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CONSENSUS

SIAMS-ONIG Consensus on hormonal treatment in gender identity disorders*

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BACKGROUND: WHY THE HORMONAL TREATMENT?

Usually, gender identity (GI) and biological sex are physiologically consistent, but this is not the case when individuals have a GI disorder (GID) and thus require hormonal and/or surgical feminization/masculinization to reduce the discrepancy between the sense of self and sexual characteristics.

They (the transgenders) are a heterogeneous population for age of first referral to a specialist, type and amount of adjustment required, and for clinical situations.

The GI is the perception that the subject has of his/her belonging to a gender, regardless of biological sex. Therefore, the diagnosis of GI can only be self-reported, and "cross-sex" hormonal treatment (HT) plays a key role in the process of transition: anatomical and psychological changes, when properly prescribed in the above-mentioned cases can significantly improve the psycho-social quality of life and indirectly confirm the diagnosis. HT itself represents the confirmation of GI to the subject.

Quality of life improvement thanks to HT reduces any psychiatric co-morbidity often associated with GID.

Finally, according to ONIG (Osservatorio Nazionale sull'Identità di Genere) Italian Standards of Care for Sex Reassignment in Gender Identity Disorders (1), HT is a priority, necessary and propedeutic in cases that require sex reassignment surgery (SRS), and is essential in post-surgery.

PURPOSE OF HT IN ADULTS

The aim of HT is to change the secondary sexual characteristics to reduce gender dysphoria and facilitate a gender presentation consistent with the perceived sense of self.

This aim is obtained through:

- elimination or mitigation of secondary sexual characteristics of biological sex through medical castration;
- induction or accentuation of the desired sex characteristics through the administration of cross-sex hormones.

SEX REASSIGNMENT PATH IN ADULTS

Since 1982 an Italian law (legge 14 aprile 1982, n, 164: "Norme in materia di rettificazione di attribuzione di sesso". G.U. 19482, n. 106, pag. 2879) regulates sex reassignment through the authorization to undergo the medical and surgical treatments required and subsequent change of name and sex at the register of births (art. 3 legge 164/82). It authorizes by a single event both hormonal and surgical sex reassignment, but, after a pronouncement of the Turin Court (Tribunale Ordinario di Torino, Sez. VIII Civ., 6 ottobre 1997), in our country HT is prescribed without prior submission to the Court of residence, which is mandatory at the end of the real life experience (RLE) to undergo SRS. Therefore, those persons who only want hormonal reassignment do not undergo the legal path, but both, accordingly to ONIG Standards of Care, must undergo a preliminary medical and psycho-social assessment, prior to HT beginning. HT has to be continued for at least 1 year under endocrinological and psycho-social monitoring (RLE). Once successfully completed this period, the candidate may apply to the Court to claim the authorization for the SRS.

METHODS OF PRESCRIPTION OF HT IN ADULTS

Prior to initiation of the endocrine reassignment therapy, the applicant should be first assessed by a transcompetent mental health professional with special expertise in psycho-sexology, who submit the applicant to a diagnostic assessment for a period of time according to age and living conditions of the subject, in accordance with the ONIG Standards of Care. This assessment aims to analyze the GI and the ability of the subject to perform a positive path and to exclude severe psychiatric co-morbidities. At the end of this period of psychological evaluation, the psychological-psychiatric team will issue a report attesting the applicant's suitability to begin or continue the cross-hormone therapy. This certification is essential to proceed to the endocrine specific treatment.

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*SIAMS: Società Italiana di Andrologia e Medicina della Sessualità (Italian Society of Andrology and Sexual Medicine); ONIG: Osservatorio Nazionale sull'Identità di Genere (National Observatory of Gender Identity).

Key-words: Cross sex treatment, gender identity disorders (GID), real life experience (RLE), sex reassignment.

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The endocrinologist who takes charge of a transgender person has the responsibility to determine eligibility and readiness for the HT or for SRS.
It is absolutely recommended that all professionals ("psi", endocrinologists, surgeons, *etc.*) work in close liaison, scheduling regular meetings to monitor the programs agreed and signed with the patients.

