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REVIEW

Gynecologic Oncology Needs for Trans-Masculine and Trans Feminine Persons

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Abstract

Purpose of the Review Persons with gender identity that is not congruent with their sex assigned at birth have unique needs in relationship to gynecologic malignancy screening and treatment. Providers of gynecologic oncology care require knowledge of these specific concerns and inclusive practices to avoid under screening and offer evidence-based treatments. This review seeks to collate data on the most common clinical situations gynecologic oncology providers encounter.

Recent Findings Transmasculine persons who have a cervix need access to appropriate prevention and screening for cervical cancer but may face obstacles to obtaining this care. Transfeminine persons may develop HPV infection of the neovagina but cancer development rare and prevention is largely unknown. Abnormal uterine bleeding in transmasculine persons either taking gender affirming hormone therapy or not can present a diagnostic challenge which requires careful consideration to rule out malignancy. Concerns about testosterone use and the relationship of androgen receptor to ovarian cancer progression have been raised but conclusive data is lacking. There are no effective strategies for ovarian cancer screening and unnecessary exams should be avoided.

Summary Large population based studies are needed to develop evidence based HPV screening guidelines that align with reproductive organ inventories, rather than gender or simply sex assigned at birth. HPV vaccination, utilization of HPV self swab in those for whom pelvic examination is dysphoric and careful evaluation of neovaginal tissue are first steps in reducing HPV related cancer burden. In addition, providers need to carefully evaluate abnormal uterine bleeding in transmasculine persons in gender inclusive ways to adequately detect endometrial pathology. Androgen receptor presence on ovarian cancer remains a biologic concern for transmasculine persons on gender affirming hormone therapy but risk of ovarian cancer appears small. Further long term studies of testosterone hormone therapy in this population are needed.

Keywords Transgender · Transfeminine · Transmasculine · Cervical cancer screening · Gynecologic oncology

Introduction

Gender is a social construct. Gender identity is how one feels about the gender they are attributed by their social position. Most often this aligns with the biological sex assigned at birth. However, for some, the sex assigned at birth does not reflect the gender of their innate identity. Broadly described as gender dysphoria – Knudson et al., - defined this as the "discomfort or distress that is caused by a discrepancy between a person's gender identity and that person's sex assigned at birth" [1, 2]. Gender dysphoria can be eased by social transition to one's self identified gender. This transition process may include socially visible changes such as gendered clothing, hairstyles etc. or less visible changes such as taking hormones, such as testosterone for those assigned female at birth or estrogen for those assigned male at birth or even surgery to change breast tissue or genitals [3]. These changes create opportunities to reflect on how medical care is delivered in the historically gender specific landscape of gynecologic oncology.

Gynecologic oncology is the study, treatment, and prevention of malignant diseases of the female reproductive tract. These organs don't have a gender but nearly all the work surrounding the prevention and treatment of these cancers has been done from a white, hetero, and cis-feminine perspective. Cancer screening has previously been gender

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based but recent advances have seen gender neutral and transgender affirming cancer screening guidelines [4, 5]. Data is limited on what reproductive malignancy risk individuals taking cross gender hormones have and what if any changes should be considered in their hormone therapy if they develop a gynecologic cancer [6].

This article will discuss the current strategies for gender inclusive gynecologic cancer screening of the cervix, consideration of HPV related dysplasia of the neovagina, discussion of the role of abnormal uterine bleeding in the presentation of endometrial cancer in the transmasculine person, and lastly, discuss the current data regarding androgen receptors and ovarian cancer risk and considerations for treatment. This is not an exhaustive list of the needs of transgendered persons seeking gynecologic oncology care but endeavors to be a set of frequently encountered clinical situations where data is emerging.

Inclusive Cervical Cancer Screening

Cervical cancer remains the most common cancer for humans with a cervix globally. The American Cancer Society reports that while screening has decreased incidence of the disease since the 1970s, this decrease has plateaued in the 2000s. In fact, in the last few years, the incidence of cervical cancer in ages 30–35 has increased by 1.7% [7]. HPV vaccination has been available since 2006 and there are recent data that demonstrate decreasing incidence of cervical cancer in younger age groups [8]. However, transgender and gender nonconforming people may not be adequately screened [9, 10•].

