

# EVALUATION AND TREATMENT OF GENDER-DYSPHORIC/GENDER INCONGRUENT ADULTS

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#### ABSTRACT

Gender dysphoria refers to the suffering due to an incongruence between one's sex assigned at birth and one's self-perceived gender. Primary care physicians often play an important role in diagnosis and initiation of treatment of gender dysphoria. However, gender dysphoria is preferentially diagnosed by a specialized psychologist or psychiatrist. This does not imply that gender dysphoria in itself is a mental disorder, but comorbidity needing attention, is frequently present. The prevalence of transgender people who receive medical treatment has steeply increased in the last decades. The current prevalence is estimated at 1:2,800 for transwomen (male sex assigned at birth, female gender identity) and 1:5,200 for transmen (female sex assigned at birth, male gender identity). Treatment of transgender people often includes gender-affirming hormonal therapy and/or surgery, and is optimally provided by a multidisciplinary team consisting of psychologists, endocrinologists, plastic surgeons, gynecologists, urologists. otorhinolaryngologists, and/or dermatologists. Medical treatment usually improves the quality of life of transgender people, but might also have side-effects such as increased risk for cardiovascular disease or hormonesensitive tumors. There is still little known about the optimal therapy (for specific transgender subpopulations) and its long-term side-effects. Nowadays, guidelines are mainly based on clinical experience instead of evidence. However, transgender medicine is a growing field and the increasing number of good quality studies are helping to improve care of transgender people. In this contribution we mainly focus on what is known about the side-effects of

hormonal therapy. In addition, we provide information about surgical and fertility preservation options for transgender people. We conclude this contribution with remarks about special conditions such as older age and unsupervised hormone use.

#### INTRODUCTION

Gender identity is the personal sense of one's own gender. A significant incongruence between one's physical phenotype and one's gender identity is defined as gender dysphoria. While care for transgender people has long been based on a binary understanding of gender (male versus female), the existence of non-binary or gender queer genders is getting increasing attention. Non-binary or gender queer people identify with a gender that is neither exclusively male nor female, but is composed of both, oscillates between genders, is situated beyond the binary, or rejects the binary (1). Gender dysphoria is usually diagnosed by a specialized psychologist, which does not imply that it is a mental disorder per se. People who have a male sex assigned at birth but have developed a female gender identity are called transwomen and people who have a female sex assigned at birth but experience a male gender identity are called transmen. The prevalence of transgender people who seek medical treatment has dramatically increased in the last years, and a recent Dutch study estimated a prevalence of 1:2,800 for transwomen and 1:5,200 for transmen (2). While the

etiology is complex and probably multifactorial, the most widely believed hypothesis is that transgender people have experienced a sex-atypical differentiation of the brain during fetal development (3,4).

To many physicians, transgender medicine is a novel area of medicine. Most physicians need intensive interaction with a transgender individual to empathize the suffering, and to arrive at the insight that hormonal and surgical treatment might alleviate gender dysphoria-related distress. It is usually assumed that medical interventions can only be justified when objective, identifiable pathological processes account for human suffering. The role that biological factors play in the development of gender identity is still not solidly established but an increasingly number of reports provide evidence that androgens play a role in the development of gender identity. The association is not absolute, and the information is not robust enough to draw solid conclusions. Nevertheless, it has been demonstrated that genderaffirming hormonal therapy and/or surgery, which is only recommended in people with well-documented gender dysphoria (5), contributes to an improved well-being (6). Medical treatment is preferably provided by а multidisciplinary team consisting of psychologists, endocrinologists, plastic surgeons, gynecologists, urologists, otorhinolaryngologists, and/or dermatologists.

Transgender people can suffer in many ways. Some concerns are intrinsic to their situation and cannot be avoided. Others take the form of accumulating small indignities that arise from a simple lack of sensitivity and understanding to their predicament. For instance, transgender people experience widespread discrimination in healthcare, housing, and employment (7). As a result transgender people have a higher risk of psychiatric diseases such a (severe) depression and anxiety disorders (8).The implementation of policies to ensure correct conduct by all health professionals involved in the care of people with gender dysphoria, would be a considerate gesture and build trust.

