender women, routine endometrial ultrasound screening is never recommended, not even in cisgender women with PCOS (*Yin et al., 2019*). The only advice on endometrial ultrasound screening relates to post-menopausal women. Here, screening is only recommended when a patient presents with post-menopausal vaginal blood loss. An endometrial biopsy is taken when the endometrial thickness exceeds 4 mm on transvaginal ultrasound (TVU) (*ACOG, 2018*). The lack of scientific evidence has led to conflicting guidelines for endometrial screening in transmasculine people. The World Professional Association for Transgender Health Standards of Care guidelines do not make a recommendation (*Coleman et al., 2012*), US guidelines advise against asymptomatic screening (*Deutsch, 2016*) and Dutch guidelines advise a routine uterine ultrasound and potential endometrial biopsy every 5 years (*Specialisten, 2018*).

Endometrial thickness as shown on TVU in transmasculine people using testosterone is rarely described. To help bridge this knowledge gap, we report previously unpublished data of endometrial measurements from a study by *Caanen et al. (2017)*. The aim of the present study was to describe endometrial thickness of endometrium exposed to testosterone in transmasculine people compared with unexposed endometrium in cisgender women determined by transvaginal ultrasound (TVU).

MATERIALS AND METHODS

In the present study, the ultrasound characteristics of the endometrium in transmasculine people using GAHT, testosterone and cisgender female controls with endometrial thickness as our primary outcome measure were analysed. The TVU was conducted during a previous study that aimed to compare ovarian morphology between transgender men and cisgender female controls. In this prospective, observational case-control study (*Caanen et al., 2017*), further details on study design and cohort characteristics are reported.

Study design

This single centre, cross-sectional cohort study was carried out at the Centre of Expertise on Gender Dysphoria in Amsterdam, the Netherlands, between 2013 and 2015. This study was approved by the local Ethical Committee on 4 September 2014 (reference number: 2014.402), and written informed consent was obtained from all participants. The trial was registered in the Dutch National Trial Registry (trial registration number NTR4784).

Participants

All eligible transmasculine adults, treated with testosterone for at least 1 year and who were eligible for GAS, in this case, hysterectomy and bilateral salpingo-oophorectomy, were invited to participate in the study. Baseline characteristics included age, height, weight, medical history, medication, type of testosterone, duration of testosterone use, current or prior gonadotrophin releasing hormone agonist (GnRHa) use (cessation ≥1 year), menstrual status and lifestyle factors, i.e. smoking, alcohol and drug use were retrieved from medical records.

Controls were obtained from the control group of the Dutch LATER-VEVO study (trial registration number NTR2922) (*Overbeek, 2012*), a large nationwide

study on reproductive function, ovarian reserve and premature menopause in female childhood cancer survivors. All controls were cisgender female adults from the general population, recruited via general practitioners or approached via participating childhood cancer survivors. Eligibility criteria, detailed study characteristics and both types of controls have been previously described by *Overbeek et al. (2012)*. Baseline characteristics were retrieved from a large self-reported questionnaire.

Participants were excluded in case of disorders of sexual development, endocrine pathology including polycystic ovary syndrome, excessive smoking, alcohol, drug abuse, or both, and the use of hormonal contraceptives.

Gender affirming hormone treatment

Following the European protocol (*Dekker et al., 2016*), GAHT in adults consists of transdermal testosterone administration: Androgel®, 25 or 50 mg, daily (Besins International, Belgium), Tostran® 40 mg, daily (ProStakan, Galashiels, Scotland), and intramuscular injection (Nebido®, 1 g, per 10–14 weeks) (Bayer, Leverkusen Germany); or Sustanon®, 250 mg per 2–4 weeks (Aspen Pharma Trading Limited, Dublin Ireland).

Before testosterone treatment, adolescents may start with puberty suppression treatment with gonadotrophin-releasing hormone agonist (GnRHa) desensitization to prevent (further) development of secondary sex characteristics not fitting with the experienced gender identity. When transitioning from GnRHa to testosterone, GnRHa was continued for several months, sometimes even until undergoing GAS.

In clinical practice, transmasculine people were advised to discontinue their GAHT before GAS for 2–6 weeks, to prevent a then assumed additional risk of blood clots during and after surgery.

Transvaginal ultrasound

Endometrial thickness (in mm) was measured by TVU in longitudinal, two-dimensional view using the HD11 XE ultrasound system with a three-dimensional transvaginal probe (3–9 MHz; EnVisor HD) (Philips Medical Systems, Eindhoven, the Netherlands) in both groups according to the same ultrasound protocol. The transmasculine people underwent TVU, carried out by two experienced research physicians, at the time of GAS while under general anaesthesia. Controls underwent the same TVU measurements in an outpatient clinical setting on cycle day 2–5 by several experienced sonographers. All images were evaluated by two blinded research team members. Endometrial thickness was determined by both researchers via a standardized protocol and an average of both measurements was used. If the endometrial thickness measurements reported by both team members were too far apart to determine a reliable average, a third person (supervisor) would repeat the measurement. During TVU, abnormalities of the endometrium and uterus were also documented.

