GUIDANCE NOTES FOR TRANSGENDER COMMUNITY ON HORMONE REPLACEMENTTHERAPY

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Disclaimer

This document is developed as a part of Transgender health program in Pakistan. Theactivity was conducted by consortium of four transgender led organizations namely, The Khawaja Sira Society (KSS), Gender Interactive Alliance (GIA), Wajood Society .

Acronyms and Abbreviations

AIDS	Acquired Immunodeficiency Syndrome
FtM	Female to male transition
GnRH	Gonadotrophin releasing hormone
HIV	Human Immunodeficiency Virus
HRT	Hormone Replacement Therapy
MtF	Male to female transition
MHP	Mental Health Professional
OCP	Oral contraceptive pills or 'birth-control pills'
PLHIV	People Living with HIV/ AIDS
TG	Transgender
UHC	Universal Health Coverage
WHO	World Health Organization
WPATH	World Professional Association for Transgender Health

Glossary of Medical Terms Used

Androgen Hormones	Masculinizing hormones in male body
Coronary artery disease	Disorder of blood supply, to heart muscle, clinically manifests as angina or heart attack
Cerebrovascular disease	Disorder of blood supply, to brain tissues, clinically manifests as stroke or paralysis of body parts controlled by the part of brain damaged
Estrogen	Feminizing hormones predominantly in females
Gender	The differences between women and men within the same household and within and between cultures that are socially and culturally constructed and change over time.
Gender Expression	Refers to a person's presentation of their gender identity, and/or the one that is perceived by other (Defined in Transgender Act 2018)
Gender Identity	A person's innermost and individual sense of self as male, female or a blend of both or neither; that may or may not correspond to the sex assigned at birth
Gender non-conforming	a person whose gender identity differs from that of gender binary social norms of society or simply 'the third gender'
Gender incongruence	the mismatch an individual feels because of the discrepancy experienced between their gender identity and the gender they were assigned at birth
Gonads	Primary reproductive organs, ovary in females and testis in males
Genitalia	Sexual or reproductive organs, can be classified as

internal genitalia e.g. uterus, ovary in females and

	external genitalia i.e. clitoris and labia in females and penis in males
Hormone	chemical substance produced by endocrine glands and released in bloodstream which produce physiological effects in body
Hormone Replacement Therapy	Replacement of hormone for either, therapeutic purposes in intersex individuals or as means of gender reaffirmation in transgender individuals
Hypertriglyceridemia	Abnormal increase of fats in blood
Hypertension	Increase blood pressure (more than 140/90 mmHg)
Phalloplasty	Surgical construction of penis
Progestin	Feminizing hormone necessary for development of breast and maintenance of pregnancy
Ova or ovum	Egg, female gamete
Orchidectomy	Excision of testis
Penectomy	Excision of penis
Sperm	Male counterpart of egg
Sex	This refers to attributes that characterize biological maleness or femaleness. The best known attributes include the sex-determining genes, the sex chromosomes, the gonads, sex hormones, internal and external genitalia, and secondary sex characteristics
Sexual Orientation	A person's sexual identity in relation to the gender to which he or she is attracted
Sexual Characteristics	Physical attributes by which we identify sex such as man or woman

Macroprolactinoma	Prolactin hormone secreting tumor which causes milk formation, decreased libido and vision loss, even in males
Transgender	A person whose gender identity differs from sex assigned at birth
Transgender man	(also: trans man, female-to-male, transgender male): This refers to individuals assigned female at birth but who identify and live as men.
Transgender woman	(also: trans woman, male-to female, transgender female): This refers to individuals assigned male at birth but who identify and live as women.
Transition	This refers to the process during which transgender persons change their physical, social, and/or legal characteristics consistent with the affirmed gender identity
Transsexual	This is an older term that originated in the medical and psychological communities to refer to individuals who have permanently transitioned through medical interventions or desired to do so
Thromboembolic disease	Thrombus is a blood clot in blood vessels, where embolus is the thrombi lodging distant from its origin. It can cut off blood supply and may lead to death of tissues supplied by the vessel e.g. in brain can cause stroke which can manifest as paralysis
Vaginoplasty	Surgical construction of vagina