When providing transgender care, physicians are confronted with a lack of systematically and accurately collected data. Transgender people are not a well-defined group, and show considerable heterogeneity, for instance in age of onset, in the degree of suffering, and in the wish for treatment. The attention that transgender people receive in medicine is certainly improving, however transgender people still experience health disparities. There is a dearth of research and evidence-based guidelines for treatment, and the specific health needs for transgender people are understudied. It is problematic to include sufficient numbers of participants to perform statistically robust studies with regard to the best transgender hormonal therapy, and the long-term sideeffects of treatment. Nowadays, physicians with extensive clinical experience have drafted guidelines based primarily on empiric observation. Fortunately, the number of good quality studies is currently increasing.

#### HORMONAL THERAPY

In transwomen, hormonal therapy usually consists of estrogens ± antiandrogens (e.g. cyproterone acetate, spironolactone, or GnRH analogues) (9,10). Estrogen in the form of estradiol is recommended to minimalize the risk of venous thrombosis and cardiovascular disease. Since progestogens. other than progestogenic antiandrogens, have not been proven to have an additional effect on feminization in transwomen, they are usually not recommended (5,9,10), although they might have beneficial effects in cisgender women (11). In transmen, hormonal therapy usually consists of testosterone only (10). See Table 1 for an overview of the hormonal options for transwomen, and Table 2 for the hormonal options for transmen. For details on the hormonal regimens for transwomen and transmen the Endocrine Society Clinical Practice Guideline is an excellent source of information (10).

Table 1. Hormonal Regimens Regularly Used in Transwomen	
Estrogens	Recommended Dose
Oral estradiol	2-6 mg daily
Intramuscular estradiol valerate/cypionate	10-20 mg/1-2 weeks
Estradiol patch*	50-100 mcg/24 hours
Estradiol gel*	0.75 mg-2.25 mcg daily
Antiandrogens**	
Cyproterone acetate	10-50 mg daily
Spironolactone	50-200 mg daily
GnRH analogue	Varies per preparation

\* Transdermal preparations are recommended in transwomen aged ≥40 years or in those with an increased cardiovascular risk

\*\* Antiandrogens are discontinued after orchiectomy

Table 2. Hormonal Regimens Regularly Used in Transmen	
Testosterone	Recommended dose
Intramuscular enanthate or cypionate*	100–200 mg/2 weeks
Intramuscular mixed esters (Sustanon®) Intramuscular undecanoate	250 mg/2-3 weeks 1000 mg/12 weeks OR 750 mg / 8 weeks**
Testosterone gel	25-100 mg/day
Testosterone patch	2 or 4 mg/day

Preparation availability will differ between countries

\* Due to associated serum testosterone peaks, these injections may not the best option for transmen who develop polycythemia (12)

\*\* The above are the conventional dosages for cismen. To virilize transmen 50-75% of these dosages are usually sufficient

# **Effects of Hormonal Therapy**

#### TRANSWOMEN

In transwomen, hormonal therapy induces feminization such as breast growth, skin softness, fat redistribution, and a decrease of body hair (9,10). Figure 1 shows the expected effects of hormonal therapy in transwomen, and the period over which achievement of maximum effects could be expected (9,10,13). Most of the hormone-induced effects start within the first months of treatment. It is important to realize that transwomen might not achieve the desired breast size; one year of hormonal therapy in transwomen usually results in less than an AAA cup size (13). As a result, many transwomen choose for breast augmentation surgery (14). It is also important to note that for complete permanent removal of (facial) hair, additional laser skin treatments are required. Furthermore, hormonal therapy does not induce voice changes. Therefore, transwomen who desire raising of their voice pitch may benefit from referral to a speech therapist (10).





Figure 1. Hormone Effects and the Term of Maximum Expected Effects in Transwomen

#### TRANSMEN

In transmen, hormonal therapy induces masculinization such as an increase in facial and body hair, an increase in muscle mass and strength, a masculinized voice, and a cessation of the menstruation. Figure 2 shows the expected effects of hormonal therapy in transmen, and the term that maximum effects could be expected (10). Most of the hormone-induced effects start within the first months of treatment. In most cases the menses cease during testosterone therapy. However, some transmen who experience persistent vaginal bleeding need additional therapy such as the progestin lynesterol or GnRH analogues, which suppress gonadotropin secretion.