TABLE 1 BASELINE CHARACTERISTICS OF TRANSMASCULINE PEOPLE AND CISGENDER WOMEN

Characteristics	Transmasculine people (cases) (n = 51)	Cisgender women (controls) (n = 77)	P-value
Age, years	22.6 (19.3–26.3)	34.0 (30.9–36.0)	<0.001[a]
BMI, kg/m^2	23.5 (21.1–28.7)	22.0 (20.8–23.5)	0.005[a]
Testosterone use, months	30.2 (8.8)	–	–
Type of testosterone			
Intramuscular	33 (65%)	–	–
Transdermal	18 (35%)	–	–
GnRHa use, ever	24 (47%)	–	–
GnRHa use, at time of TVU	15 (29%)	–	–
Progesterone	7 (14%)	–	–

Data are expressed in mean (SD), median (IQR) and numbers (%).

[a] P-values for continuous variables non-parametric Mann–Whitney U test.

BMI, body mass index; GnRHa, gonadotrophin releasing hormone agonist; TVU, transvaginal ultrasound; –, not applicable".

Statistical analysis

SPSS version 20.0 (SPSS, Inc., Chicago, IL, USA) was used for all statistical analyses. Baseline characteristics and outcomes are reported as mean (SD), median (interquartile range) or number (percentages). Non-parametric Mann–Whitney U test was carried out when appropriate. Linear regression analyses were conducted to correct for possible confounders, current GnRHa use (yes/no), current progesterone use (yes/no), type of testosterone used, age and body mass index (BMI). A two-tailed $P < 0.05$ was considered significant.

RESULTS

In total, 128 participants were included: 51 transmasculine people and 77 cisgender controls. Baseline characteristics are presented in TABLE 1. The transmasculine people were younger and had a higher BMI ($P < 0.001$ and $P = 0.005$, respectively). The mean duration of testosterone use was 30.2 months (SD 8.8). The most common type of testosterone administration was via intramuscular injection (65%), the other people used transdermal gel (35%). Forty-seven per cent of transmasculine people used GnRHa during their medical transition. Twenty-nine per cent were still using GnRHa at the time of participation in this study. Furthermore, 14% of participants were using a type of progesterone for cycle regulation or contraceptive needs. No data on menstrual status were available.

Endometrial thickness in transmasculine people and cisgender controls are presented in FIGURE 1. Endometrial thickness was significantly lower in the transmasculine people with a median of 3.9 mm compared with 4.9 mm in the controls ($P < 0.001$). When conducting linear regression analyses, only current GnRHa use was identified as a confounding factor. Age, BMI, progesterone use and type of testosterone were not confounders. After correcting for current GnRHa use, this difference in endometrial thickness remained significant ($P < 0.001$).

Abnormalities of the endometrium were not found in any of the participants. In five transmasculine people and in seven controls, the uterus was described as abnormal owing to the presence of fibroids.

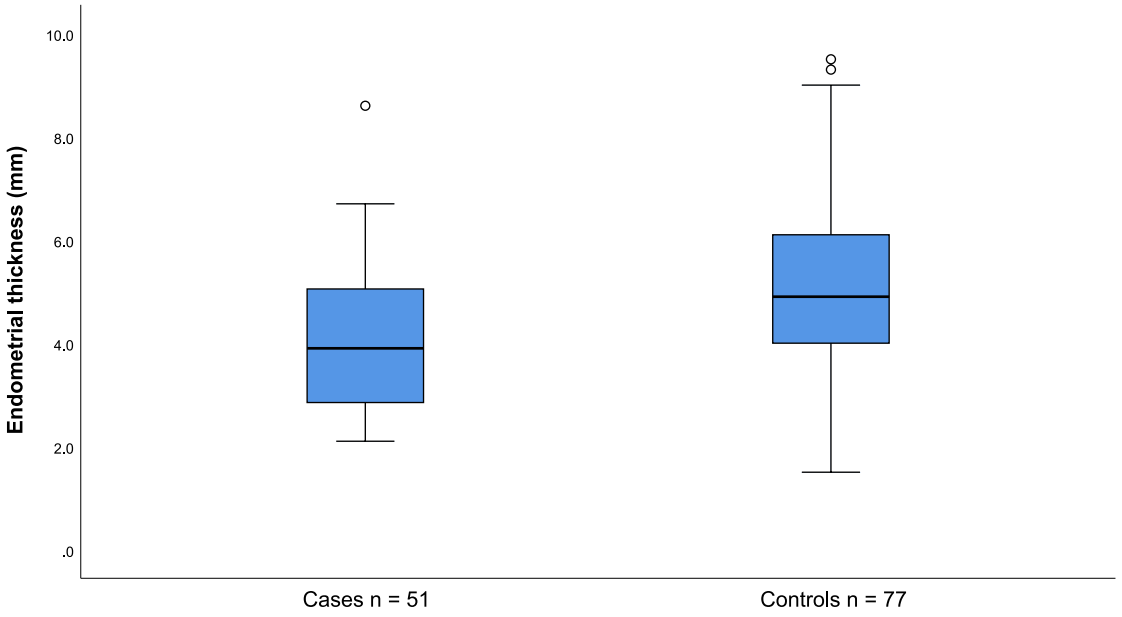

FIGURE 1 Endometrial thickness in transmasculine people (51 cases) and cisgender women (77 controls) assessed by transvaginal ultrasound. Box and Whisker plot shows median, interquartile range, maximum and minimum values and outliers. Median endometrial thickness was 3.9 mm (2.8–5.1) and 4.9 mm (4.0–6.3) in cases and controls, respectively. The crude *P*-value was <0.001 and the adjusted *P*-value in linear regression analyses (adjusted for confounding factor, current gonadotrophin releasing hormone agonist use) was <0.001.