Eligibility criteria

The minimum criteria that each applicant for HT must comply to, whether or not they wish to undergo reassignment surgery, are:
- age >18 years
- ability to give written informed consent
- exclusion of intersex conditions
- preliminary diagnostic evaluation in psychiatric-psychological context for the issuing of the report confirming the diagnosis of GID according to the Diagnostic and Statistical Manual of Mental Disorders (4th ed. Text Revision) (DSM IV TR) (2) and the ability to HT even for those who have already autonomously started RLE
- be informed of the effects and risks.

Readiness criteria

Is the person ready for HT? We must verify:
- the consolidation of GI during the previous psychiatric-psychological evaluation
- mental stability, or improvement of previous psychosocial problems (addiction, sociopathies, neurosis, *etc.*)
- good/improved general health and lifestyles (smoking, diet, hypertension, diabetes, *etc.*)
- the possibility of taking hormones in a responsible manner, including knowledge of what hormones can and cannot do and their risks. Acceptance of the endocrinological prescriptions (drugs, dosages, and lifestyle changes) and compliance to prescribed checks and examinations.

The presence of a GID in Klinefelter Syndrome, polycistic ovary syndrome or congenital adrenal hyperplasia does not contraindicate HT.

IMPACT AND LIMITS OF HT

There is great individual variability in the entity of changes induced by hormone treatment and outcome predictive criteria are scarce. Therefore, the endocrinologist must have a thorough knowledge of the effects of hormonal preparations and present them in detail to the applicants, together with possible negative side-effects and risks to their health. It is of fundamental importance that the applicant has realistic expectations.
Although there are not enough conclusive data in the literature, we agree that the speed and degree of change (final phenotype) in both sexes is dependent both on the type of preparations, their dosage and route of administration, and on the individual sensitivity and age at the time of treatment initiation: the earliest the treatment is initiated, the greater the success. Recently, we are gaining information about the functionality of steroid receptors that determine, ultimately, the effect of hormones on target organ (3, 4).
Treatment duration is very important as well: there is unanimous agreement on the need for at least 2 years of continuous therapy to assess the maximum effect (5).
In cases of poor outcome due to lack of receptor responsiveness, it is incorrect to further increase the dosage in an attempt to force the genetic limit.

Male to female (MtF)

HT has 2 purposes:
a) to block androgens-testicular secretion and minimize systemic effects;
b) to induce a female phenotype.

The feminization occurs gradually over years, and changes include:
- mammary gland growth and development of the nipple, one of the most desired effects. It usually starts after a few months, is gradual and highly variable and is complete in 2 or more years with effect both on acini and on lobules. The entity of the mammary gland development is linked more to perypheral sensitivity, which is genetically determined, than to the dosage and the characteristics of the molecule used
- gradual and partial redistribution of body fat, decreased muscle mass and strength, in 1-6 months
- skin and annexes androgenization: skin thinning and changes in the pattern of hair growth. Facial and body hair become thin and their growth slows; baldness is reduced
- testicular hypo-atrophy with hypo- or aspermia and infertility
- marked changes in sexual function: desire decrease, reduction or disappearance of spontaneous erections, orgasms and ejaculate, in 3-6 months
- mood improvement
- hyperprolactinemia in >60% of cases, sometimes with galattorrhea. Prolactinomas are very rare (6).

Female to male (FtM)

HT has 2 purposes:
a) to reduce the estrogen secretion and their action at the systemic level;
b) to induce a male phenotype.

The masculinization gradually occurs over the years, and changes include:
- mild hypotrophy of the mammary gland
- redistribution of fat mass and increase in muscle mass, strength, and body weight
- increased appetite and mood improvement
- increased facial and body hair growth, and increased baldness
- permanent voice deepening
- irreversible clitoral hypertrophy, amenorrhea, infertility; increased sexual desire and sometimes aggressiveness.