Figure 2. Hormone Effects and Term of Maximum Expected Effects in Transmen

#### **Hormonal Effects on Bone Health**

Before puberty, the size and volume of the skeleton are similar in the two sexes. But upon the rise of androgens during puberty, a higher peak bone mass is attained in boys than in girls. Bone mass accrual, bone growth and maintenance of skeletal integrity in adulthood are critically determined by sex hormone production. In both sexes, hypogonadism leads to loss of bone. In men a significant role of estrogens in bone metabolism has been demonstrated. It is of note that testosterone is partially aromatized to estradiol, and it is well established that estradiol also plays a pivotal role in the bone health of men (15,16). These mechanisms underscore that hormonal therapy in transgender people will affect bone metabolism.

#### TRANSWOMEN

Unexpectedly, transwomen have a lower bone mineral density than controls before starting with hormonal therapy. This might be explained by a less active lifestyle and/or a lower vitamin D status (17,18). As remarked above, in both sexes' estrogens are important in the maintenance of bone health in adulthood. Initial studies examining the effect of long-term hormonal therapy on bone mineral density showed contradictory results. However, most of these studies were small cross-sectional studies in which a baseline difference in bone mineral density was not taken into account (19-21). The most recent cohort study in transwomen showed that hormonal therapy does not have negative effects on bone mineral density, and that the lower bone mineral density in transwomen found in previous studies is solely based on a baseline lower bone mineral density (18). Therefore, it would be worthwhile to give lifestyle advice regarding physical exercise, adequate vitamin D status, and calcium intake to transwomen.

In postmenopausal women, bone mineral density depends on estrogens derived from aromatization of ovarian androgen production (22). Many transwomen have undergone orchiectomy in the process of their transition. Their status could probably be compared with a surgicallyinduced menopause in a ciswoman. Women with a surgically-induced menopause experience rapid bone loss during the first five years after oophorectomy. Based on this information, it has become clear that complete discontinuation of hormonal therapy in transwomen above the age of 50 leads to a profound loss of bone strength. Therefore, it is advisable to not discontinue estrogen therapy in older transwomen (23).

#### TRANSMEN

In contrast to transwomen, transmen show no lower bone mineral density before starting hormonal therapy (24,25). Furthermore, no negative effects of testosterone therapy on bone mineral density have been found (18,20,24).

#### Hormonal Effects on Cardiovascular Health

Cardiovascular disease is a prominent cause of morbidity and mortality in both women and men. Sex is known to affect one's risk for cardiovascular disease. Men have a higher (age-adjusted) risk of strokes and acute coronary events than women (26-28). Strokes are 33% more incident in men than in women (28), and acute coronary events 172% (29). In addition, during reproductive age, women have a 100% higher risk of venous thromboembolic events than men (30,31). These data suggest that sex hormones play a role in the occurrence of cardiovascular events. Based on this information, it is surprising that recent studies found that estrogen therapy (without progestogen) increases the risk for developing strokes in menopausal women (32). There is also suggests a relationship evidence that between testosterone therapy and an increased risk of cardiovascular events (33–35). If exogenous sex hormones indeed have impact on the cardiovascular system, this might have consequences for transgender people receiving hormonal therapy. At the Amsterdam University Medical Center, the Netherlands, we have analyzed the development of cardiovascular disease in the population of the Gender Clinic. The Gender Clinic started in 1972 and there is now a large cohort of transgender people being followed-up including a growing number of older transgender people. The findings are summarized below.

#### TRANSWOMEN

Upon analysis of our transgender population in 1989 and in 1997 (36,37), cardiovascular disease, other than venous thromboembolism, was not increased in transwomen

compared to cismen. However, the most recent evidence from 2011 and 2018 shows that transwomen receiving hormonal therapy have an increased risk for strokes and venous thromboembolism (but not acute coronary events) compared to cismen (38,39). The current estimated incidence rate for strokes in transwomen on hormonal therapy is 127 per 100,000 person-years, which is 80% higher than in cismen. The current estimated incidence rate for venous thromboembolic events is 320 per 100,000 person-years, which is 355% higher than in cismen (38). While the increased cardiovascular risk in transwomen was initially attributed to the usage of ethinylestradiol, recent studies found that transwomen who use other types of estrogens also have an increased risk for strokes and venous thromboembolism (38-40). The hypercoagulable effect of hormonal therapy (41) may be one of the mediators of the increased cardiovascular risk in transwomen.

