Review Article

Hormonal Gender Reassignment Treatment for Gender Dysphoria

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Summary

Background: No data are available at present on the prevalence of gender dysphoria (trans-identity) in Germany. On the basis of estimates from the Netherlands, it can be calculated that approximately 15 000 to 25 000 persons in Germany are affected. Persons suffering from gender dysphoria often experience significant distress and have a strong desire for gender reassignment treatment.

Method: This review is based on pertinent publications retrieved by a selective search in the PubMed database employing the searching terms "transsexualism," "transgender," "gender incongruence," "gender identity disorder," "gender-affirming hormone therapy," and "gender dysphoria."

Results: In view of its far-reaching consequences, some of which are irreversible, hormonal gender reassignment treatment should only be initiated after meticulous individual consideration, with the approval of the treating psychiatrist/psychotherapist and after extensive information of the patient by an experienced endocrinologist. Before the treatment is begun, the patient must be extensively screened for risk factors. The contraindications include severe preexisting thromboembolic diseases (mainly if untreated), hormone-sensitive tumors, and uncontrolled preexisting chronic diseases such as arterial hypertension and epilepsy. Finding an appropriate individual solution is the main objective even if contraindications are present. Male-to-female treatment is carried out with 17β-estradiol or 17β-estradiol valerate in combination with cyproterone acetate or spironolactone as an antiandrogen, female-to-male treatment with transdermal or intramuscular testosterone preparations. The treatment must be monitored permanently with clinical and laboratory follow-up as well as with gynecological and urological early-detection screening studies. Prospective studies and a meta-analysis (based on low-level evidence) have documented an improvement in the quality of life after gender reassignment treatment. Female-to-male gender-incongruent persons often have difficulty being accepted in a gynecological practice as a male patient.

Conclusion: Further prospective studies for the quantification of the risks and benefits of hormonal treatment would be desirable. Potential interactions of the hormone preparations with other medications must always be considered.

Cite this as:
Meyer G, Boczek U, Bojunga J: Hormonal gender reassignment treatment for gender dysphoria. Dtsch Arztebl Int 2020; 117: 725–32.
DOI: 10.3238/arztebl.2020.0725

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Gender dysphoria—or gender incongruence or transsexuality–is characterized by a mismatch between the biological sex and the inner sense of gender (gender identity). A transgender woman is a biologically male person with female gender identity; correspondingly, a transgender man is a biologically female person with male gender identity. In the Netherlands, the prevalence of gender dysphoria is estimated to be 0.02–0.03% (1). For Germany, no estimates have yet been published. Based on the above figures, it can be assumed that approximately 15 000 to 25 000 people are affected. While earlier studies (1, e1, e2) reported a gender ratio of transgender women to transgender men of approximately 2 : 1, more recent studies found increasingly similar proportions (e3) or even a reversal of this ratio (2).

With the onset of puberty, transgender persons typically experience significant psychological distress (gender dysphoria) and consequently seek gender-affirming—or gender reassignment—treatment (e4). With 9% to 11% and 1.5% to 2%, the rates of suicide attempts (3) and committed suicides (4), respectively, are increased among people with gender dysphoria compared to the general population. In 2010, a meta-analysis found a decrease in mental and physical complaints as well as an increase in quality of life after the start of gender-affirming hormone therapy (GAHT) (5), but the data quality of this study was limited. However, later prospective studies confirmed these findings (6, e5). The two-year follow-up after GAHT revealed the following differences compared to the pre-treatment status:

- Decrease in depressive symptoms (Beck Depression Inventory [BDI] II scores: transgender women −1.41, $p<0.001$; transgender men −1.31, $p<0.001$)
- Reduction in body uneasiness (Body Uneasiness Test [BUT] index: transgender women −0.24, $p<0.001$; transgender men −0.24, $p = 0.001$)
- Decrease in gender dysphoria (GIDYQ AA score: transgender women −0.06, $p<0.001$; transgender men −0.05, $p = 0.001$) (6).

For persons with gender dysphoria, treatment with cross-sex hormones delivers a sense of identity. However, since gender-affirming hormone therapy has a significant effect on a person's hormonal balance, it is associated with a risk of adverse effects which is particularly high in the event of unsupervised treatment or overdosing.