DISCUSSION

To the best of our knowledge, the present study is the first to describe endometrial thickness assessed by TVU in transmasculine people using GAHT compared with cisgender women. In our cohort, the endometrial thickness was significantly lower in transmasculine people compared with early follicular phase values in cisgender women even after correcting for confounding factor, current GnRHa use (3.9 mm versus 4.9 mm, $P < 0.001$).

The findings of our study are in line with the limited research on TVU in transmasculine people undergoing GAHT. One observational study by *Mueller et al. (2007)* described a significant reduction of endometrial thickness and no noticeable endometrial pathology on TVU in transmasculine people 1 year after starting GAHT. The endometrial thickness was 9.9 mm (SD 4.2) at baseline and 5.7 mm (SD 1.4) at 12 months follow-up (*Mueller et al., 2007*). One retrospective case series by *Grimstad et al. (2019)* described 23 documented TVUs of transmasculine people before GAS. In this study, the mean endometrial thickness was 4.9 mm (SD 2.1) (95% CI of 4.0 to 5.9).

In the present cohort, 47% of transmasculine people previously used GnRHa during their medical transition and 29% were still using it at time of TVU. On the basis of their ability to bind to GnRH receptors and to interfere with the activity of natural GnRH, GnRHa are key regulators in the reproductive hormone cascade. Gonadotrophin releasing hormone agonist affects the endometrium by inducing a hypogonadal state by blockading ovarian oestrogen secretion, resulting in amenorrhoea. Secondary, locally expressed GnRH receptors are also associated with a significant antiproliferative activity of the endometrium (*Maggi et al., 2016*). Consequently, current GnRHa use was the most important anticipated, and only confirmed, confounder in the study. Nevertheless, after correcting for current GnRHa use, the difference in endometrial thickness between transmasculine people and cisgender controls remained statistically significant. As the desensitizing effect of GnRHa is completely reversible after prolonged discontinuation, prior GnRHa use was not anticipated to be a possible confounder (*Maggi et al., 2016*).

A known risk factor for developing endometrial cancer is oestradiol unopposed by progesterone (*Amant et al., 2005*; *Barry et al., 2014*; *Grimstad et al., 2019*), possibly still present in transmasculine people undergoing GAHT. Other risk factors for developing endometrial cancer are obesity and increasing age, with the highest incidence around 70 years of age in postmenopausal cisgender women (*Amant et al., 2005*). In the present cohort, the duration of testosterone use was short (mean 30.2 months), and the participants were young (median age in transmasculine people 22.6 years and 34.0 years in controls), making it overall unlikely to find a pathologic thick endometrium. In clinical practice, the mean age of the transmasculine population is still relatively young. This makes long-term follow-up mandatory as it is important to increase data on pre-menopausal endometrium characteristics. This will facilitate the development of a suitable screening strategy for transmasculine people undergoing GAHT wishing to retain their reproductive organs.

In the present study, TVU was carried out before GAS under general anaesthesia. This method was deliberately chosen as internal examination, i.e. TVU is burdensome for transmasculine people (*van Trotsenburg, 2009*; *Deutsch, 2016*). This reiterates the need for evidence-based recommendations on the need for endometrial screening as the transmasculine patient may be spared a burdensome examination if screening is deemed unnecessary. Although TVU is superior to a transabdominal

ultrasound when accurately assessing the endometrium (*Coleman et al., 1988*), this procedure may be considered a more ethical first step if screening for endometrial pathology is necessary. Transvaginal ultrasound must only be carried out after careful consideration and consultation with the patient.

At the time of study, the preoperative protocol was to discontinue GAHT for 2–6 weeks before GAS to prevent an additional risk of thrombosis during and after surgery. One potential event as result of GAHT cessation is the possibility of the menstrual cycle reoccurring and consequently the endometrium developing. This preoperative cessation protocol was terminated in 2017 in our clinic, after sufficient reassuring evidence on the risk of thrombosis was published (*Defreyne et al., 2018*). Unfortunately, no data are available on the menstrual cycles of transmasculine people in those weeks of GAHT cessation and on which cycle day their GAS and TVU were carried out.

In conclusion, endometrial thickness in transmasculine people exposed to exogenous testosterone is significantly lower compared with cisgender women when assessed by TVU. These results reassure us about the postulated increased risk for developing endometrial hyperplasia or cancer in transmasculine people using testosterone. Burdensome routine ultrasound screening in asymptomatic transmasculine people may, therefore, be unnecessary. Further research, however, is necessary to determine the risk of long-term exposure to exogenous testosterone.

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