Do No Harm

HORMONAL INTERVENTIONS FOR MINORS WITH GENDER DYSPHORIA CAUSE SIGNIFICANT HARM

ENDOCRINOLOGY BASICS

HORMONES

"Hormone" is a word derived from the Greek for "setting in motion." Almost every function of the body is regulated (or "set in motion") by hormones. Hormones are chemical molecules that are produced in one part of the body by specialized hormone-producing tissues or glands. Hormones are released into the bloodstream (the circulation) and act on other tissues elsewhere in the body.

For example, insulin is a hormone made by the pancreas that makes it possible for cells throughout the body to turn the food we eat into energy. Thyroid hormones are made in the thyroid gland. They are released into the circulation to regulate the body's metabolism.

Human sexual development is a complex process "set in motion" by hormones. Two main groups of hormones regulate sexual development: those produced in the brain and those produced in the sex organs. Those produced in the brain come from the hypothalamus, which sends a signal to the pituitary gland, the endocrine gland at the base of the brain. At puberty, this signal leads the pituitary to release gonadotropins, which activate the sex organs to produce a significant quantity of sex hormones. These sex hormones produce the physical differences we recognize as characteristic of men and women.

With the onset of puberty in boys, the testes grow in size and increase their production of testosterone, the main sex hormone in boys. With the onset of puberty in girls, the ovaries grow in size and increase their production of estrogen, the main sex hormone in girls.

Hormones are only a small part of the fundamental differences between boys and girls, men and women. Their role, however, is critical, starting in utero. In the womb, one's sex is determined through hormonal events that are controlled by one's sex chromosomes. Notwithstanding rare disorders of sexual development or chromosomal abnormalities, boys have XY chromosomes in every cell of their body, while girls have XX chromosomes in every cell of their body.

A boy's cells are uniquely designed to respond to testosterone. Boys' penis and testes are known as their primary sex characteristics and are present at birth. After the onset of puberty, boys develop secondary sex characteristics which include growth in male genitalia, coarse body and facial hair, increases in the size and strength of bones and muscle, and changes in the voice box leading to a deeper voice.

A girl's cells are uniquely designed to respond to estrogen. Girls' uterus, ovaries, fallopian tubes, vagina, and vulva are their primary sex characteristics and are present at birth. After the onset of puberty, girls

will develop secondary sex characteristics, which include widening of the hips, development of breast tissue, and an increase in breast size.

Completion of puberty without disruption leads to mature reproductive capacity. Girls will experience onset of menstruation and ovulation, releasing ova (eggs) that can be fertilized. Boys produce sperm that can fertilize an ovum.

Hormone levels in the blood differ markedly in the two sexes. By age 18, boys have levels of testosterone in their blood that are about 10- to 20-fold higher than those in girls. By age 18, girls have levels of estrogen in their blood that are about 5- to 10-fold higher than those in boys.

Administering opposite sex hormones to bodies designed for same-sex hormones causes harm. It is rational and clinically appropriate to prescribe testosterone to men who have verifiable medical conditions such as impaired testicular function, which result in low testosterone. Doing so is consistent with biological reality. Similarly, it is rational and clinically appropriate to prescribe estrogen to women who have a verifiable medical disorder such as premature ovarian insufficiency causing an earlier-than-normal decrease in estrogen levels. However, prescribing opposite sex hormones, i.e., estrogen to boys or men, and testosterone to girls or women, is contrary to normal biology. The U.S. Food and Drug Administration (FDA) has not approved the use of testosterone for women or estrogen for men except as palliative treatment for men with advanced prostate cancer.[1] While there are times when medications are prescribed "off-label" (i.e., outside of FDA-approved use), these instances are typically when there is enough well-established experience with those uses as well as the medication's safety to determine that the benefits outweigh the risks. This is not the case with opposite-sex hormones in children where high-quality studies are lacking and safety concerns are abundant, as outlined in this guide.

Hormonal interventions do not provide benefit for minors with gender dysphoria and cause significant harm.

HORMONAL INTERVENTIONS IN GENDER DYSPHORIA

HORMONES HAVE POWERFUL EFFECTS

Most of the data on the effects of opposite sex hormones come from studies in adults; there are very little data in minors and there are no satisfactory studies on the safety of opposite sex hormones in children with gender dysphoria. The Cass Review, an independent review of gender identity services for children and young people in the United Kingdom, found a "lack of high-quality research assessing the outcomes of hormone interventions in adolescents with gender dysphoria/incongruence."[2] Furthermore, pediatricians and pediatric endocrinologists are unlikely to see the long-term harms of opposite sex hormones begun in childhood, because they usually do not provide care for adults.

Testosterone is the principal male hormone. The dose of testosterone recommended by the Endocrine Society for gender dysphoric females would produce levels 20 to 40 times higher than the normal blood level of testosterone in females.[3]

Estradiol is the main female hormone. Males normally have levels below 30 pg/ml.[4] For gender dysphoria in males, the Endocrine Society recommends an estradiol level of 100 to 200 pg/ml, about 5 to 10 times higher than that found in a normal male.[5]

It is not clear how opposite sex hormones impact the brain and mental health of adolescents, particularly in the long term. Longer follow-up studies are needed to understand the long-term effects of opposite sex hormones, especially on adolescents.[6] In its abstract, one study noted that "there is little to no empirical data guiding clinical practices of cross sex hormone therapy in early pubertal adolescents, highlighting the need for further research."[7]

FEMALES TAKING TESTOSTERONE

SEXUAL AND REPRODUCTIVE SYSTEM RISKS

- **Infertility** is frequent in females taking testosterone[8, 9, 10, 11]
- Associated with **pelvic pain** as well as **vaginal pain/discomfort during sexual activity**[12, 13]

CARDIOVASCULAR RISKS

- 3.5x increased incidence of **heart attacks** compared to women not taking testosterone[14,15]
- Increase in **LDL ("bad") cholesterol**, increase in **triglycerides** (blood fats), and **decrease in HDL ("good") cholesterol**[16, 17]
- Associated with modest **increase in body mass index (BMI)**[18, 19]
- Associated with increased risk for **metabolic syndrome** – a group of conditions that together increase one's risk of cardiovascular disease, type 2 diabetes, and stroke[20]
- 7-fold higher rate of **erythrocytosis** (increase in red blood cell concentration which may increase risk of blood clots, leading to heart attack and stroke) compared to men not taking testosterone[21]

CANCER RISKS

- Causes **abnormalities in the Pap smear** making it more difficult to diagnose cervical cancer[22]
- **Endometrial cancer** (cancer of the uterine lining) appears to increase with duration of testosterone use in the setting of severe obesity[23]

OTHER

- **Acne, baldness, facial** and **body hair**; the **voice irreversibly deepens**[24, 25, 26, 27, 28]

MALES TAKING ESTROGEN

REPRODUCTIVE SYSTEM RISKS

- Interferes with testicular function including sperm production, which may cause **infertility**[29, 30]

CARDIOVASCULAR RISKS

- > 4x increased incidence of **venous thromboembolism** (clots in veins that can pass to the lung and cause death) compared to men not taking estrogen[31]
- Increased risk of **retinal vein occlusion** (blockage in blood flow from the eye)[32, 33]
- Increase in **triglycerides** (blood fats)[34]
- Nearly 2-fold increased incidence of **strokes** compared to men not taking estrogen[35]

CANCER RISKS

- Increase in **testicular cancer**[36, 37]
- 46-fold increase in **invasive breast cancer** compared to men not taking estrogen[38]
- > 2-fold increase in the risk of **thyroid cancer**[39]

ENDNOTES

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