Using treatment data from a large Dutch gender identity clinic collected in the period from 1980 to

BOX

Recommendations for pre-treatment screening und possible contraindications (according to [9, 10])

- **Medical history**
  - Cardiovascular disease
  - Thromboembolic disorders
  - Hormone-sensitive cancers (endometrial, breast, cervical, prostate)
  - Dyslipidemia
- **Family history**
  - Cardiovascular disease
  - Thromboembolic disorders
  - Hormone-sensitive cancers (endometrial, breast, cervical, prostate)
  - Dyslipidemia
- **Physical examination**
  - Medical examination, including weight, blood pressure
  - Secondary sexual characteristics (breast, genitals, body hair pattern)
  - Biological women: Gynecological screening, including at least transabdominal ultrasound of the internal genitalia
  - Biological men >40 years: urological screening
- **Laboratory testing**
  - Liver function tests
  - Blood count
  - HbA1c, if required fasting glucose levels
  - Lipid profile
  - Hormonal status (TSH, LH, FSH, estradiol, testosterone, prolactin; in biological women in addition DHEAS, androstenedione)
  - In biological men: PSA
  - Coagulation status (INR, PTT)
  - Thrombophilia screening in patients with a positive personal or family history
- **Contraindications**
  - Uncontrolled pre-existing chronic conditions (diabetes mellitus, arterial hypertension, epilepsy)
  - Severe thromboembolic pre-existing condition
  - Ischemic cardiovascular or cerebrovascular pre-existing condition
  - Refractory migraine
  - Hepatic insufficiency, liver cirrhosis
  - Hormone-sensitive cancers (endometrial, breast, cervical, prostate)
  - Severe psychiatric disorder (e.g. acute psychosis) influencing the decision or treatment
  - Current alcohol or drug abuse
  - Non-adherence
  - Desire to have children

DHEAS, dehydroepiandrosterone sulfate; FSH, follicle-stimulating hormone; HbA_{1c}, hemoglobin A_{1C}; INR, international normalized ratio ; LH, luteinizing hormone; PSA, prostate-specific antigen; PTT, partial thromboplastin time; TSH, thyroid-stimulating hormone

2015, Wiepjes et al. demonstrated a 20-fold increase in newly started GAHT (1). Similarly, many treatment providers in Germany have observed an increase in the number of affected persons in recent years (personal communication from colleagues of other institutes). Factors potentially contributing to this trend include growing societal acceptance and a significant increase in public attention and media coverage (e6–e10). Nevertheless, in Germany, too, those affected do frequently not receive optimal care (7, 8, e4, e11).

The aim of this article is to provide up-to-date insights into and recommendations for gender-affirming hormone therapy (GAHT) as well as information about special aspects that should be taken into account by general practitioners and specialists involved in the care of transgender persons.

Overall, the evidence from studies on the effects and risks of GAHT—which also forms the basis of the guidelines of the Endocrine Society which were initially created under US and European co-authorship in 2009 and then updated in 2017 (9)—is weak. Most studies are retrospective data analyses, frequently based on comparatively few cases. Prospective studies are scarce. There are no randomized controlled trials and, ultimately, it is difficult to imagine that studies designed will ever be conducted, not least for ethical reasons. A German or European guideline on GAHT has not yet been created.

Method

This review is based on a selective search of the PubMed database for original publications and review articles up to December 2019. The following search terms were used: "transsexualism", "transgender", "gender incongruence", "gender identity disorder", "gender affirming hormone therapy", "gender dysphoria".

Requirements

Treatment with GAHT quickly causes marked and partly irreversible changes. Thus, prior to the start of treatment, it is critical to confirm the diagnosis and to ensure that a clear, written indication for GAHT is established by a psychotherapist or psychiatrist (9–11, e12). There are no strict requirements for the duration of preceding psychotherapy and, given the very different circumstances and needs of the affected individuals, any such requirement may not be helpful after all.

GAHT can be started at about age 16 years, provided a written, documented informed consent is obtained from the adolescent's parents or guardian and the adolescent is mature enough to make this decision. In gender-dysphoric younger children and adolescents, a reversible puberty-suppressing therapy with gonadotropin-releasing hormone (GnRH) analogs can be initiated with the onset of puberty (9). In minors, confirmation of the indication by an

independent second therapist should be required (9). Prior to the initiation of treatment, the patient must be informed in detail about the treatment effects, their course over time, the limitations of the treatment and potential adverse effects (9, 10).

Medical diagnostic work-up prior to treatment initiation

A comprehensive pre-treatment risk screening, including thorough medical history, family history and physical examination as well as clinical chemistry testing of relevant parameters is required to identify potential contraindications and risk factors. This screening also helps to adapt the planned treatment to a patient's individual risk profile (*Box*).