In both biological sexes, cross-sex treatments induce infertility; in some countries, methods able to preserve gametic cells are recommended. In Italy, nowadays, these procedures must be considered useless because after change of personal data (Law 164/1982) the person will not be able to draw back his/her cryosamples.

INITIAL CARE AND ASSESSMENT BEFORE HT

The preliminary evaluation consists of 3 endocrinological sessions over 6 months. The goals are:

- to establish a therapeutic relationship, discuss goals and expectations
- to explain the sex reassignment path and deliver information matherial (www.onig.it)
- to assess the capacity to fully understand and accept the treatment and to provide informed consent
- to assess the general health status through:
  - history collection:
    family history
    physiological history
    general health history (medications)
    sexual health history [sexual orientation, sexual function, HT and/or feminizing/masculinizing interventions; sexually transmitted infections (STI)]
    psychosocial history
  - physical examination
  - prescription and evaluation of general, hormonal and genetic blood tests to exclude or confirm a possible chromosomal aneuploidy
  - evaluation of any contraindications
- to define the opportunity to initiate the required HT considering the individual general health.

The baseline assessment should always take place in parallel with the psychological evaluation, even if the person requests only hormonal reassignment or has already begun hormone therapy and/or has undergone cosmetic surgery. Situations that require special clinical attention are summarized in Table 1.

Diagnostic tests for MtF and FtM

General blood and urine tests

Complete blood cell count (CBC), fasting glucose (glycosylated hemoglobin in the case of diabetes), creatinine, lipid profile (total cholesterol, HDL cholesterol, triglycerides), liver enzymes, bilirubin, Na+, K+ (in case of hypertension only), urine analysis.
Hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb), hepatitis C virus (HCV), human immunodeficiency virus (HIV), treponema pallidum hemoagglutination (TPHA).

In MtF only:
- prostate specific antigen (if age >45 years)
- in view of estrogen treatment, parameters currently approved for the assessment of congenital thrombophilic risk are accordingly with recent Consensus (7) listed in Table 2.

Hormonal examinations

FSH, LH, total testosterone, 17βestradiol (17βE2), SHBG, PRL, TSH.
In FtM also: 17α-hydroxyprogesterone (17αOHP) within the 4th day from the beginning of menstrual flow for evaluation of possible non-classical adrenal hyperplasia.

Genetic evaluations

Karyotype, in case of a surgical reassignment, or according to clinical indication.

Radiological and ultrasound examinations

MtF: testicular ultrasound (US);
FtM: lower abdomen US for ovarian morphology.

Table 1 - *Special clinical attention to:*

	MtF	FtM
Risk/history of vascular disease (venous thrombosis, atherosclerosis)	X	X
Metabolic syndrome	X	X
Cholelithiasis and liver disease	X	
Migraine	X	
Smoke/pneumopathies	X	X
Hormone-related cancers	X	X

MtF: male to female; FtM: female to male.

Table 2 - *Assessment of congenital trombophilic risk.*

Congenital factors
Factor V mutations [G1691A – H1299 (R2)]
Proteins C and S
Prothrombin G 20210A mutation
AT III

AT III: antithrombin III.

Other evaluations according to clinical signs.

ABSOLUTE AND RELATIVE CONTRAINDICATIONS

It is unwise to start HT in subjects not in good general health. The endocrinologist must first assess and compensate all pathological conditions potentially interfering with HT and recommend correct lifestyles (nutrition, smoking, drug abuse).
The absolute contraindications include:
- serious diseases [non-compensated arterial hypertension, dilated cardiomyopathies, recent or actual thromboembolic events, polycythemia vera, serious congenital or acquired liver and biliary diseases, advanced chronic kidney disease (CKD), severe otosclerosis, porphyria]
- endocrine-metabolic diseases (acute thyrotoxicosis, non-compensated Cushing syndrome, prolactinomas, acromegaly, non-compensated diabetes mellitus, severe dyslipidemia, obesity with body mass index >40 kg/m^2, obstructive sleep apnea syndrome)
- active oncological affections and treated meningiomas

The relative contraindications include:
- internal diseases (hypertension, valvular heart disease, congenital or acquired thrombophilic conditions, liver disease, CKD)
- endocrine-metabolic diseases (diabetes mellitus, dyslipidemia)
- previous cancer
- smoking
- severe sleep/wake cycle alterations.

