Current Evidence on Estrogen Therapy, Neurodevelopment, and Genetics in Transgender Women

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White Paper
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by Paula Aurélie Fisher

This educational white paper summarizes themes from the peer-reviewed literature identified in this conversation, these being available as references at the summary of this white paper. It distinguishes established clinical findings from biologically plausible hypotheses and areas of ongoing research.

The primary reason for producing this is quite simple in it's complexity. I know a vast amount of trans-gender women and what is apparent is the simple fact that they function remarkably well on low testosterone and normal female levels of estrogen. A normal biological male on low testosterone exhibits various levels of dysfunction, these obviously include libido, but lethargy too and other mental faculties are significantly impacted.

Trans-gender women on the other hand, excluding the low libido generally do not suffer from any of those issues and mostly seem to thrive on estrogen. Why is this ? Is there some deeper biological nuance we are missing ? Given that the 21st century has given us a multitude of genetics, neuroscience and the related brain scan studies, all of which significantly indicate the empirical evidence that trans-gender people are in fact born trans-gender, i.e. their incongruence is a genetic event during roughly week 11 and week 19 gestation, therefore given the evidence of a brain cortex developed off of estrogen vs testosterone, then it's feasible then that as an adult, there is a clear need to function with estrogen.

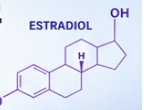
This white paper, while it highlights significant findings supporting estrogen-based trans-gender women with development as such in-utero, there are still much more definitive research that is needed as you can read below, some evidence is modest in the evaluation, but still present and a viable candidate, however in other areas, there is strong supporting evidence.

While I do not have a medical background, I do have expertise in big data and enterprise level systems, meaning I understand data and have the ability to read technical papers. This white paper then is a correlation of multiple medical references from subject matter experts in the field on genetics and neuroscience.

This paper is also the selected evidence related to the below informative graphic …

WHY ESTROGEN IS OFTEN THE RIGHT HORMONE FOR TRANSGENDER WOMEN TO FUNCTION THEIR BEST

A MEDICAL & SCIENTIFIC OVERVIEW



Current evidence from genetics, neurobiology, endocrinology and clinical research indicates that many transgender women function better overall when their bodies are aligned with an estrogen-dominant environment.

BIOLOGY • BRAIN • HORMONES • WELL-BEING

KEY POINTS

- Gender incongruence has strong biological roots beginning in-utero due to genetic, hormonal and neurodevelopmental factors.
- Brain development and genital development occur on different timelines, making divergence biologically possible.
- Many transgender women have neurodevelopment consistent with greater sensitivity and responsiveness to estrogen.
- Estrogen therapy reduces gender dysphoria and improves mental health, quality of life and overall well-being.
- For many transgender women, an estrogen-dominant state is more congruent with their brain and body—allowing them to function better medically, psychologically and socially.

1. PRENATAL ORIGINS: THE FOUNDATION IS LAID EARLY

Brain sexual differentiation occurs after genital differentiation

WEEKS 6–12
Genital Differentiation

Influenced primarily by testosterone and DHT

WEEKS 12–30+
Brain Sexual Differentiation

Influenced by:
- Steroid hormones
- Receptor sensitivity
- Genetic variants
- Epigenetic regulation
- Neural development

BIRTH & BEYOND
Gender Identity Emerges

Identity develops from brain circuits for self, body and social perception

This separation in timing allows the brain and body to be influenced differently, which can result in gender incongruence.

2. STRONG EVIDENCE FOR BETTER OUTCOMES ON ESTROGEN

REDUCTION IN GENDER DYSPHORIA
Most studies show marked and sustained reduction.
EVIDENCE: STRONG

IMPROVED MENTAL HEALTH
Lower rates of depression, anxiety, suicidality and distress.
EVIDENCE: STRONG

BETTER QUALITY OF LIFE
Improved body congruence, self-esteem, relationships and social functioning.
EVIDENCE: STRONG

BRAIN ADAPTATION
Estrogen therapy is associated with changes in brain structure, connectivity and function toward female-typical patterns in many regions.
EVIDENCE: MODERATE

PHYSIOLOGICAL ALIGNMENT
Estrogen supports cardiovascular, metabolic, bone and emotional health consistent with the patient's gender identity.
EVIDENCE: MODERATE

Outcomes vary by individual, but the overall trend across studies is clear and consistent.

3. GENETIC & EPIGENETIC INFLUENCES

Multiple genes influence how the developing brain responds to hormones.