Many healthcare payers require that a somatic variation of sex development is ruled out before treatment is started (e13). These differential diagnostic conditions, such as Klinefelter syndrome and complete androgen resistance syndrome, are rare and can be excluded based on the medical history, physical examination and measuring of basal hormone levels. Only in the presence of major clinical abnormalities and grossly abnormal laboratory findings, further diagnostic work-up, including chromosomal analysis, should be performed.

Pre-existing conditions, such as arterial hypertension, diabetes, dyslipidemia, and HIV, require adequate treatment. Adequately controlled, they are not considered absolute contraindications. In the presence of elevated liver enzyme levels, a pre-existing hepatic condition should be ruled out. Further diagnostic testing may be required.

GAHT is so essential for patients with gender dysphoria that priority even over contraindications can be given to this treatment on an individual basis after detailed discussion of associated risks. The decision to provide the treatment should also be broadly supported by all clinicians involved in the patient's care. Absolute contraindications are very rare. Unsupervised self-medication is associated with high risks. Thus, instead of withholding therapeutically controlled hormone treatment in patients with contraindications, ideally an experienced endocrinologist should carefully evaluate each case individually to find a personalized solution.

Male-to-female gender dysphoria

Treatment recommendations

GAHT of male-to-female transsexuals is based on the oral or transdermal administration of 17ß-estradiol or 17ß-estradiol valerate (9). Because of the significantly more unfavorable risk profile, treatment with ethinyl estradiol is obsolete (12–14). Since thromboembolic complications are more common with oral estradiol treatment (15), preference is given to the transdermal route of application if additional risk factors, such as overweight, older age and smoking, are present.

Since reducing androgen levels is another important requirement for the desired feminization of the body (16, e14), patients also receive supplementary anti-androgen therapy. Here, the standard treatment is the administration of cyproterone acetate (17). Alternatively, treatment with spironolactone may be considered. Administration of a GnRH analog is another treatment option, but the significantly higher costs of this approach need to be taken into consideration. Anti-androgen treatment is discontinued, at the latest, once orchiectomy has been performed as part of the gender-affirming surgical procedure. An additional benefit on breast development by supplemental progesterone treatment has not yet been confirmed (18, 19). There is a lack of randomized controlled trials evaluating this aspect. Given the increased risk of breast cancer and thromboembolic events associated with hormone replacement therapy in postmenopausal women (e15), additional administration of progesterone in transgender women is currently not recommended (9). Information about the medications used for GAHT and their standard dosing schedules is provided in *Table 1*.

TABLE 1

Medications used and dose recommendations (according to [9])

Medication	Preparations	Recommended doses
Feminizing hormone therapy for male-to-female gender dysphoria		
Estradiol	Oral: estradiol or estradiol valerate Transdermal: gel Transdermal: patch	2–6 mg/day 1.5–3 mg/day 25–200 µg/24 hours
Anti-androgen medication	Cyproterone acetate Spironolactone GnRH analogs: e.g. leuprorelin	10–50 mg/day PO 100–300 mg/day PO 3.75 mg every 4 weeks or 11.25 mg every 12 weeks SC
Virilizing hormone therapy for female-to-male gender dysphoria		
Testosterone	Transdermal gel	40–125 mg/day
	Testosterone undecanoate	1000 mg every 10 to 16 weeks IM
Additive menstruation suppression (if necessary)	Progestins: Medroxyprogesterone Dydrogesterone	 5–10 mg/day 10–20 mg/day
	GnRH analogs: e.g. leuprorelin	3.75 mg every 4 weeks or 11.25 mg every 12 weeks SC

GnRH, gonadotropin-releasing hormone; IM, intramuscular; PO, per os; SC, subcutaneous

Course and limitations of treatment

Table 2 gives an overview of the course of treatment over time and its limitations. GAHT cannot alter the size and shape of the male larynx and consequently the pitch of the voice. While body and facial hear growth are diminished, they usually do not stop completely; consequently, epilation treatment is required in most cases.