There is a misconception that without penetrative vaginal intercourse, HPV cannot be acquired and pap testing or HPV testing is not necessary in this population [11]. While recent penile contact increases risk of HPV infection, this is not the only mechanism of HPV transmission [12•]. Transmasculine persons report the following: higher rates of abnormal cervical cancer screening results [13], higher likelihood of not receiving CCS in their lifetime (37% TM vs. 10% cisgender women) [14]; and lower likelihood of receiving regular CCS (56% TM vs. 72% cisgender women, $p = .001$) [15]. Providers need to offer cervical cancer screening to all persons with a cervix. However, barriers to a speculum examination exist for some patients [10•]. Careful attention to offering a gender affirming and sensitive exam is imperative to reduce patient discomfort and pain [16•, 17•]. HPV self-swab may be an alternative for some patients [9]. HPV testing alone every 5 years starting at age 30 to age 65 has been identified by the USPTF and endorsed by ACOG and SGO [18, 19]. The role of the gynecologic oncologist in screening may be limited in some settings as screening with pap testing or HPV testing may have led to an abnormal result which is the reason for consultation, perhaps for colposcopy or for the management of an abnormal biopsy finding.

Cervical dysplasia management relies on excellent visualization of the cervix for colposcopy with biopsy or for treatment with excisional biopsy. These procedures should be carefully explained with special regard to gender affirming language and offering options for patient's comfort needs [16•]. Some transmasculine persons find vaginal examinations intolerable and may need adjustments to routine support, such as having a support person in the room, having a sedative, or even having a procedure under anesthesia.

Considerations of HPV Related Dysplasia of the Neovagina

As part of their journey with gender-affirming care, some transfeminine persons may undergo vaginoplasty to create a functional and cosmetic vulva and vagina. Penile-inversion vaginoplasty, where the penile and scrotal skin are used to create the vulva and vaginal canal, is the most common method of neovaginal construction and the most common gender-affirming genital surgery [18].

There are multiple case reports of HPV-related neovaginal cancers in transfeminine individuals who have undergone vaginoplasty, but there is a lack of research on HPV-related dysplasia of the neovagina [19–22]. While neovaginal cancers are overall quite rare, it is important to develop screening guidelines for HPV-related dysplasia of the neovagina, especially as the prevalence of vaginoplasties and types of vaginoplasties increase and gender affirming surgical care becomes more accessible [20]. In most case reports of neovaginal cancer, patients presented with advanced HPV-related squamous cell carcinoma (SCC) with lymph node involvement, recto-neovaginal fistula, and/or bone and lung metastases. The authors of all the included case reports recommend surveillance for HPV-related dysplasia for patients who have undergone vaginoplasty to avoid these outcomes [19–22]. A recent systematic review of neovaginal HPV prevalence in transfeminine persons included 15 studies that estimate the prevalence of high-risk HPV (hrHPV) in the neovagina from 8.3% to 20% [23]. These estimates, however, were pulled from studies with low-moderate grade evidence and low statistical power. They also combine studies looking at neovaginal HPV in transfeminine patients and patients with Müllerian agenesis.

There are currently no standardized guidelines recommending when and how to screen for HPV-related neovaginal dysplasia in transfeminine persons [24]. Some have recommended following the cervical cancer screening guidelines for developed for cisgender women with a cervix [25]. Others propose that notable anatomic and physiologic differences between the neovagina and the natal vagina/

cervix require new tools to evaluate for HPV-related dysplasia in transfeminine patients post vaginoplasty [23, 24]. Large, diverse cohort studies are necessary to understand the true prevalence of neovaginal hrHPV and its precancerous phenotypes and to inform the creation of preventative care guidelines for transfeminine patients with neovaginas.