Glossary of Other Terms used in document

Dera	Dera is a house in hijra sub culture where hijras live

together

Eunuch	Eunuch is a male by birth person who undergoes genital excision or castration
Guru	Guru is a spiritual leader/ elder in Hijra culture, who gives guidance and identity to its apprentice. Its equivalent to 'patriarch' in Hijra Culture
Harassment	Sexual, physical, mental and psychological harassment which means aggressive pressure or intimidation intended to coerce, unwelcome, sexual advance, request for sexual favors or other verbal or written communication or physical conduct if a sexual nature or sexually demeaning attitudes, causing interference with living, mobility or work performance or creatingan intimidating, hostile or offensive work or living environment including the attempt to punish the complainant for refusal to comply with such requestsor to bring forth the complainant (defined Transgender Act 2018)
Hijra	Word used in Indian Sub-continent for person born male at birth who identify as third gender or woman
Sex worker	someone who exchanges sex for favors in material or in kind

Intended users

The document is intended to be used for non-profit organizations, activists, transgender community, healthcare providers and policy-makers for guiding the process of transition. The aims at providing adequate information to transgender community so they can make informed choices in best interest of themselves regarding the transition process specifically about Hormone Replacement Therapy. The document strongly discourages self-medication of hormones and other substances for the purpose of transition. It should be noted that clinical guidelines change from time to time. Hence, practitioners must concern recent medical literature before prescribing any therapy or conducting surgery. However, the core competencies of practitioners and generic guidelines of process of transition are given in the document.

Need of the document

The Parliament of Pakistan promulgated the Transgender Person(s) Protection of Rights Act, in 2018. The Act enfranchises fundamental human rights including right to identity to the transgender community residing in Pakistan. Under the Act *ibid*, Chapter V Sec 12 (c) *the government shall ensure to transgender persons access to all necessary medical and psychological gender corrective treatment.*

The transgender led organizations in country are cognizant of medical and psychological needs of community and hence, undertaken the task to produce guidance notes for community as well as medical practitioners on these treatments in best interest of community.

Most of the transgender people require hormone replacement therapy however, due to non-availability of medical care, self-medicate themselves with hormone combinations available. They are also not aware that hormone therapy takes time to show effects on body, hence they increase dose themselves. Many a times the dose range is above safety profile and these individuals then face many side effects including strokes, heart attack and mood disorders.

The purpose of this document is to serve guidance to those involved in sexual healthcare of transgender community. The document does not propose any new guidelines, rather simplifies the guidelines already available. Two prime sources consulted for the development of this document are The Endocrine Society Clinical Practice Guidelines (2017) and Standard of Care Guidelines (2012) by The World Professional Association of Transgender Health.

For the convenience of non-medical readers a glossary of medical terms is given separately which can be consulted as one goes through main text.

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1. Normal Physiology of Sexual Development

Human beings are born because of reproductive process that involves fertilization of an ovum (from females) and sperm (from males). Females and males have 46 chromosomes, arranged in 23 pairs, which determine the genetics of a human. Forty-four of these chromosomes or 22 pairs are alike, however the 23rd chromosome set is different in males and females and thus determine sex of the individual. This 23rd pair of chromosome is XX in females and XY in males. The genetic contribution of an individual is 50% from mother and 50% from father. Hence, the eggs of a mother carry X chromosome. However, in males half of the sperms have X chromosome while half have Y. The fusion of this Y chromosome carrying sperm with egg that leads to birth of male child. While the fusion of X sperm leads to female child (XX). This is shown in schematic diagram below.

Figure 1. Schematic diagram showing the chromosomal pattern in eggs (left) and sperms (right).