THERAPY PRESCRIPTION

In Italy, drugs can be prescribed only for registered indications. All preparations used for HT in GID subjects are prescribed off such indications ("off-label") on the basis of established scientific literature and after obtaining the patient's informed consent. These drugs, because of the

prescribed off-label record, are entirely at the patient's charge and it is important that prescribers have checked the appropriateness according to the prescription regulations actually active on the matter.
Two regions (Tuscany, Piedmont) have provided for the direct delivery of drugs for subjects treated in ONIG Public Health Service Gender Teams during the reassignment period.

RECOMMENDED REGIMENS AND DURATION OF TREATMENT

Initially, regimens used by Italian Endocrinologists were based on published specific literature and from the experience of professionals belonging to World Professional Association for Transgender Health (WPATH) [formerly Harry Benjamin International Gender Dysphoria Association (HBIGDA)] and on personal clinical experience (8-10).
Currently in GID HT evidence-based criteria are at low level because adequate randomized controlled studies are scarce. Furthermore, the protocols should not be considered as rigid guidelines, but must be tailored to the specific needs of each patient. It is essential to consider the subject's preferences in order to get a good therapeutic collaboration. In fact, there is great variability of applications both in terms of targets and of time required to achieve them.
Therefore, the HT must be individualized on the basis of:
- goals of the patient
- risk/benefit ratio
- other medical conditions
- social and economic aspects

The HT must be maintained continuously for at least 1 yr before SRS can be requested (5, 11-16).

INDUCTION OF CHARACTERISTICS OF THE DESIRED SEX

MtF

Feminization is achieved by direct or indirect antagonism of androgen effects and induction of female physical characteristics.
We recommend a combination of estrogen and androgen antagonists.

Estrogens

Estrogen is the principal agent used to induce and maintain the female characteristics, and act primarily through a direct receptor stimulation in target tissues. Doses required to induce a significant feminization of a biological male are on average higher than those used for replacement therapy in genetic women.
Estrogen preparations are the milestone of treatment because they can determine the evolution of phenotype in a female: fat redistribution, increased breast volume, refining of body proportions, *etc.* Along with anti-androgens they concur in determining pharmacological castration thanks to their anti-gonadotrophic effect.
There is no evidence that a specific molecule induces feminization more than another, or that the effects are different depending on the chosen route of administration although there are reports that the parenteral preparations are slightly faster than the oral/transdermal estrogens, probably because of their active catabolites.
They can be administered:
a) orally
   1) estradiol valerate: 2-6 mg/day
   2) micronized estradiol: 2-6 mg/day
b) transdermally (TD): especially indicated for patients >40 yr old, or with relative contraindications:
   1) patch: 100-400 μg/week
   2) gel: 2 or more doses per day (2.5 g sachet =1.5 mg E2). They can also be used in the mammary region at the same dosage in attempt to increase the effect in this target.
c) intramuscularly (im): im formulations are very welcomed by patients because they are believed to be more effective. However, they are not the first indication due to fluctuations in plasma levels. Anyway, they could be very useful in patients with thrombophilic mutations. Nowadays they have disappeared from the Italian market.

Androgen antagonists

They complete and enhance the effects of estrogens on feminization. They are extremely useful to antagonize the action of androgens on body and scalp hair distribution, sebaceous secretion, erectile activity. Moreover, some antagonists increase the breast growth and block testosterone production. Some anti-androgens with combined central and peripheral action have also anti-gonadotrophic effects.