Possibly, venous and arterial cardiovascular side-effects become more prominent past the age of 40-50 years, and in people with cardiovascular risk factors. While strong evidence is currently lacking, transdermal estradiol might be preferred over oral estrogens in these transwomen (9,42,43). In addition, one should be aware that progestogenic antiandrogens (e.g. cyproterone acetate) further increase one's risk may for venous thromboembolism (44), and should therefore be continued no longer than necessary. Modifiable cardiovascular risk lipid factors such as concentrations, alucose concentrations, and blood pressure should be regularly monitored and treated in accordance with guidelines for ciswomen.

# TRANSMEN

As in transwomen, first analyses from our center did not show an increased risk of cardiovascular disease in transmen using testosterone (36,37,45). However, the most recent analysis shows an increased risk for acute coronary events in transmen receiving testosterone, with a current estimated incidence rate of 100 per 100,000 person-years, which is 269% higher than the rate in ciswomen (38). The increased risk of acute coronary events in transmen receiving testosterone may be (partly) explained by the testosterone-induced combination of increases in hematocrit, thromboxane, triglycerides, and low-density lipoprotein cholesterol, and a decrease in plasma high-density lipoprotein cholesterol concentrations (35,46,47). Although, the design of the study made it impossible to draw any conclusions about a causal relationship we recommend to regularly monitor cardiovascular risk factors in transmen on testosterone therapy.

#### Hormonal Effects on Tumor Risk

Malignant neoplasms are the second leading cause of death worldwide (48). The risk for certain types of tumors differs between men and women. While this is obvious for neoplasms that develop in sex-specific organs such as the ovaries or the prostate, it is also the case for other types of tumors such as those of the meninges (49) and thyroid gland (50). Some of these differences are attributed to the exposure of sex hormones. Combined hormonal therapy in postmenopausal women has been found to increase the risk of breast cancer and death from lung cancer (51). In women with polycystic ovary syndrome a higher risk for endometrial cancer has been described, which is probably explained by the prolonged endometrial exposure to unopposed estrogen that results from anovulation (52). Testosterone therapy in hypogonadal men is not clearly associated with an increased cancer risk, but breast cancer risk in prostate cancer patients who receive estrogen therapy seems 3.91 times higher than in prostate cancer patients not receiving estrogen therapy (53). If exogenous sex hormones indeed are able to induce cell proliferation, this might have consequences for transgender people receiving hormonal therapy. It is good to keep in mind that transwomen and transmen remain susceptible to cancers of reproductive organs that are no longer in alignment with their gender. For example, postsurgical transwomen, and attending physicians, might not recognize their persisting risk of prostate cancer (the prostate is not removed during vaginoplasty). In addition, transmen who have not undergone removal of the uterus still have risk for cervical cancer. It is also important to realize that transgender people may opt out of cancer screening and examinations because of emotional or physical distress associated with the discordance between their experienced gender and their birth assigned sex.

To date, large-scale studies investigating neoplasms in transgender people are scarce and the literature mainly consists of case reports. One of the first reviews was presented in 2008 (54), and an extensive, high quality review appeared in 2017 (55). A cautious comparison of the two reports helps us to provide insight into the neoplasm-related morbidity and mortality in transgender people.