TABLE 2

Effects and course of gender-affirming hormone therapy (according to [9, 10])

Effect	Start	Maximum effect
	Course shows marked inter-individual heterogeneity.	
Feminizing hormone therapy for male-to-female gender dysphoria		
Breast growth	3–6 months	2–3 years
Fat redistribution	3–6 months	2–3 years
Reduction of muscle mass and strength	3–6 months	1–2 years
Softening of the skin	3–6 months	
Decrease in body and facial hair	6–12 months	> 3 years
Reduction of libido and spontaneous erections	1–3 months	3–6 months
Decrease in testicular size	3–6 months	2–3 years
Virilizing hormone therapy for female-to-male gender dysphoria		
Suppression of menstrual periods	2–6 months	
Low pitched voice	3–12 months	1–2 years
Virilization of body build, increase in muscle mass	6–12 months	2–5 years (training-dependent)
Facial and body hair growth	3–6 months	3–5 years
Clitoral growth	3–6 months	1–2 years

Adverse reactions and risks

Table 3 gives an overview of adverse reactions and risks. The development of venous thromboembolism (VTE) is a relevant risk. Older, retrospective data from the time when ethinyl estradiol (today considered obsolete) was still commonly used show a significant increase in the risk of thromboembolism with the occurrence of a VTE in 5.5% to 6.3% of ethinyl estradiol-treated patients (12, 20). With the advent of modern treatment regimens, the prevalence of VTEs has declined to about 0.6% to 2% (21, 22). To date, no studies evaluating the perioperative risk of thromboembolism have been conducted in patients receiving feminizing hormone therapy. Studies investigating this risk in postmenopausal women receiving hormone replacement therapy found heterogeneous results (e16–e18). Transdermal estradiol therapy without coadministration of progestin appears to be no significant additive risk factor in this patient population. The potential negative effect of temporarily discontinuing GAHT on mind and body, the risk profile and the treatment used have to be taken into consideration when making recommendations on the perioperativen management of GAHT (23). Most treating clinicians currently recommend to discontinue the hormone therapy for two weeks prior to scheduled surgical interventions (24).

Occasionally, weight gain of 3 to 4 kg, on average, is observed (25, 26). In addition, older studies showed an increase in triglycerides (26, 27) from 76 mg/dL to 128 mg/dL, on average, ($p<0.001$) and in 11% of cases a maximum increase in liver enzyme levels to the 2.5-fold of the upper limit of normal (ULN) (12). When transdermal estradiol formulations are used, unfavorable changes in these laboratory parameters are significantly less common (27) or levels even decrease to the female reference range (17).

Long-term data on cardiovascular risk are scarce. However, a recent study found an increased occurrence of cerebral ischemia in transgender individuals receiving GAHT compared to age-matched women (2.4-fold risk increase) and men (1.8-fold risk increase) (28). The rate of myocardial infarction was higher compared to biological women but comparable with the rate in age-matched men (28, 29). From about age 50 years onwards, it is recommended to reduce the estradiol dose, mimicking the normal age-related hormonal changes (30). Nevertheless, it may be useful to continue treatment with a low maintenance dose beyond the statistical age of menopause to preserve bone density (31). If additional risk factors for osteoporosis are present and especially in the rare cases where GAHT is not continued after orchiectomy, e.g. because of contraindications, it is recommended to measure bone density using dual-energy X-ray absorptiometry (DXA) (9). However, the costs of DXA for this indication are not covered by German statutory health insurance funds.

While, especially in patients receiving high doses of estradiol, mild increases in prolactin levels are common and considered acceptable, relevant increases of prolactin levels >2x ULN may require an adjustment of the estradiol dose, once functional causes of hyperprolactinemia (e.g. preceding palpation of the breast) have been ruled out. If elevated levels persist, magnetic resonance imaging (MRI) of the pituitary gland should be performed since isolated cases of prolactinoma have been reported among patients receiving long-term high-dose estradiol therapy (32). In a recent Dear Doctor letter ("Rote-Hand-Brief"), a dose-dependent increase in the risk of meningioma occurrence has been described for patients treated with cyproterone acetate.

Fertility

GAHT leads to testicular atrophy and over the course of treatment potentially to irreversible infertility (33). Information about theses consequences of the therapy and the options for preserving fertility (*eBox*) should be an integral part of the informed consent discussion.

Female-to-male gender dysphoria

Treatment recommendations

Gender-affirming hormone therapy of female-to-male transsexual persons is based on testosterone administered as a transdermal gel or intramuscular depot preparation. A progestin can be added

TABLE 3

Adverse reactions and risks of gender-affirming hormone therapy (adapted from [9, 10])

	Feminizing hormone therapy	Virilizing hormone therapy
Risk markedly increased	Venous thromboembolism*1	Erythrocytosis (hematocrit >50) Acne
Risk moderately increased	Cerebral ischemia*1 Cardiovascular complications*1 Hyperprolactinemia /prolactinoma*1 Hypertriglyceridemia*1 Increase in liver enzyme levels*1, *2 Depressive symptoms/aggravation of a pre-existing depression*2 Weight gain*1, *2 Meningioma*2	Weight gain Increase in liver enzyme levels Dyslipidemia Cardiovascular complications Hypertension
Risk not/not clearly increased	Breast cancer Prostate cancer	Breast cancer Ovarian cancer Endometrial cancer, cervical cancer

*1 Potential side effects of estradiol
*2 Potential side effects of cyproterone acetate

temporarily to the regimen to suppress menstruation until adequate suppression of the gonadotropic axis is achieved by testosterone (9). Progestin preparations need to be taken very regularly to ensure reliable menstrual suppression. Typically, treatment is started with a low dose taken once daily. If this is not successful, the dose can be increased to twice daily or, alternatively, a GnRH analog may be used. Further information about the preparations used and the recommended doses is presented in *Table 1*.