Central and peripheral anti-androgens

Most commonly used are:
1) cyproterone acetate (CPA): it is the most widely used in Europe.
   Oral: 25-200 mg/day. It has also progestagen effects which are very useful to stimulate the mammary gland;
2) spironolactone (SP): unanimously reported as a very effective anti-androgen, it has a anti-rententive effect. It has direct effects in reducing the male hair growth pattern and may induce irreversible gynecomastia due to its anti-androgen, progestagen, and estrogen-like effect.
   Oral: 25-300 mg/day. It requires periodic Na+, K+ monitoring.

Peripheral anti-androgens

They act at the receptor site and enhance the desired effects on skin and hair.
1) flutamide: pure non-steroid receptor inhibitor; the risk of hepatotoxicity at usual doses (125-250 mg) is almost negligible, but it is good practice to check liver enzymes every 2-3 months. It is ideal for the clinical condition of excessive seborrhea with related complications. It is much more expensive than CPA and therefore is usually not used routinely in GID.
2) azasteroids (5α reductase inhibitors). In case of persistent/disturbing skin androgenization, baldness or seborrhoic acne. It may be associated with central antiandrogens.
   Finasteride: oral: 2.5-5 mg/day.
   Dutasteride: oral: 0.25-0.5 mg/day.

Progestins

We do not recommend routine use in feminization therapy because of potential adverse effects (depression, weight gain, changes in lipid profile), and the breast cancer risk; we believe the use of CPA/SP is best appropriate to promote mammary gland development.
They can rarely be indicated when estrogen is not tolerated, or is absolutely contraindicated.

GnRH analogues

They downregulate the pituitary and block the hypothalamus-pituitary-testicular axis. They are used by some professionals who treat children or adolescents with MtF GID (17) to block the pubertal development, waiting for clarification of GI. It is reasonable to plan the introduction of GnRH analogues (GnRHA) in the treatment of adequately selected adolescents with dosages able to inhibit Gn accordingly to scientific literature.
They may be exceptionally prescribed "off-label" in adults with GID in cases of serious side-effects with antiandrogens, or absolute contraindications to estrogen (18). Their routine use in adults is not justified in terms of cost-benefit analysis.

FtM

The masculinization is achieved antagonizing estrogen effects and inducing male physical characteristics.
It requires testosterone administration.

Testosterone

Testosterone is the agent used to induce and maintain male characteristics. It acts by direct stimulation of receptors in target tissues. The doses necessary to virilize a biological female are on average higher than those used for replacement therapy in genetic males.
It determines a pharmacological castration thanks to his anti-gonadotrophic action. The cessation of menses is the first effect, usually occurring within 1-2 months. Endometrial subatrophy follows even though sometimes a moderate endometrial stimulation persists due to the presence of estrogen derivatives from androgenic precursor aromatization.
It is the milestone of treatment because it can determine the evolution of male phenotype: within 1-3 months, it induces the redistribution of adipose tissue, increases muscle mass and strength, and induces voice deepining. Beard growth, hair distribution, and characteristic changes (thickness of facial and body hair, baldness), increased sebaceous skin secretion, clitoral hypertrophy (with a maximal length of up to 6 cm when stretched) are complete after 1 to 2 years.
Testosterone can be administered:

a) orally: only in rare cases (fear for injections, intolerance to TD, *etc.*).
   Testosterone undecanoate: 160-240 mg. It is safer than the old 17-alkylated preparations (totally obsolete because hepatotoxic), but it is less effective than im or TD testosterone and much more expensive than the traditional testosterone esters.
b) im (esterified testosterone): this is now the preferred route of administration.
   1) testosterone undecanoate: 1000 mg/6-12 weeks. It is very popular for the convenience of administration and tolerability (19-20)
   2) testosterone enanthate: 100-250 mg/1-2 weeks
   3) mixtures of esters: 1 ampoule every 10-15 days.
c) TD: gel: 50-100 mg/day. It is often poorly effective to induce rapid and complete amenorrhea and not always locally well tolerated. Local application on the face may be useful to directly stimulate beard growth.

Progestins

They may be indicated in those rare patients who take testosterone for >3 years and are not expected to undergo hysterectomy, to avoid possible endometrial hyperplasia.