#### TRANSWOMEN

#### Breast Cancer

Estrogen in combination with antiandrogen therapy in transwomen stimulate the development of breast lobules, ducts, and acini which are histologically identical to those of ciswomen (56). While for a long time it was believed that the risk of breast cancer in transwomen receiving hormonal therapy was not higher than those of men (57,58), most recent evidence show that transwomen receiving hormonal therapy do have a 46-fold higher risk for breast cancer compared to men (59). As became clear in the Women's Health Initiative study, addition of progestin to estrogen leads to an increase of the risk of breast cancer in women (60). Although evidence regarding breast cancer and the usage of the progestogenic cyproterone acetate is lacking, the above described data suggest that cyproterone acetate should be continued no longer than necessary. In addition, based on the most recent study that shows a much higher risk of breast cancer in transwomen compared to men, it is reasonable to recommend transwomen on hormonal therapy to participate in population-based breast cancer screening programs (9).

# Prostate Cancer

While in the past, estrogens have been used to treat prostate cancer, estrogen and its related compounds have also been suggested as potential causative agents (61). Current literature, suggests that prostate cancer is very rare among transwomen. The few cases that have been reported in transwomen were in those who had not been screened for prostate cancer before starting hormonal therapy. Consequently, it remained unclear whether the prostate cancer was already present before hormonal therapy had been initiated (62). While prostate cancer has been rarely reported, underdiagnosis is possible due to lack of close prostate monitoring. Based on available evidence it does not seem necessary to screen transwomen in a different way to cismen, for which population-based screening is not recommended. But similarly, a transwoman with a first-degree male relative with prostate cancer should be made aware of her increased risk and prostate cancer [PSA] testing should be discussed to allow informed decision making. However, when interpreting PSA values in this context, it has to be kept in mind that suppression of testosterone by antiandrogens or due to gonadectomy lowers PSA values. A cross-sectional study of Wierckx et al. (63) found median PSA levels of 0.003 ng/mL with an interquartile range of 0.03 to 0.09 in a group of 50 postoperative transwomen using hormonal therapy on an average of 10 years. Therefore a serum level of PSA >1.0 ng/mL may already be a reason for suspicion in transwomen (64).

# Prolactinoma

Serum prolactin concentrations usually rise slightly in response to estrogen administration and more so by cyproterone acetate (65,66). Based on case reports, it was believed that prolactin concentrations initially in transwomen had to be regularly monitored because of their increased risk for prolactinomas. Surprisingly, a very recent cohort study suggests that the occurrence of prolactinomas in transwomen using hormonal therapy is not higher than that in ciswomen, and that regular prolactin checks are not necessary (67). However, cyproterone acetate should be continued no longer than necessary.

# Meningioma

Several meningiomas have been reported in transwomen. The current estimated incidence rate of this type of tumor is 33 per 100,000 person-years. This incidence rate is 4 times higher than the incidence rate in ciswomen and 12 times higher than the incidence rate in cismen (67,68). It has been suggested that the occurrence of meningiomas in transwomen is mainly related to cyproterone acetate usage as progesterone receptors are abundantly expressed in human meningiomas (67). Since the occurrence of meningiomas is still rare in transwomen, regular screening for this type of tumor seems not necessary. It is recommended to continue cyproterone acetate no longer than necessary.

# Other Types of Cancer

As sexually transmitted infections may be more prevalent in transwomen, tumors related to sexually transmitted infections, such as Kaposi sarcoma or anal cancer, may also occur more often. Indeed, disproportionately high incidences of these types of tumors have been found in the transgender population (55,69). Some case reports have been published on cancer in surgically constructed organs like the neo-vagina in transwomen (70,71). While the incidence of these types of tumors seem to be very low it is important to be aware of this possibility.

# TRANSMEN

#### Breast Cancer

Cases of breast cancer have been reported in transmen before mastectomy (59,72,73). It is important to know that because of cosmetic reasons not all glandular tissue is removed during a mastectomy in transmen. Indeed, several cases of breast cancer have been reported in transmen who already had received mastectomy (59,73-75). The incidence of breast cancer in transmen who have received mastectomy seems higher than in cismen, but much lower than in ciswomen (59). While physicians and transmen have to be aware of their risk of breast carcinoma after mastectomy, it seems unnecessary for transmen to participate in the screening programs for women. However, for transmen with а aenetic predisposition for breast cancer, more radical forms of mastectomy could be considered.