KEY CANDIDATE GENES

ESR1	Estrogen Receptor α	Regulates gene transcription in response to estrogen
ESR2	Estrogen Receptor β	Neuronal development, plasticity, emotional regulation
AR	Androgen Receptor	Responds to testesterone/DHT; variant activity affects brain masculinization
CYP19A1	Aromatase	Converts testosterone to estradiol in the brain
CYP17A1	Steroidogenesis Enzyme	Produces androgen and estrogen precursors
CYP11A1	Steroidogenesis Enzyme	Initiates steroid hormone synthesis
SRD5A2	5α-Reductase Type 2	Converts testosterone to DHT

These genes act together in pathways that regulate hormone synthesis, receptor function and neural development. Epigenetic mechanisms fine-tune gene expression during critical windows in-utero.

4. NEURAL RECEPTORS INVOLVED IN ESTROGEN RESPONSE

Estrogen acts on multiple receptors throughout the brain to regulate development and function.

- **ESR1** — Estrogen Receptor α: Gene transcription, neuronal growth, synaptic formation
- **ESR2** — Estrogen Receptor β: Neuronal maturation, synaptic plasticity, neuroprotection
- **GPER1** — G Protein-Coupled Estrogen Receptor: Rapid signaling, calcium flux, kinase activation
- **PGR** — Progesterone Receptor: Works with estrogen in neural development
- **AR** — Androgen Receptor: Interacts with estrogen pathways; variant activity can alter sensitivity

These receptors are influenced by genetic variants and epigenetic regulation, shaping how the brain develops and responds to hormones.

5. WHY ESTROGEN OFTEN ALIGNS BETTER FOR TRANS WOMEN

TESTOSTERONE-DOMINANT STATE

May increase:
- Gender dysphoria
- Anxiety & depression
- Body incongruence
- Discordance with neurodevelopment

VS.

ESTROGEN-DOMINANT STATE

Associated with:
- Reduced dysphoria
- Emotional stability
- Better body congruence
- Improved quality of life
- Greater social & cognitive well-being

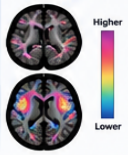
For many transgender women, an estrogen-dominant environment is more congruent with their brain's neurodevelopmental wiring—allowing them to thrive.

6. BRAIN IMAGING EVIDENCE

MRI studies show that after estrogen therapy, transgender women exhibit changes in:

- **Cortical Thickness** — Shifts toward female-typical patterns
- **White Matter Connectivity** — Increased integrity in female-typical networks
- **Brain Metabolism** — Changes in regions related to self-perception
- **Functional Connectivity** — Networks align more closely with cisgender women

These changes support the idea that the adult brain remains responsive to estrogen.



7. CLINICAL OUTCOMES WITH ESTROGEN THERAPY

DOMAIN	COMMON IMPROVEMENTS
Mental Health	Lower depression, lower anxiety, reduced suicidality
Gender Dysphoria	Significant reduction, improved body congruence
Quality of Life	Higher life satisfaction, better relationships, greater social participation
Cognitive & Emotional	Improved emotional regulation, self-awareness and well-being
Physical Health	Improved bone density, cardiovascular markers, skin, fat distribution, and overall vitality* (*with appropriate medical supervision)

Research consistently shows that gender-affirming estrogen therapy is safe, effective and life-improving when medically supervised.

8. LEADING RESEARCHERS & THEIR QUALIFICATIONS

- **J. Graham Theisen, MD** — Physician-scientist in reproductive endocrinology and infertility; expertise in human genetics and genomics.
- **Vincent Harley, PhD** — Molecular geneticist; Head of Molecular Genetics and Development, Hudson Institute of Medical Research; expert in sex determination genetics and molecular endocrinology.
- **Foreman M.** — Research scientist with expertise in molecular genetics and statistical genetics.
- **Lynley Jones** — Research scientist with expertise in molecular genetics and hormone receptor polymorphisms.
- **Julie Bakker, PhD** — Professor of Neuroendocrinology; expert in developmental neuroendocrinology and sexual differentiation of the brain.
- **William Reiner, MD** — Pediatric urologist and professor; expert in disorders of sex development (DSD) and development of gender identity.

THE BOTTOM LINE

Transgender women are not "choosing" estrogen—many have brains that were organized in-utero in ways that are more responsive to estrogen. Aligning the body's hormonal environment with the brain helps reduce suffering, improves functioning and allows them to live healthy, authentic, productive lives.

ESTROGEN THERAPY IS NOT JUST AFFIRMING—IT IS OFTEN MEDICALLY NECESSARY.