GnRH analogues

They downregulate the pituitary and block the hypothalamus-pituitary-ovaries axis. They are used by some professionals who treat children or adolescents with FtM GID (17) to block the pubertal development, waiting for clarification of GI. It is reasonable to plan the introduction of GnRHA in the treatment of adequately selected adolescents with dosages able to inhibit Gn accordingly to scientific literature.
They may be exceptionally prescribed "off-label" in adults with GID in cases of serious side-effects or absolute contraindications to classic androgenic treatment (18).
Their routine use in adults is not justified in terms of cost-benefit analysis.

MAINTENANCE OF DESIRED SEX CHARACTERISTICS BEFORE GONADAL REMOVAL

MtF

Feminization, achieved antagonizing androgen effects and inducing female physical characteristics, is usually maintained through a combination of estrogen and antiandrogens as previously described. Sometimes a small dose reduction (30%) is possible.

FtM

Masculinization, obtained antagonizing estrogen effects and inducing male physical characteristics, is maintained through the administration of testosterone as previously described. When traditional esters are used, a slight dose reduction may be possible before hystero-adnexectomy.

Table 3 - *Evaluations to be performed in real life experience.*

	MtF	FtM
Blood pressure	X	X
Weight	X	X
Assessment of cardiovascular risk		X
Thromboembolic risk assessment	X	X
Symptoms (galattorrhea) referable to hyperPRL	X	
Cholelithiasis	X	
Cancer risk	X	X
Deterrence by cigarette smoking	X	X

MONITORING RECOMMANDATIONS OF HT IN THE RLE

The main aspects to be monitored from the internistic and endocrinological point of view are: the effectiveness of hormonal reassignment therapy (evaluation of the degree of feminization/masculinization reached), and the possible appearance of adverse reactions and/or complications. The aspects to be carefully evaluated, are given in Table 3.

In case of sexual activity at risk for STI (mercenaries and not), it is desirable to support sex and health education to prevent STI.

During the 1st year of therapy, when changes are greater, patients should be examined every 3 months to update clinical history, perform physical examination and laboratory tests. It is mandatory that, at this stage of the RLE, the mental health professional continues to follow the patient in his/her adaptations to the deep physical and psychosocial changes induced by therapy, in close collaboration with the endocrinologist.

After the 1st year, visits are recommended every 4-6 months for the 2nd year and then once a year for those who choose only hormonal reassignment, with particular attention to the genital organs not removed.

LABORATORY AND INSTRUMENTAL TESTS

MtF

General blood tests

- Three months after the initiation of HT: fasting glucose (glycosylated hemoglobin in the case of diabetes), creatinine, lipid profile (total cholesterol, HDL cholesterol, triglycerides), liver enzymes, bilirubin.
- Every 6 months: CBC, and Na, K if taking SP.
- Before SRS: aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ-glutamyl-transferase (γGT), HBsAg, HBsAb, HCV, HIV, TPHA.

Hormonal evaluations

- Three months after the initiation of HT: LH, testosterone, 17βE2, PRL. Testosterone should stabilize at values <0.5 ng/ml
- Every 3-6 months: 17βE2, PRL. Testosterone if not yet in women range.

Radiological and US examinations

- After 1 year of HT: breast US/mammography.
- Before SRS: lower abdomen (possibly transrectal) US.

FtM

General blood tests

- Three months after the initiation of HT: CBC.
- Every 6 months: CBC, fasting glucose (glycosylated hemoglobin in the case of diabetes), creatinine, lipid profile (total cholesterol, HDL cholesterol, triglycerides).
- Before SRS: AST, ALT, γGT, HBsAg, HBsAb, HCV, HIV, TPHA.

Hormonal evaluations

- Three months after the initiation of HT: total testosterone (SHBG), 17βE2.
- Every 3-6 months: total testosterone (SHBG); 17βE2 if higher than the upper range for men.