A number of articles evaluating neovaginal cytology and HPV prevalence report difficulty interpreting neovaginal cytology because of these differences from the natal vagina [26–28]. Grosse et al., who specifically evaluated neovaginal samples in relation to natal vaginal cytology, found only 10% of neovaginal samples were cytologically similar to natal vaginal samples—meaning the samples had superficial, intermediate and parabasal cells and Döderlein bacilli present [27]. The Bethesda System for Reporting Cervical Cytology (TBSRCC)—the evaluation metrics for pap testing—has been used in cytology studies of the neovagina but has limitations with regards to these samples. Specifically, the TBSRCC requires a sample to have 5,000 nucleated squamous cells to be considered adequate. It is often difficult to obtain a neovaginal sample with 5,000 *nucleated* squamous cells because of the highly keratinized epithelium of most neovaginas created from inverted penile skin which is cytologically distinct from natal cervical and vaginal epithelium [24, 26, 27]. New cytology criteria must be developed to account for the tissue of the neovagina, which may be either squamous epithelium (most common) or from peritoneal grafts or colonic tissue. Additionally, more research is needed to develop the proper cytology technology to examine the neovagina.

While there are still no agreed upon guidelines for neovaginal cancer screening, expert opinion recommends a combination of routine screening visits with exams post-vaginoplasty, HPV vaccination, consideration of cytology with HPV co-testing, after a shared decision-making process between the patient and provider [24]. Gynecologic oncologists need to be aware of the limitations of current technology and provide thoughtful evaluations to those patients referred for either testing or abnormal results. Multidisciplinary discussion with pathology may be valuable to arrive at a diagnosis and plan.

Abnormal Uterine Bleeding and the Risk of Uterine Cancers in Transmasculine Persons

Transmasculine persons are usually born with typical female pelvic anatomy and are, therefore, at risk of gynecologic malignancies including endometrial cancer—the most common gynecologic cancer in the Unites States. Despite the risk of gynecologic malignancies, transmasculine people face barriers to accessing gynecologic care [29]. There are currently no specialized screening guidelines for endometrial cancer in transmasculine people and no consensus on the role of abnormal uterine bleeding (AUB) in the transmasculine population as a presenting symptom of endometrial hyperplasia or malignancy. Expert opinion recommends that AUB, in transmasculine people who are not using exogenous testosterone, should be worked up according to standard guidelines [30]. The suspected etiology of the bleeding should guide evaluation. Care should be taken to ensure that the history taking, physical exam, and any testing or procedures are done in a gender-affirming manner and avoids traumatizing the patient. It may be prudent, for example, to begin an AUB workup with a transabdominal ultrasound to avoid potential distress from an transvaginal ultrasound [30].

More research is needed to guide the evaluation of AUB in transmasculine persons who are using testosterone gender-affirming hormone therapy (T-GAHT). The interaction between exogenous testosterone use and proliferation of the endometrium remains unclear. Cessation of menses normally occurs within a few months of initiating T-GAHT, but breakthrough bleeding is not uncommon [31]. A retrospective cohort study of adolescent transgender and gender diverse participants using T-GAHT, found 25% of participants had breakthrough bleeding [32]. Although many transmasculine patients on T-GAHT achieve menstrual suppression, there is evidence that a proliferative endometrium can persist. Retrospective studies evaluating the pathology specimens from hysterectomies performed on transmasculine patients taking T-GAHT have demonstrated 40% to 69% of specimens had a proliferative endometrium [33, 34]. Two proposed mechanisms have been presented to explain the presence of a proliferative endometrium in some transmasculine people on T-GAHT. First, both testosterone and dihydrotestosterone (DHT) act on the endometrial epidermal growth factor receptor, which regulates endometrial cell growth [35]. Second, peripheral aromatase activity converts testosterone to estrogen, stimulating endometrial proliferation [30, 35]. Either one or both of these mechanisms may account for the presence of a proliferative endometrium in amenorrheic transmasculine persons using T-GAHT. It has been hypothesized that exposure to T-GAHT, is similar to the way in which PCOS, another hyper androgen state, increases the risk of endometrial cancer [36].