During fetal life i.e. in womb of the mother, these chromosomes lead to the formation of primitive or earliest form of gonads. It is these gonads, which perform two primary functions in the body:

i. Formation of sperms and ova i.e. it contributes to fertility but only after puberty

ii. Producing feminizing or masculinizing hormones, called estrogens and androgens respectively (Figure 2). In both females and males, both estrogen and androgens are present but the levels of estrogen are more in females and androgens in males.

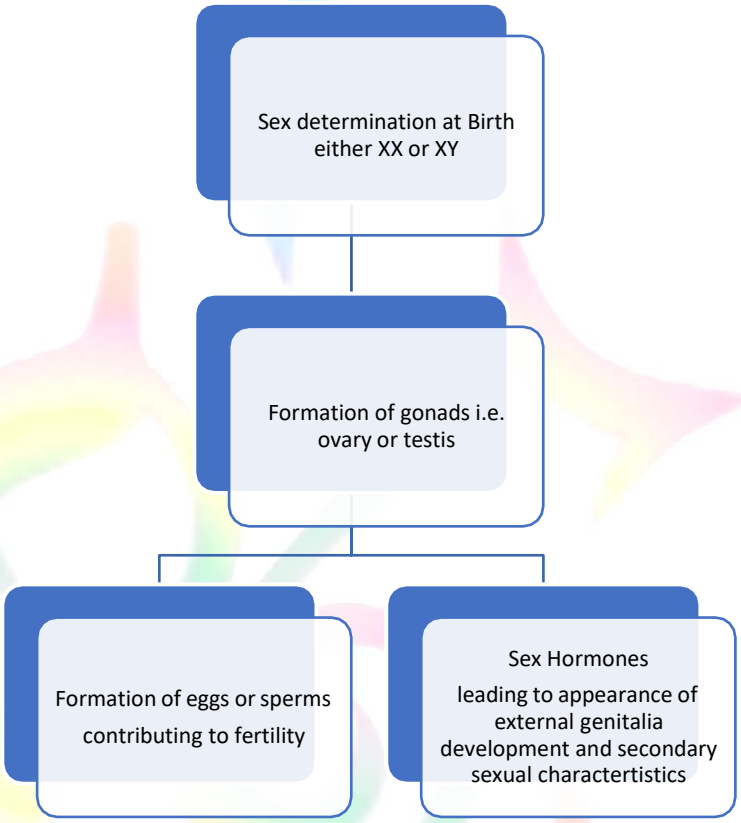

Figure 2. Schematic diagram showing the sexual development in humans and functions of gonads.

These hormones then influence the development of external genitalia (primary sexual characteristic) as well as set of changes in non-reproductive parts of the body, called secondary sexual characteristics. The gonads i.e. the testis in male and ovary in female produce these hormones since fetal life. However, the secondary sexual characteristics are prominent in puberty. There are changes in breast and external genitalia of both male and female during puberty, which are classified according to Tanner Staging as shown in the image below. Table 1 lists down secondary sexual characteristics in male and female.

Sr. No.	Males		Females	
	Secondary sexual characteristics	Age in years	Secondary sexual characteristics	Age in years
1.	Growth of testis and scrotum	10-13	Growth of breasts	7-13
2.	Growth of pubic hair	10-15	Growth of pubic hair	7-14
3.	Body growth	10-16	Body growth	9-14
4.	Growth of penis	11-14	First menses	10-18
5.	Change in voice	11-14	Underarm hair	9-16
6.	Facial, underarm hair	12-17		
7.	Oily skin and acne	12-17	Oily skin and acne	9-16

Table 1. List of Secondary Sexual Characteristics in males and females and their respective age of appearance (years).