Course and limitations of treatment

Table 2 gives an overview of the course of treatment over time and its limitations.

Adverse reactions and risks

Adverse reactions and risks are listed in *Table 3*. Acne is the most common adverse reaction of testosterone therapy (17, 34). Depending on the severity and form of acne, topical retinoids, benzoyl peroxide, adapalene, azelaic acid, or clindamycin are used. Systemic treatment with retinoids or antibiotics is reserved for severe forms of acne (e19). Combination oral contraceptives with anti-androgenic progestin component are not suitable for the treatment of transgender men (35). In transgender men receiving retinoid treatment who are sexually active with biological men, reliable contraception has to be ensured because of the teratogenicity of the drug.

In the experience of the authors, an increase in aggressive behavior is occasionally reported. This issue should already be addressed prior to the start of treatment and regularly discussed over the course of therapy.

Because of the effect of testosterone on erythropoiesis, up to 11% to 17% of these patients develop erythrocytosis. This risk increases with increasing duration of the hormone therapy and the size of the testosterone dose, but essentially even patients with normal testosterone levels are at risk (17, 36). If side effects occur, the dose of testosterone should be reduced or the injection interval extended. Currently there is no reliable answer to the question whether erythrocytosis in transgender men increases the risk of thrombosis to an extent which is similar to that seen in patients with myeloproliferative disorders (24).

Body weight can increase by 2 kg to 4 kg on average (25, 26); however, an increase in muscle mass is also noted. While some studies indicated an unfavorable effect on lipid metabolism (increase in LDL cholesterol and decrease in HDL cholesterol) (25, 26), other studies found that blood lipid levels rather tend to align with the male reference range (17). Overall, there is some evidence indicating a somewhat increased risk of cardiovascular events (28, 29). It appears that if modern, guideline-based treatment regimens are used, relevant increases in liver enzyme levels occur significantly less frequently (17, 27) compared to the rates reported in earlier studies (12).

Contraception/fertility

Testosterone therapy alone does not provide adequate contraception before gonadectomy is performed. Safe contraceptive options which can be used in combination with GAHT include barrier methods, oral progestins as well as hormone-free or progestin-releasing intrauterine devices (37). In the informed consent discussion, the issue of contraception as well as the options for preserving fertility (*eBox*) must be addressed.

Follow-up examinations

After the initiation of treatment, a regular clinical and laboratory follow-up of the patients is required (9). During the first year, checks at three-month intervals are useful; in the long term, checks should be performed every 6 to 12 months and be continued even after the patient underwent gender-affirming surgery. It

TABLE 4

Potential drug interactions associated with gender-affirming hormone therapy (based on summaries of product characteristics)

	Co-medication	Potential drug interactions	Recommendation
Estradiol	Anticonvulsants – Carbamazepine – Phenobarbital – Phenytoin	Decreased effect of estradiol due to induction of cytochrome P-450 enzymes	Dose adjustment for estradiol, if required, depending on the clinical findings and the serum levels measured
	Anti-infectives – Rifampicin – Efavirenz – Nevirapine		
	St. John's wort products		
	Antibiotics Activated carbon	Reduced absorption of oral estradiol preparations	Because typically a temporary co-medication, no dose adjustment required
	Ritonavir Nelfinavir	In co-medication with estradiol, enzyme-stimulating properties	Note that plasma levels change in case of co-medication with other sensitive medications
	Metoprolol Imipramine	Increased effect in combination with oral estradiol preparations	Give preference to transdermal estradiol administration
	Anticoagulants Antidiabetic agents Paracetamol Benzodiazepines	Reduced effect in case of co-medication with oral estradiol preparations	Give preference to transdermal estradiol administration
Because of potential drug interactions primarily with oral estradiol preparations, a transdermal route of administration should generally be preferred in patients requiring long-term co-medication.			
Testosterone	Oral anticoagulants (especially coumarin derivatives)	Increased effect in co-medication with testosterone	Coagulation monitoring at close intervals
		In patients treated with coumarin derivatives, testosterone should not be injected intramuscularly; when DOACs are used, the applicable intervals between DOAC intake and intramuscular injection should be observed.	
Estradiol/ testosterone	When medications are used which may cause elevated liver enzyme levels (e.g. antidepressants), it is recommended to regularly perform liver function tests; as part of hormone therapy monitoring, these checks are anyway performed.		