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Executive Summary

Strong clinical evidence indicates that feminizing hormone therapy reduces gender dysphoria and improves quality of life for many transgender women when medically supervised.

Converging evidence from developmental biology, genetics, neuroimaging, endocrinology, and epigenetics supports a prenatal neurodevelopmental contribution to gender identity.

No single gene, receptor, biomarker, or imaging test currently diagnoses gender incongruence or predicts response to estrogen. The available evidence identifies several biologically plausible candidates, but it he picture is of interacting pathways rather than a single receptor defect, I.E. polygenic.

Clinical Evidence

Consistent reductions in gender dysphoria after estrogen-based hormone therapy.

Improvements in anxiety, depression, body congruence, and patient-reported well-being are reported across many studies.

Brain imaging demonstrates hormone-responsive changes in structure and connectivity, although these findings do not provide a causal mechanism. This being a limitation of imaging technology and the associated interpretive software. However the brain imaging aspect of the reference material will not be pertinent to evaluation of genetic hormonal relationships chemically.

Proposed Biological Framework

- Polygenic susceptibility involving multiple genes of small effect.
- Prenatal hormone signaling, receptor sensitivity, and epigenetic regulation influence fetal brain development.
- Brain sexual differentiation occurs after genital differentiation, providing a biologically plausible developmental window for divergence.
- Estrogen therapy may provide a more congruent endocrine environment for some transgender women, but receptor-level mechanisms remain under investigation.

Candidate Genes and Biological Pathways

Gene	Primary Role	Research Context
AR	Androgen receptor	Steroid signaling; candidate-gene association studies
ESR1	Estrogen receptor α	Estrogen signaling and neural development
ESR2	Estrogen receptor β	Neuronal maturation and plasticity
CYP19A1	Aromatase	Local estradiol synthesis
CYP17A1	Steroidogenesis	Hormone precursor synthesis
CYP11A1	Steroidogenesis	Initial steroid hormone synthesis
SRD5A2	5α-reductase	Conversion of testosterone to DHT

Medical overview of receptors

1. Estrogen Receptor α (ESR1)

This is one of the strongest candidate receptors.

Function

- Nuclear estrogen receptor
- Regulates transcription of hundreds of genes
- Highly active during fetal brain development
- Influences neuronal differentiation and synapse formation

Brain regions

High expression occurs in:

- hypothalamus
- amygdala
- hippocampus
- prefrontal cortex

Why it matters

Variants in the **ESR1** gene have been reported in some candidate-gene studies of transgender populations. Since ESR1 influences how cells respond to estrogen, differences in receptor expression or function could alter developmental responses to prenatal hormones.

Current evidence: Moderate; associations have been reported, but replication is still needed.

2. Estrogen Receptor β (ESR2)

Another major candidate.

Function

- Regulates neuronal maturation
- Modulates synaptic plasticity
- Influences dendritic spine formation
- Has anti-inflammatory and neuroprotective effects

Importance

ESR2 is particularly abundant in cortical and limbic regions involved in cognition and emotion.

Some studies have identified ESR2 variants in transgender cohorts, suggesting it may contribute to susceptibility.

Current evidence: Moderate.

3. Androgen Receptor (AR)

Although not an estrogen receptor, AR is central to the model.

Function

- Binds testosterone and dihydrotestosterone (DHT)
- Regulates androgen-responsive gene transcription

Relevance

Several studies have examined polymorphisms in the **AR** gene, including CAG repeat length, which can influence receptor activity. Reduced androgen receptor signaling is one proposed mechanism by which brain development could diverge from genital development.

Current evidence: Moderate, with inconsistent findings across studies.

4. Aromatase (CYP19A1)

Strictly speaking, aromatase is an enzyme rather than a receptor, but it is crucial.

Function

Converts:

- testosterone → estradiol

within many tissues, including the brain.

Importance

Local estrogen production in the fetal brain is essential for aspects of sexual differentiation.

Variants affecting aromatase activity could influence the amount of estrogen available to activate ESR1 and ESR2.

Current evidence: Moderate.

5. Steroid Receptor Co-regulators

The receptor itself is only part of the signaling system.

Estrogen receptors recruit proteins such as:

- NCOA1 (SRC-1)
- NCOA2
- NCOA3
- NCOR1
- NCOR2

These co-activators and co-repressors determine how strongly estrogen-responsive genes are expressed.

These proteins have not been established as markers for gender incongruence, but they are biologically plausible contributors.

Current evidence: Preliminary.

6. Progesterone Receptor (PGR)

Progesterone signaling interacts with estrogen during brain development.