Radiological and US examinations

- Lower abdomen ultrasound after 2-3 years of testosterone therapy waiting hystero-adnexectomy or in absence of the event for evaluation of endometrial thickness.
- Cervical PAP smear in case of prolonged androgen treatment

Electrocardiogram (ECG)

Within 1 year of HT, expecially in case of smoking and/or hypertension.

ADVERSE EFFECTS AND COMPLICATIONS

Usually, with the above-mentioned regimens administered by trans-trained endocrinologists, serious adverse effects and complications are uncommon (21) and oncological risk very low (22).

MtF

- Liver complications: essentially none by using the proposed schemes.
- Thromboembolic complications: rare if following the proposed schemes.
- Weight gain: often present and sometimes sought; usually mild, is linked to increase and redistribution of adipose tissue, as well as to water retention.
- Panniculitis and lymphedema of the lower limbs: not frequently described, requiring temporary treatment suspension.
- Mood alterations and reduction of sexual desire: possible during CPA treatment.
- Increase in PRL: almost always present, only partially dose-dependent; usually requires no specific therapy or HT dosage reduction (up to values ≤100 ng/ml) and contributes to the development of the mammary gland. In the presence of PRL values above this limit pituitary magnetic resonance imaging is recommended. Cases of prolactinomas are rare.

FtM

- Liver complications: no case with parenteral or transdermal testosterone.
- Cardiovascular complications: rare when using the proposed schemes.
- Weight gain: always present, it is usually welcome and attributable mainly to increased muscle mass and partly to that of adipose tissue.
- Facial and/or back and shoulders acne: frequent, mild to moderate.
- Androgenic defluvium: more or less marked according to genetic and age.
- HDL decrease and LDL increase: constant and requires monitoring in heavy-smoking overweight or obese subjects especially with family history of cardiovascular disease.
- Improvement in mood and increase in sexual desire: very frequent.
- Increased aggressiveness: rare.

HT EFFECT REVERSIBILITY

Changes induced by HT are only partially reversible after therapy discontinuation, not predictable with certainty, according to the duration of hormone administration and the specific response of single target organs.

MtF

The development of the mammary gland and nipple-areola complex is irreversible. It is not known whether fertility is fully recoverable.

FtM

Modifications in voice, clitoris, beard growth, as well as the generalized hirsutism and baldness are not reversible. It is not known whether fertility is fully recoverable.

TREATMENT DISCONTINUATION BEFORE SRS

MtF

HT must be temporarily interrupted not only before surgical reassignment, but also before any major surgery to avoid thrombo-embolic complications.

- Estrogens:
  oral/im: 2 to 4 weeks before surgery
  TD: 1 week before.
- Anti-androgens:
  Systemic:
    CPA: 1 month before
    SP: unnecessary suspension.
  Peripheral: not necessary suspension.

FtM

Testosterone: does not require suspension.

HT RESUMPTION FOLLOWING SRS

In MtF, HT can be resumed as soon as the subject has a physical recovery that allows self-sufficiency and walking, preferably using TD E2 at full replacement dose for at least the 1st month following the SRS.

CHRONIC TREATMENT OF SURGICAL HYPOGONADISM AND FOLLOW-UP

After the SRS, HT has 2 purposes:
a) to treat hyatrogenic hypogonadism;
b) to maintain the acquired phenotype.
Primary hyatrogenic hypogonadism following orchiectomy in MtF and ovariectomy in FtM requires life-long treatment with sex hormones, except in case of occurrence of medical contraindications.
Dosages, which are on average only slightly lower than presurgery ones, must guarantee physiological hormone concentrations according to age and a general well being.

MtF

Hormone replacement is guaranteed by the administration of estrogen which, also, maintains the acquired phenotype; androgen antagonists are prescribed when peripheral androgenization symptoms persist, and to prevent baldness.

Estrogens

Required doses are on average higher than those used for replacement therapy in genetic women up to 50-60 yr, and then gradually reduced in dosage.
They can be administered:
a) orally
  1) estradiol valerate : 2-4 mg/day
  2) micronized estradiol: 2-4 mg/day
b) TD
  1) patches: 100-200 mg/week
  2) gel: 1-2 sachets/day (1.5-3 mg E2)

Androgen antagonists
Central and peripheral antiandrogens

Most commonly used are:
1) CPA: 25-100 mg/day orally.
2) SP: 25-200 mg/day orally.