#### Endometrial Cancer

Not all transmen choose to remove their uterus. Menstruation usually ceases in transmen receiving testosterone therapy. Testosterone can be converted into estradiol, which may induce proliferation of the endometrium. These mechanisms may induce a higher risk of endometrial cancer in transmen. Women with polycystic ovary syndrome who do not menstruate and suffer from hyperestrogenism, have a thicker endometrium and a higher risk of endometrial cancer (76). It is also possible that the risk for endometrial cancer in transmen using testosterone is lower due to complete atrophy of the

endometrium (55). There is currently only 1 case of endometrial cancer reported in a transman using testosterone (77). But it is important to know that, until recently, many countries required removal of female sex organs before transmen could change their sex on the birth certificate. Therefore, long-term follow-up data about testosterone receiving transmen with a uterus are lacking. This makes it impossible to draw hard conclusions. Nevertheless, in transmen with non-cyclic vaginal blood loss, we recommend to perform a vaginal ultrasound.

#### Cervical Cancer

Transmen in whom the uterus has not been removed have a risk of cervical carcinoma. Human papilloma virus is the most important risk factor for developing cervix carcinoma. Studies in ciswomen show that testosterone may also be a risk factor (78). To date, only 2 cases of cervical carcinoma in transmen have been described (77,79). Again, it is important to keep in mind that, until recently, many countries required removal of female sex organs before a transman could change the sex on the birth certificate, which makes the data available limited. As there is no evidence for a decreased risk of cervical carcinoma in transmen, it seems reasonable for transmen with a uterus to participate in screening/HPV vaccination programs for ciswomen. It is important to inform transmen about the need for this screening as they probably do not receive invitations from screening organizations.

#### Ovarian Cancer

Endometrial epidermal growth factor receptor, which is stimulated by testosterone, is commonly found in ovarian cancer cells, and its expression has been associated with poor prognosis (80). However, whether testosterone therapy increases the risk for ovarian cancer in transmen has not been elucidated yet. To date, 3 cases of ovarian cancer have been reported in transmen using testosterone (81,82). Future studies need to provide more evidence about the risk of gynecological cancers in transmen. Until then, screening for ovarian cancer seems unnecessary.

# EVALUATION OF TRANSGENDER PEOPLE RECEIVING HORMONAL THERAPY

Since hormonal therapy is associated with several sideeffects it is recommended that medical conditions which

can be exacerbated by hormonal therapy are addressed before the start of therapy. During hormonal therapy it is advisable to regularly measure hormone concentrations and maintain them in the normal physiological range. For transwomen estradiol levels between 100 to 200 pg/mL (367 pmol/L to 734 pmol/L) and testosterone levels of <50 ng/dL (<2 nmol/L) are recommended. For transmen, the testosterone level is dependent on the specific assay, but is typically 320 to 1000 ng/dL (11 nmol/L to 35 nmol/L) (10). However, the peak testosterone level after a short acting testosterone injection is often (much) higher than 1200 ng/dL (42 nmol/L). It is also recommended to regularly measure glucose concentrations, lipid panel, and blood pressure during hormonal therapy in both transwomen and transmen, hematocrit in transmen, and electrolytes in transwomen receiving spironolactone (in the first year at baseline and 3 and 12 months, hereafter every 6 months to 2 years).

# SURGERY

Many transgender people choose to have surgery in addition to hormonal therapy. There are several surgical options. While some types of surgery affect fertility, such vaginoplasty in transwomen as or oophorectomy/hysterectomy in transmen, others do not, such as breast surgery in both transwomen and transmen. For surgery which affects fertility, most guidelines recommend the usage of gender-affirming hormones for at least 12 months, which is based on expert consensus that 12 continuous months of living in the experienced gender role is needed for transgender individuals to experience and socially adjust in the desired gender role (5,10).

# **Surgical Options in Transwomen**

# ORCHIECTOMY

Orchiectomy can be performed independently or as part of a vaginoplasty. Orchiectomy is a relatively low-risk procedure (83). After orchiectomy the antiandrogens are no longer necessary and can discontinued.