2. Sex, gender, transgender and intersex

Sex refers to attributes that characterize biological maleness or femaleness. The best known attributes include the sex-determining genes, the sex chromosomes, the H-Y antigen, the gonads, sex hormones, internal and external genitalia, and secondary sex characteristics (Hembree, 2017). In contrast, gender refers to one's internal, deeply held sense of gender. It is determined by the differences between women and men within the same household and within and between cultures that are culturally and socially constructed. These may change over time. It is not necessary that one has experienced gender and thus its expression is same as the biologically assigned sex at birth. It can different and sometimes referred as gender incongruence. It may led to significant psychological distress. This distress, previously called, Gender Identity Disorder in Diagnostic and Statistical Manual DSM-IV and International Classification of Diseases ICD-10. However, it is realized that it is not a disorder of gender identity but rather a distress due to incongruence, hence, the recent versions of DSM and ICD label Gender identity disorder as Gender dysphoria. It should also be noticed that not all those who experience gender incongruence are gender dysphoric. For that experience, gender incongruence distress stems from socially unacceptability, stigma, harassment, discrimination at school, workplace or home etc. It may lead to significant impairment to attain ones best educational and professional goals according to their potential. Gender dysphoria is however, different and one's stress stems from what many people describe as 'trapped in wrong body'. Detailed criteria of Gender Dysphoria from DSM-V is given in Appendix 1.

The gender experts do not view gender as a binary construct (Tharp, 2016). In fact, it is seen as a spectrum with men and women at two extremes and a continuous progress between the two points. Hence, ones perceived gender can lie on any point between the two extreme points and may even change its position over time, termed as gender fluid (Figure

3).

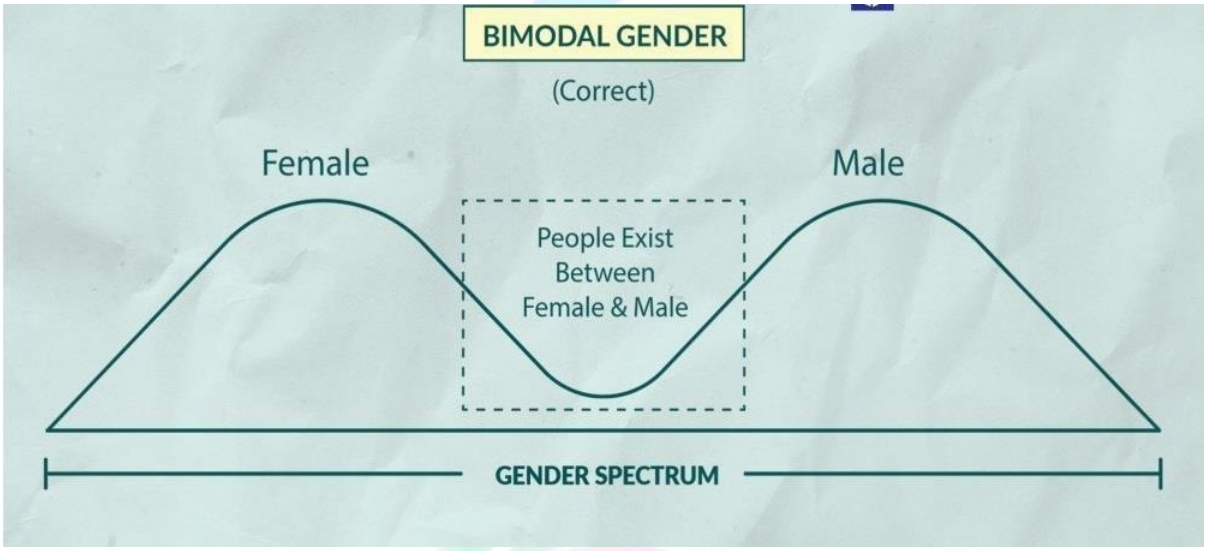

Figure 3. The Gender Spectrum.

Transgender are one of many categories of those falling under category of gender incongruence. These individuals wish to transition socially and / or physically according to their perceived gender. Other experiencing gender incongruence may not wish to transition and may have different sexual orientation such as gay, lesbian, bisexual etc.

In contrast, to transgender people, intersex are people who have physical sexual attributes in between men and women. Intersex, are sometimes called abnormality of sexual development. Such individuals need hormonal, psychological and surgical treatment much similar to transgendered people while managing medical diagnosis in alignment with persons perceived gender.