DOAC, direct oral anticoagulants

is useful to measure serum sex hormone levels to assess the required dosing and, above all, to prevent overtreatment. In transgender women, the goal should be to achieve estradiol levels in the middle of the reference range for premenopausal women (<200 pg/mL) and testosterone levels within the reference range for women (< 55 ng/dL). The development of a female breast shows marked interindividual differences, occurs mainly during the first one to two years of hormone therapy and frequently remains incomplete at puberty level. Several studies have shown that breast development does not correlate with the estradiol levels measured (17, 18, 38). Increasing the estradiol dose beyond the normal limit does not result in further growth of the breast, but increases the risk of adverse long-term effects of the hormone therapy.

In transgender men, the goal is to achieve a testosterone level within the male reference range (approx. 250–840 ng/dL). Hemoglobin and hematocrit are important markers of the effect of testosterone (17, 36) and should be regularly monitored over the course of treatment because of the risk of erythrocytosis, among others.

In addition, patients should be screened for potential adverse reactions and risks on a regular basis. During screening, patients should be asked about risk factors and possible co-medications. Furthermore, body weight, blood pressure, liver enzyme levels, lipid status, blood count, and, in patients receiving feminizing treatment, also prolactin levels should be checked (9).

Gynecological and urological care

Male-to-female gender dysphoria

In a retrospective analysis of more than 2000 transgender women receiving feminizing GAHT, a recent study from the Netherlands has shown a 46-fold increase in breast cancer risk among transgender women compared to men. However, with a standardized incidence ratio of 0.3, the incidence of breast cancer in transgender women remains below the incidence observed in biological women (39). It is recommended that transgender women attend the standard gynecological screening program (9).

Since the prostate gland is not removed during genital gender-affirming surgery but remains in situ and sporadic cases of benign prostatic hyperplasia (40) and prostate cancer (e21) have been reported in transgender women receiving hormone therapy, annual checks of prostate-specific antigen (PSA) levels

and clinical examinations of the prostate gland are recommended (9).

Female-to-male gender dysphoria

Since testosterone is aromatized to estradiol, patients receiving GAHT are in principle still at risk for hormone-dependent cancers. While related data are scarce, overall hysterectomy with bilateral salpingo-oophorectomy is recommended. It is also recommended that until patients have undergone this procedure, or as an alternative if no surgery is performed, they should attend regular gynecological screening examinations (9).

Despite their importance, these screening examinations are frequently not or only irregularly attended. The psychological barrier for transgender men to undergo a gynecological examination is often high. Reports of transgender men finding it very difficult to be accepted by a gynecologist's practice are not uncommon (7). It is critical that transgender men have access to gynecological care—even after their legal sex status has been changed and their registered gender is male.

Treatment of pre-existing chronic conditions and intercurrent diseases

Attention should be paid to a few peculiarities and potential drug interactions (*Table 4*).

Key messages

- Since gender-affirming hormone therapy (GAHT) quickly leads to significant and partly irreversible changes, it is crucial to ensure that the treatment is clearly indicated.
- Prior to initiation of GAHT, risk factors (especially substance abuse, overweight, age, personal or family history positive for thrombophilia or hormone-sensitive cancer) and pre-existing chronic conditions (e.g. arterial hypertension, diabetes, dyslipidemia, chronic hepatitis B and C, HIV) should be identified and adequately treated.
- As recommended in the available guidelines, 17ß-estradiol (valerate) in combination with an anti-androgen is used for feminizing therapy. The use of ethinyl estradiol is obsolete due to the significantly worse side effect profile. For virilizing GAHT, transdermal or intramuscular testosterone preparations are used.
- After the initiation of therapy, clinical and laboratory checks should be performed at regular intervals.
- For persons with gender dysphoria, access to regular gynecological/urological care has to be ensured—even after their legal sex status has changed.

Dedication
In memory of Dr. Sophinette Becker, 1950–2019, former Head of the Sexual Medicine Outpatient Clinic of the Frankfurt University Hospital, longstanding co-publisher of the "Zeitschrift für Sexualforschung" and co-founder of the Rhein-Main Working Group on Transidentity.