# VAGINOPLASTY

During a vaginoplasty an orchiectomy (if not previously performed) is performed, in combination with an amputation of the penis, the creation of a neovaginal cavity with lining, the reconstruction of a urethral meatus, and the creation of labia and clitoris. The most frequent procedure is penile inversion vaginoplasty during which the penile skin is used a pedicled flap for the vaginal lining. Since the amount of penile skin is limited, the penile skin flap is often combined with a scrotal skin flap. To prevent hair in the posterior lining of the vagina, hair removal therapy is desirable before penile inversion vaginoplasty is intestinal vaginoplasty, which is a good option in cases in which insufficient skin is available (for example in transwomen who have received puberty blockers during adolescence (83)).

# BREAST AUGMENTATION

Many transwomen choose for breast augmentation since they are not satisfied with their hormone-induced breast growth. The breast augmentation procedure does not differ from an breast augmentation in ciswomen (83).

# FACIAL FEMINIZATION SURGERY

Facial feminization surgery includes a wide range of craniomaxillofacial surgical procedures which are designed to create more feminine facial features. Overall, facial feminization surgery seems a highly efficacious and beneficial procedure for transwomen (84).

# VOCAL CORD SURGERY

Surgically shortening of the vibrating vocal cords or increasing the vocal cord tension can raise the voice pitch in cases that voice therapy does not achieve the desired effect (83).

# CHONDROLARYNGOPLASTY

During chondrolaryngoplasty (tracheal shaving) the prominence of the thyroid cartilage is reduced. Chondroplasty can be performed alone or in combination with vocal cord surgery. Reduction of the Adam's apple can have positive effects on the psychological well-being of transwomen (85).

# **Surgical Options in Transmen**

#### SUBCUTANEOUS MASTECTOMY

Most transmen choose mastectomy. A mastectomy in transmen which is performed for aesthetic reasons differs from a mastectomy in ciswomen which is performed because of breast cancer. During the mastectomy in transmen not all glandular tissue is removed. In addition, (more) attention has to be paid to reduction and adequate positioning of the nipple areola complex, destruction of the inframammary fold, and minimization of scars (83).

#### HYSTERECTOMY

Many transmen desire uterus extirpation with or without a salpingo-oophorectomy for gender affirmation, pelvic pain, persistent vaginal blood loss, or cancer-risk reduction. It is preferred to use a vaginal approach instead of a transabdominal approach although this could be technically challenging as many transmen have not experienced penetrative intercourse and are on testosterone therapy (86). Transmen who also want a colpectomy can also choose to have a robot-assisted laparoscopic hysterectomy (with salpingo-oophorectomy) in combination with a robot-assisted laparoscopic colpectomy (87).

#### COLPECTOMY

Transmen may choose for a colpectomy (removal of the vaginal epithelium) for several reasons, such as unwanted vaginal discharge in general or as result of sexual arousal, or the wish for phalloplasty with urethral extension. There are two options for colpectomy, the vaginal approach and the robot-assisted laparoscopic colpectomy in combination with hysterectomy and salpingo-oophorectomy. The robot-assisted procedure seems to be safer than the vaginal approach (87).

# PHALLOPLASTY

Phalloplasty is the surgical creation of a full-size penis. It is a difficult surgical procedure with high rates of complications such as urethral stenosis. An ideal phallus has sufficient length for vaginal penetration, has sensibility, and, if desired, enables the transman to urinate in standing position. Multiple flaps have been used to create the

#### METADOIDIOPLASTY

During a metoidioplasty a microphallus is created by using the testosterone-induced hypertrophied clitoris. While a metadoidioplasty gives a lower risk for complications than a phalloplasty, it cannot be guaranteed that voiding in the standing position is possible. In addition, vaginal penetration will not be possible (83,88).

#### FERTILITY PRESERVATION

It is estimated that about 47% of transgender individuals would like to have a child to whom they are genetically related (89). Gender affirmation therapy, both hormonal and surgical, is an indication for fertility preservation since hormonal therapy adversely affects fertility, and surgery may include gonadal removal. While the adverse effects of hormonal therapy may be reversible when the therapy is ceased, it is important to discuss fertility preservation options with a transgender individual before the start of hormonal therapy (90). In transwomen the percentage that would have frozen sperm if this option was offered, varied from 13% in asexual or heterosexual (being attracted to men) transwomen to 56% in homosexual (being attracted to women) and bisexual transwomen (91). It is estimated that about 37% (92) of the transmen wish to have their gametes preserved before any gender affirming therapy. For transgender adolescents it is important to involve parents in the fertility preservation counseling as they play an important role in exploring options for their children and usually have to give their consent to interventions. A recent study found that parents overall did not emphasize the importance of their child having children to whom they are genetically related but they agreed that that fertility preservation counseling is relevant (93).