At the time of this writing, there are six documented cases of endometrial cancer in transmasculine patients taking T-GAHT [37–42]. All of the six patients presented with symptoms of AUB, underwent evaluation and were found to have endometrial cancer [37–42]. Another patient was diagnosed with endometrial intraepithelial neoplasia (EIN) on pathology after hysterectomy for gender affirmation [36]. He retroactively endorsed prior vaginal spotting while on T-GAHT. Only one patient was found to have Lynch syndrome [38] and no other patients were believed

to have hereditary cancer syndromes. Additionally, it is important to highlight that all seven cases reported some vaginal bleeding on T-GAHT. Despite these seven cases, endometrial hyperplasia and endometrial cancer in transmasculine persons remains extremely rare [36].

Although there are no clear guidelines for the role of AUB in the presentation of endometrial cancer in transmasculine persons, it is evident that transmasculine men on T-GAHT can still have active endometrial tissue and develop dysplasia, even when amenorrheic. Therefore, transmasculine patients with AUB should undergo proper evaluation to rule out malignancy. Both breakthrough vaginal bleeding and engagement in gynecologic care can be cause stress and induce gender dysphoria in transmasculine persons [29, 32, 34]. Therefore, the evaluation of AUB in transmasculine persons must been done in gender-affirming manner with shared decision making about modalities of workup including type of imaging, pelvic examination and endometrial biopsy. Larger, prospective cohort studies are needed to evaluate the prevalence of endometrial hyperplasia and malignancies in transmasculine persons and the interaction between T-GAHT and the endometrium, in order to inform future guidelines for gynecologic oncology care of transmasculine patients.

Ovarian Cancer, Androgens and Transmasculine Patients

As previously discussed for cervical cancer, all other gynecologic malignancies have been documented in transgender persons as described by Stenzel et al. [43]. Androgen receptor has been reported in some epithelial ovarian cancers and aromatization of testosterone has been suggested as a potential mechanism for ovarian tumorigenesis [44]. Cases of epithelial ovarian cancer in transmasculine persons on testosterone therapy have been reported [45]. As noted by the American Board of Obstetrics and Gynecology and the National Comprehensive Cancer Network guidelines, there is no effective ovarian cancer screening [45]. Pelvic exams, transvaginal ultrasounds or blood tests are unnecessary unless there are symptoms, such as pain, bloating, or early satiety. At present, there is insufficient evidence to clearly define the risk of ovarian cancer for those taking testosterone for gender affirmation. However, for patients with ovarian cancer who are taking testosterone, tumor androgen receptor testing should likely be offered to aid in shared decision making with patients. Large population-based studies of transmasculine patients on T-GAHT are needed to define the risk of androgens in tumorigenesis in this population.

Take Aways:

- Transmasculine persons with a cervix need cervical cancer screening.
- HPV related dysplasia is rare in transfeminine women. Symptoms such as bleeding or discharge should be evaluated promptly with careful exam and consideration of HPV testing.
- Abnormal uterine bleeding should be fully evaluated in transmasculine persons, regardless of testosterone use.
- While some ovarian cancers express Androgen Receptor (AR) there is insufficient evidence to suggest that testosterone use increases ovarian cancer risk.

Conclusion

The needs of the transmasculine and transfeminine patient in the gynecologic oncology setting are diverse. Provider trust relies on the physician to be both compassionate and knowledgeable about the patient and their condition. Understanding our biases, working on cultural humility, and recognizing both the historical and present realities of gender non-conforming persons is central to our care. In addition, large population-based studies of gynecologic cancer risk are needed. Developing these studies presents specific challenges in the gender minority population as definitions of gender and paths to gender affirmation are diverse. Dissemination of accurate information about transmasculine and transfeminine persons is needed with continuing education.

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Data Availability No datasets were generated or analysed during the current study.

Compliance with Ethical Standards

Competing of Interest BJ Rimel MD declares that she has no conflict of interest relative to this manuscript. She has participated in advisory boards for Merck, AstraZeneca, Immunogen and GSK. Luke Murphy declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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