3. Transition process of Transgender community

As mentioned above, transgender are people who face gender incongruence so strongly that they wish to align ones sex according to perceived gender. The process is known as transition. In addition, a transgender person may wish to change their legal status consistent with their perceived gender.

a. Steps of transition

Transition can be divided into two main steps:

i. Social transition
ii. Physical transition

Social transition involves activities and maintaining appearance in alignment with social gender roles. This includes laser therapy for hair removal, gender appropriate dressing, make over or speech therapy etc. Though all of these are reversible changes, but the stigma associated with social transition requires a careful decision guided by peers, psychologists and parents. Transgender organizations may provide support to those opting this early stepsof transition by individual or group support whether in person or online.

Physical transition from male to female body (MtF) or female to male body (FtM) requires hormone therapy and sex reaffirming surgery. Since, a male or female body has both masculinizing and feminizing hormones, blocking one estrogen or androgen and facilitating the action estrogen or androgen will help in physiological changes related to transition. A detail timeline and changes produced are given in Appendix 4 and 5. Some of these changes such as skin, hair, and libido related and fat redistribution are reversible while other such as breast development, clitoral enlargement etc. are irreversible. The timelines should be displayed in transgender organizations in local language and anyone in process of transition must be fully aware of that changes require some time. This is very important given the fact that many transgender persons may over dose prescribed medicines or lose patience during the process. HRT does not substantially increase risk of HIV, furthermore, drug interactions with antiretroviral medicines are possible and needed to be guided by specialized care. HRT and ART medicines such as tenofovir increase risk of liver damage especially in those suffering from liver disorder such as hepatitis; hence, screening is recommended as perWHO or

country guidelines.

The other step of transition in surgical interventions. This include orchidectomy, penectomy, phalloplasty and vaginoplasty. Core competencies of a provider and criteria are highlighted in section above. Transmen may opt 'top' surgery, which is removal of breasts, before any surgical genital reconstruction/ excision. All these surgical procedures are irreversible. However, if standard of care is followed regret after these procedures is rare. Infect, there is documented improvement in mental wellbeing of transgender persons after these procedures.

b. Who can guide transition process

There are two steps in transition process:

a. Ascertaining capacity of the individual to consent, alongside detailed mental health examination to evaluate psychiatric morbidity
b. Prescription of hormone replacement therapy or performing sex reaffirmingsurgeries

In Pakistan, we recommend a mental health professional to evaluated gender dysphoria, capacity to consent and evaluate psychiatric morbidity. This is because general medical practitioners are not trained in detailed psychiatric evaluation neither the psychiatric curriculum is standardized at undergraduate or post-graduate level. Hence, only a licensed psychiatrist or clinical psychologist should only be allowed to do this. This guidance is in accordance with guidelines from Hembree et al (2017). To save the practitioner from any litigation issues, he or she must keep full documentation of the process. Likewise, a medical professional prescribing HRT or conducting sex reaffirming surgery must require a written referral from a MHP that the person meets criteria (Appendix 2 and 3) to undergo the procedure.

In regards to the prescription of HRT after puberty, we recommend a gynecologist, internal medical specialist or endocrinologist to initiate the therapy, which can be latter maintained in less specialized settings. However, this needs to be taken up before the Endocrine Society of Pakistan to ensure uniform provision of care and establish criteria for referral, re-referral between general medical and specialist care.

For sex reaffirming surgeries, it is highly recommended that only a trained plastic surgeon who has expertise in these surgeries to carry out the procedure. However, castration or

orchidectomy or penectomy can be done by General Surgeon provided a documentedreferral from MHP.