#### Transwomen

Semen cryopreservation using specimens obtained from masturbation or penile vibratory stimulation is technically the most easy, reliable and inexpensive method for fertility preservation in transwomen. However, for some transwomen this option may not be possible because of the psychologically distress induced by this procedure, or the difficulties in erection and ejaculation. Alternatives are electro-stimulation or surgical sperm retrieval, or in case of azoospermia, testicular sperm extraction (90). The obtained sperm can be used to fertilize the partner of the transwoman if this partner is female. In case of a male partner a gestational surrogate is needed for fertilization.

# Transmen

For transmen fertility options are embryo cryopreservation, oocyte cryopreservation, and ovarian tissue cryopreservation. As long as the ovaries and uterus are in situ, it is also possible for a transgender man to become pregnant spontaneously. Since testosterone therapy may be dangerous for fetal development it is important that testosterone therapy be discontinued before the transman becomes pregnant. In contrast to the other options, ovarian tissue cryopreservation is more experimental and not widely available. For embryo creation or to fertilize a preserved oocyte, sperm from an intimate partner or an anonymous donor, is needed. When a transgender man does not want to carry the child, a gestational surrogate is also needed. However, surrogacy for transgender individuals is still not widely available due to ethical and legal issues. Furthermore it is important to note that all fertility options in transmen are sooner or later accompanied with controlled ovarian hyperstimulation, which could be very distressing for a transman (90).

#### SPECIAL TOPICS

# Hormonal Therapy in Older Transgender People

Some transgender people start the transition to their experienced gender at an older age (often after a long time of struggling), even past the age of 50 or 60 years (23,94). The majority of these people are currently transwomen (94), but the number of transgender individuals, and especially transmen is currently rapidly growing, possibly due to a greater tolerance and acceptability in society (2). There is no evidence that the manifestations of biological effects of sex hormones will be less in the elderly than in younger people (13,95,96). Age itself should not be regarded as a contraindication to start with hormonal therapy, but the risks of side-effects may be higher at an older age (97).

#### **Unsupervised Use of Hormonal Therapy**

Ideally, the indication for hormonal therapy is the result of psychological assessment that concludes that medical treatment will bring relief to an individual suffering from gender dysphoria (98). However, it is not uncommon that transgender people self-medicate. The use of health care facilities specialized in gender care may be unaffordable, difficult to assess due to long waiting lists, or people are unwilling to undergo psychodiagnostic assessment of their gender problems. Hormones are relatively easy to obtain, and peer groups and the internet provide (sometimes misguided) information on their use (99-101). Frequently, contraceptive pills containing ethinylestradiol with its associated risks (45,102) are used in high doses. Our knowledge about self-medication in the transgender population is very limited, but a study has indicated increased side-effects with illicit use of hormones (101). Another study found 23% of applicants for treatment had used sex hormones already. Remarkably, 32% were transwomen and 6% transmen. The individuals who had used self-prescribed hormones had much less knowledge about appropriate use and potential side-effects (103). Physicians should be aware of illicit hormone use and intervene when necessary.

# CONCLUSIONS

Transgender care is a challenging, multidisciplinary, and developing field in medicine. The transgender population is rapidly growing and the existence of non-binary or gender queer genders gets increasingly more attention. Before the start of any type of therapy, the physician needs to discuss the pros and cons of the several treatment options so that the transgender individual can make a well-considered decision. Due to the increase of high-quality studies, hormonal and surgical therapy will probably be further optimized in the (near) future. Therefore, it is important for physicians who provide transgender care to stay up-todate with the latest literature. In addition, as the waiting lists may be growing due to the rapidly the increasing number of new applications to gender clinics, physicians should be aware of a growing number of transgender individuals who self-prescribed hormones. use

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