Conflict of interest
The authors declare no conflict of interest.

Manuscript received on16 January 2020, revised version accepted on 25 June 2020

Translated from the original German by Ralf Thoene, MD.

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Cite this as:
Meyer G, Boczek U, Bojunga J:
Hormonal gender reassignment treatment for gender dysphoria.
Dtsch Arztebl Int 2020; 117: 725–32.
DOI: 10.3238/arztebl.2020.0725

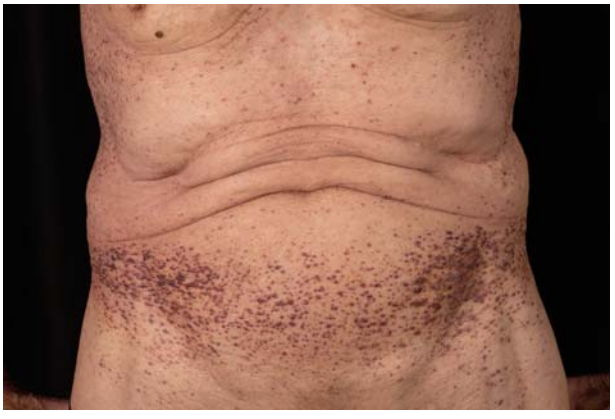
▶ **Supplementary material**

For eReferences please refer to:
www.aerzteblatt-international.de/ref4320

eBox:
www.aerzteblatt-international.de/20m0725

CLINICAL SNAPSHOT

Diagnosis of a Rare Form of Leukemia at a Glance Thanks to Pathognomonic Skin Lesions



Violaceous papules on the chest, abdomen, and flank at initial presentation

A 77-year-old man presented for investigation of violaceous papules that had suddenly appeared on his chest, abdomen, and back 6 months earlier. The patient displayed B symptoms, was underweight (BMI 18.2 kg/m^2), and his blood count showed leukocytosis (29/nL), anemia (Hb 11.8 g/dL), and thrombocytopenia (78/nL). Examination of a biopsy sample revealed medium-sized to large blastic, occasionally plasmacytoid infiltrates that were positive for CD4, CD43, and CD56 and weakly positive for CD123. The Ki-67 proliferation index was elevated (80–90%). We diagnosed blastic plasmacytoid dendritic cell neoplasia, a rare form of myeloid neoplasia that arises from precursors of the plasmacytoid dendritic cells and is often first manifested by the occurrence of cutaneous papules. The prognosis is poor, with mean survival of 12–14 months. Staging revealed the presence of enlarged cervical and mediastinal lymph nodes, and examination of a bone biopsy sample showed infiltration by atypical CD123-positive cells. There were no abnormal findings on fluorescence-activated cell sorting analysis. We prescribed off-label chemotherapy with azacitidine and venetoclax, to which the papules were responding at the time of writing.

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Conflict of interest statement: The authors declare that no conflict of interest exists.

Translated from the original German by Christine Rye.

Cite this as: Bertlich I, Enk A, Toberer F: Diagnosis of a rare form of leukemia at a glance thanks to pathognomonic skin lesions.
Dtsch Arztebl Int 2020; 117: 732. DOI: 10.3238/arztebl.2020.0732

Supplementary material to:

Hormonal Gender Reassignment Treatment for Gender Dysphoria

by Gesine Meyer, Ute Boczek, and Jörg Bojunga

Dtsch Arztebl Int 2020; 117: 725–32. DOI: 10.3238/arztebl.2020.0725

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eBOX

Options for preserving fertility

Both feminizing and virilizing hormone therapy have a negative effect on fertility. The extent to which fertility is impaired varies widely between individuals and at what point in the course of treatment these limitations will occur is unpredictable; furthermore, patients may develop irreversible infertility. Thus, prior to the start of GAHT, patients must be informed in detail about the available fertility-preserving options. The discussion should also address the legal limitations existing in Germany and the costs patients have to cover themselves: depending on the type and duration of treatment, these can be far in the five-digit euro range.

For transgender women, there is the option of cryopreservation of sperm, ideally prior to the start of treatment. To achieve pregnancy, insemination or IVF/ICSI treatment (IVF, in vitro fertilization; ICSI, intracytoplasmatic sperm injection) with egg cells of the female partner may be required, depending on the quality and amount of the available cryopreserved material. In Germany, it is legal to provide treatment for legally same-sex lesbian couples desiring to have children; however, not all centers offer this service.