For halting progression of puberty in pre-puberty gender dysphoric children, detailed mental health examination must be carried out and consent can be obtained from parents. However, endocrinologist or pediatrician trained in these interventions must do medical prescription of GnRH analogues.

c. Positive effects of Hormone replacement therapy

Gender reaffirming HRT has following effects on person's life:

i. Decrease severity of gender dysphoria
ii. Improved mental well being
iii. Satisfied sexual life
iv. Improved quality of life

The negative effects of HRT are no more than the pharmacological side effects if the guidelines for prescription are followed. These side effects are given in Appendix 7 with definition of terms given in glossary above.

d. Expectations from Hormone replacement therapy

It is highlighted in section 1 of this document that the functions of gonads are reproductive as well as development of secondary sexual characteristics. Both of these are mediated by sex hormones. However, with HRT the latter is only achievable. In fact, HRT decreases fertility of a transgender person. Hence, it is recommended that those transgender whowish to have child later may take benefit from ova or sperm preservation using scientific techniques for producing off spring later.

e. Monitoring of Hormone replacement therapy

Since, the effects of HRT is progressive and given the nature that these medicines carry side effects, there response and side effects must be monitored. Means of monitoring includes body measurement such as height, weight (for obesity) as well as blood levels of hormone (three monthly), blood hemoglobin, lipid and Vit D levels (3-6 months). For monitoring bone strength, DEXA bone scan should be done every two years for those castrated or on estrogen

therapy. See Hembree et al 2017 for guidance.

4. References

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Appendix

Appendix 1. DSM-5 Criteria for Gender Dysphoria in Adolescents and Adults

A. A marked incongruence between one's experienced/expressed gender and natal gender of at least 6 month in duration, as manifested by at least two of the following:

1. A marked incongruence between one's experienced/expressed gender and primary and/or secondary sex characteristics (or in young adolescents, the anticipated secondary sex characteristics)
2. A strong desire to be rid of one's primary and/or secondary sex characteristics because of a marked incongruence with one's experienced/expressed gender (or in young adolescents, a desire to prevent the development of the anticipated secondary sex characteristics)
3. A strong desire for the primary and/or secondary sex characteristics of the other gender
4. A strong desire to be of the other gender (or some alternative gender different from one's designated gender)
5. A strong desire to be treated as the other gender (or some alternative gender different from one's designated gender)
6. A strong conviction that one has the typical feelings and reactions of the other gender (or some alternative gender different from one's designated gender)

B. The condition is associated with clinically significant distress or impairment in social, occupational, or other important areas of functioning. Specify if:

1. the condition exists with a disorder of sex development.
2. the condition is post transitional, in that the individual has transitioned to full- time living in the desired gender (with or without legalization of gender change) and has undergone (or is preparing to have) at least one sex-related medical procedure or treatment regimen namely, regular sex hormone treatment or gender reassignment surgery confirming the desired gender (e.g.,penectomy,vaginoplasty in natal males; mastectomy or phalloplasty in natal females)

Appendix 2. Criteria for Gender-Affirming Hormone Therapy for Adults

1. Persistent, well-documented gender dysphoria/gender incongruence

2. The capacity to make a fully informed decision and to consent for treatment

3. The age of majority in a given country (if younger, follow the criteria for adolescents)

4. Mental health concerns, if present, must be reasonably well controlled

Appendix 3. Criteria for Gender-Affirming Hormone Therapy for Adolescents

Adolescents are eligible for GnRH agonist treatment if:

1. A qualified MHP has confirmed that:

- The adolescent has demonstrated a long-lasting and intense pattern of gender nonconformity or gender dysphoria (whether suppressed or expressed),

- Gender dysphoria worsened with the onset of puberty,

- Any coexisting psychological, medical, or social problems that could interfere with treatment (e.g., that may compromise treatment adherence) have been addressed, such that the adolescent's situation and functioning are stable enough to start treatment,

- The adolescent has sufficient mental capacity to give informed consent to this (reversible) treatment

2. And the adolescent:

- has been informed of the effects and side effects of treatment (including potential loss of fertility if the individual subsequently continues with sex hormone treatment) and options to preserve fertility,

- has given informed consent and (particularly when the adolescent has not reached the age of legal medical consent, depending on applicable legislation) the parents or other caretakers or guardians have consented to the treatment and are involved in supporting the adolescent throughout the treatment process,

3. And a pediatric endocrinologist or other clinician experienced in pubertal assessment

·agrees with the indication for GnRH agonist treatment,

- has confirmed that puberty has started in the adolescent (Tanner stage $G2/B2),
- Has confirmed that there are no medical contraindications to GnRH agonist treatment.