Peripheral antiandrogens

1) Flutamide: 125-250 mg/day
2) Azasteroids
  Finasteride: 2.5-5 mg/day orally
  Dutasteride: 0.25-0.5 mg/day orally

Progestins

There is no indication for their administration.

FtM

Hormone replacement is guaranteed by the administration of testosterone which also maintains the acquired phenotype.

Testosterone

Required doses are those used for replacement therapy in genetic males. It can be given:
a) im (testosterone esters)
  1) Testosterone undecanoate: 1000 mg/12 weeks on average.
  2) Testosterone enanthate: 100 mg/week or 250 mg/3-4 weeks
  3) Blends of esters: 1 ampoule every 15-20 days.
b) TD gel: 50-100 mg/day.

MONITORING RECOMMANDATIONS

After SRS, it is essential that treated subjects undergo endocrinological visits at least annually all life long as indicated in hypogonadal subjects.
Dual-energy X-ray absorptiometry (DEXA) densitometry (to the spine or femur according to age) in both sexes 2 years after SRS then every 4-5 yr depending on the clinical, hormonal, and bone mineral status.
In transwomen:
- mammographic monitoring is recommended until at least 65 years of age and even afterwards if breast augmentation mammoplasty was performed to monitor possible late implant complications;
- it is not necessary to follow up the prostate in the absence of suspicious symptoms.

In transmen:
- mammographic evaluation only if not removable gland residues are present.

FOLLOW-UP OF SUBJECTS ON HT WHO DO NOT REQUIRE SRS

In general, all criteria mentioned in paragraph "monitoring of HT during the RLE" apply.
After the 1st HT year, patients should be examined annually to update clinical history (check for way of life and good general health), perform physical examination and laboratory tests. Different schedules may apply if required by specific clinical situations. Particular attention should be paid to the non-removed genital organs. When complex psycho-social situations occur, it is appropriate to suggest that a mental health professional continue to follow the patient up in collaboration with the endocrinologist.

MtF

HT should be maintained as previously described for the "maintenance before SSR"; it is possible to reduce the dosage of the CPA to the minimum effective dose to maintain suppressed testosterone.

General blood tests

Annually: CBC, blood glucose (glycosylated hemoglobin in the case of diabetes), creatinine, lipid profile (total cholesterol, HDL cholesterol, triglycerides), liver enzymes, bilirubin, Na and K when taking SP.

Hormonal evaluations

Annually: LH, testosterone, 17βE2, PRL. Testosterone should remain <0.5 ng/ml.

Radiological and US examinations

- Breast ultrasound/mammography: every 2 years except for specific situations.
- DEXA densitometry (spine or the femur according to age) 4-5 years after HT initiation, then depending on the clinical, hormonal, and bone mineral status.

FtM

It is extremely rare in Italy that patients request to undergo life-long testosterone treatment without performing hystero-adnexectomy.
HT should be maintained as previously described for the "maintenance before SRS". A possible continuous treatment with low doses of progesterone – e.g. dihydrogesterone 2.5 mg/day – may be useful to prevent hyperplasia caused by high levels of estrogen from peripheral conversion of testosterone.

General blood tests

Annually: CBC (glycosylated hemoglobin in the case of diabetes), creatinine, lipid profile (total cholesterol, HDL cholesterol, triglycerides).

Hormonal evaluations

Annually: total testosterone, SHBG, 17βE2.

Radiological and US examinations

- PAP test and lower abdominal ultrasound at least every 2-3 years for evaluation of endometrial thickness
- DEXA densitometry (spine or the femur according to age) 4-5 years after HT initiation, then depending on the clinical, hormonal, and bone mineral status.

ECG

Annually expecially in case of smoking and/or hypertension.

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