In transsexual men, fertility can be maintained by cryopreservation of egg cells or ovarian tissue. If no gender-affirming surgery with hysterectomy and salpingo-oophorectomy has been performed, a spontaneous pregnancy can be achieved after discontinuation of GAHT. Since egg cell donation is prohibited by law in Germany, only the transsexual man himself can carry out the pregnancy—after having discontinued GAHT.

The costs of cryopreservation and later assisted reproduction are not covered by the statutory health insurance funds and must be borne by the patients themselves. Under German legislation, the transsexual woman whose sperm has fathered a child and the transsexual man who gives birth to a child remain registered as the father and mother, respectively, of the child even after their legal sex status has changed (10, e20).

Questions regarding the article in issue 43/2020:

Hormonal Gender Reassignment Treatment for Gender Dysphoria

cme plus

The submission deadline is 22 October 2021. Only one answer is possible per question.
Please select the answer that is most appropriate

Question 1

In Germany, how many people are estimated to be affected by gender dysphoria?

a) 1000 to 1500
b) 3000 to 6000
c) 5000 to 10 000
d) 15 000 to 25 000
e) 50 000 to 75 000

Question 2

Which of the following is a contraindication for gender-affirming hormone therapy?

a) Disposition to develop allergies/atopy
b) Cerebrovascular and severe thromboembolic pre-existing conditions
c) Overweight (BMI: 25–29.9) or obesity (BMI >30)
d) History of fractures
e) Depressive symptoms

Question 3

Which medication (and route of administration) is the standard treatment used in male-to-female hormone therapy?

a) 17β-estradiol intravenously and cyproterone acetate
b) Oral or transdermal ethinyl estradiol and intravenous 17β-estradiol
c) Oral progesterone and ethinyl estradiol
d) Oral or transdermal 17β-estradiol and cyproterone acetate
e) Progesterone and 17β estradiol intravenously

Question 4

Which medication is the standard treatment used in female-to-male gender-affirming hormone therapy?

a) Transdermal dehydroepiandrosterone (DHEA)
b) Testosterone, transdermal or intramuscular depot formulation
c) Testosterone, oral administration or as a suppository
d) Oral or intramuscular progesterone
e) Oral dehydroepiandrosterone (DHEA)

Question 5

Which effect of feminizing hormone therapy is typically the first to manifest?

a) Decrease in body and facial hair
b) Reduction of muscle mass and strength
c) Reduction of libido and spontaneous erections
d) Fat redistribution
e) Softening of the skin

Question 6

Acne is a common side effect of virilizing hormone therapy. What treatment should be offered to patients suffering from acne?

a) Prescription of oral contraceptives with anti-androgenic effect
b) Topical treatment with anti-androgenic agents
c) Discontinuation of hormone therapy until the acne has cleared
d) Topical treatment with retinoids, benzoyl peroxide or clindamycin
e) Systemic treatment with benzoyl peroxide over a period of four weeks

Question 7

With regard to contraception, which statement applies to patients receiving female-to-male gender-affirming hormone therapy (GAHT)?

a) Testosterone therapy provides sufficient contraception after a period of about three months; therefore, no further measures are required.
b) Progestin-releasing intrauterine devices must not be implanted.
c) With the start of testosterone treatment, a contraceptive effect is guaranteed.
d) In this situation, medications with estrogen as the sole active ingredient can be prescribed.
e) During GAHT, mechanical contraception and oral progestins can be used.

Question 8

With regard to co-medication, what needs to be considered in patients receiving estradiol as part of GAHT?

a) Anticonvulsants and anti-infectives may reduce the effect of estradiol; adjustment of the estradiol dose may be required.
b) The induction or cytochrom-P450 enzymes by various co-medications increases the effect of estradiol.
c) Because of significant drug interactions with estradiol, anticoagulants should ideally not be used as co-medication.
d) The effect of metoprolol and imipramine is reduced by estradiol; therefore, the doses of these substances may need to be increased.
e) Anticoagulants as co-medication with estradiol have an increased effect; a reduction of the anticoagulant dose is indicated.

Question 9

Which of the following risks is significantly increased in patients receiving virilizing hormone therapy?

a) Risk of ovarian cancer
b) Risk of depressive symptoms

c) Risk of cervical cancer
d) Risk of erythrocytosis
e) Risk of meningioma

Question 10

Which of the following risks is increased in patients receiving feminizing hormone therapy compared to age-matched women or men?

a) Risk of aggressive behavior
b) Risk of cerebral ischemia
c) Risk of basal cell carcinoma
d) Risk of prostate cancer
e) Risk of bipolar disorder