Adolescents are eligible for subsequent sex hormone treatment if:

1. A qualified MHP has confirmed:

- The persistence of gender dysphoria,

- Any coexisting psychological, medical, or social problems that could interfere with treatment (e.g., that may compromise treatment adherence) have been addressed, such that the adolescent's situation and functioning are stable enough to start sex hormone Treatment,

- the adolescent has sufficient mental capacity (which most adolescents have by age 16 years) to estimate the consequences of this (partly) irreversible treatment, weigh the benefits and risks, and give informed consent to this (partly) irreversible treatment,

2. And the adolescent:

- Has been informed of the (irreversible) effects and side effects of treatment (including potential loss of fertility and options to preserve fertility),

- Has given informed consent and (particularly when the adolescent has not reached the age of legal medical consent, depending on applicable legislation) the parents or other caretakers or guardians have consented to the treatment and are involved in supporting the adolescent throughout the treatment process,

3. And a pediatric endocrinologist or other clinician experienced in pubertal induction:

- Agrees with the indication for sex hormone treatment,

- Has confirmed that there are no medical contraindications to sex hormone treatment.

Appendix 4. Masculinizing Effects in Transgender Males

Effect	Onset	Maximum
Skin oiliness/ acne	1-6 month	1-2 years
Facial/ body hair growth	6-12 month	4-5 years
Scalp hair loss	6-12 month	
Increased muscle mass/ strength	6-12 month	2-5 years
Fat redistribution	1-6 month	2-5 years
Cessation of menses	1-6 month	
Clitoral enlargement	1-6 month	1-2years
Vaginal atrophy	1-6 month	1-2 years
Deepening of voice	6-12 month	1-2 years

Appendix 5. Feminizing Effects in Transgender Females

Effect	Onset	Maximum
Redistribution of body fat	3-6 month	2-3 years
Decrease in muscle mass and strength	3-6 month	1-2 years
Softening of skin/ decreased oiliness	3-6 month	Unknown
Decreased sexual desire	1-3 month	3-6 month
Decreased spontaneous erections	1-3 month	3-6 month
Male sexual dysfunction	Variable	Variable
Breast growth	3-6 month	2-3 years
Decreased testicular volume	3-6 month	2-3 years
Decreased sperm production	Unknown	>3 years
Decreased terminal hair growth	6-12 month	>3 years
Scalp hair	Variable	
Voice changes	None	

Appendix 6. Criteria for Gender-Affirming Surgery, Which Affects Fertility

1. Persistent, well-documented gender dysphoria

2. Legal age of majority in the given country

3. Having continuously and responsibly used gender-affirming hormones for 12 month (if there is no medical contraindication to receiving such therapy)

4. Successful continuous full-time living in the new gender role for 12 month

5. If significant medical or mental health concerns are present, they must be well controlled

6. Demonstrable knowledge of all practical aspects of surgery (e.g., cost, required lengths of hospitalizations, likely complications, and postsurgical rehabilitation)

Appendix 7. Medical Risks Associated With Sex Hormone Therapy

Transgender female: estrogen

Very high risk of adverse outcomes:

a. Thromboembolic disease

Moderate risk of adverse outcomes:

a. Macro-prolactinoma
b. Breast cancer
c. Coronary artery disease
d. Cerebrovascular disease
e. Gall stones
f. Hypertriglyceridemia

Transgender male: testosterone

Very high risk of adverse outcomes:

a. Increase in red blood cell, can lead to thromboembolic diseases etc,

Moderate risk of adverse outcomes:

a. Severe liver dysfunction (transaminases . threefold upper limit of normal)
b. Coronary artery disease
c. Cerebrovascular disease
d. Hypertension
e. Breast or uterine cancer