Potential roles include:

- neuronal maturation
- synaptic organization
- myelination

Evidence linking PGR directly to transgender identity is currently limited as far as in-utero development, however it's significant post-natal and has overwhelming evidence to assisting trans-gender women.

7. G Protein-Coupled Estrogen Receptor (GPER1)

Unlike ESR1 and ESR2, which mainly regulate gene transcription, GPER1 mediates rapid, non-genomic estrogen signaling.

Functions include:

- intracellular calcium signaling
- kinase activation
- synaptic modulation

It has been proposed as a candidate in neurodevelopment but has not yet been implicated specifically in transgender cohorts. Although the Kinase activation is a direct contributor to the **Cortical Thickness (CTh) Shifts:** MRI studies indicate that prior to hormone therapy, untreated trans individuals exhibit unique cerebral patterns. This then collaborates in-utero brain development.

Downstream signaling pathways

When estrogen binds ESR1 or ESR2, it can activate several intracellular pathways involved in neural development:

- PI3K–AKT pathway: cell survival and synaptic growth.
- MAPK/ERK pathway: neuronal differentiation and plasticity.
- CREB signaling: learning, memory, and gene transcription.
- BDNF pathway: neuronal survival and synaptic plasticity.

These pathways are well established in neuroscience, although their specific roles in gender identity remain under investigation.

A hypothetical integrated model

One proposed sequence, consistent with the literature but not yet proven, is:

1. **Genetic variants** affect steroid hormone receptors and enzymes.
2. **Prenatal hormone signaling** differs subtly in the developing brain.
3. **Epigenetic regulation** modifies expression of receptor-related genes.
4. **Neural circuits** involved in body perception, self-representation, and aspects of sexually dimorphic development are organized differently.
5. **In adulthood**, estrogen-based therapy may align more closely with those circuits in some transgender women, contributing to reductions in gender dysphoria and improvements in well-being.

Overall assessment

Among the receptors discussed, **ESR1**, **ESR2**, and **AR** have the strongest support from the candidate-gene literature referenced because they are directly involved in sex steroid signaling and have been investigated in association studies. **CYP19A1**, **CYP17A1**, **CYP11A1**, and **SRD5A2** are not receptors but are equally important because they regulate the synthesis and metabolism of the hormones that activate those receptors.

It's important to emphasize that **no current study demonstrates that transgender women as a group "process estrogen better" at these receptors than biological women**. The evidence supports the hypothesis that inherited variation in these signaling pathways may contribute to prenatal brain development and later hormone responsiveness, but the specific receptor-level mechanisms remain an active area of research rather than an established clinical fact.

Every year there are significant improvements in clinical research, brain scan technology and the associated technological image processing along with research into genetic evaluations.

Evidence Assessment

- Strong: clinical benefit of gender-affirming hormone therapy for appropriately selected patients.
- Moderate: prenatal neurodevelopmental model integrating genetics, endocrinology, and neuroimaging.
- Emerging: specific receptor biology, polygenic architecture, and individualized hormone responsiveness.

Selected Subject Matter Experts (SMEs)

Some of the subject matter experts from the 26 reference studies used to create this white paper.

Researcher	Qualifications	Primary Contribution
J. Graham Theisen	MD; physician-scientist in reproductive endocrinology and infertility	Candidate-gene association studies; polygenic models
Vincent Harley	PhD; molecular geneticist; Hudson Institute	Sex determination genetics; steroid signaling
Julie Bakker	PhD; Professor of Neuroendocrinology	Prenatal hormone biology; brain sexual differentiation
Antonio Guillamon	MD, PhD; Professor Emeritus of Psychobiology	Neurodevelopment; neuroanatomy
Ivanka Savic	MD, PhD; Professor of Neurology	Functional neuroimaging; neuroendocrinology
Dick F. Swaab	MD, PhD; neuroscientist	Hypothalamic development; BSTc research
Alicia Garcia-Falgueras	PhD; neuroscientist	Sexually dimorphic brain structures
William Reiner	MD; pediatric urologist and academic physician	Disorders of sex development; gender development
Peggy T. Cohen-Kettenis	PhD; clinical psychologist and researcher	Developmental and longitudinal gender identity research

Limitations

- Most genetic findings are candidate-gene associations with modest effect sizes
- Replication across larger and more diverse cohorts remains necessary
- Association does not yet establish a concise causation and remains polygenic
- Clinical decisions should follow established professional guidelines and individualized assessment
- While limitations exist, it does not preclude solid hypothesis related to the results

Conclusion

The current literature supports a biologically plausible model in which genetics, prenatal hormone signaling, epigenetic regulation, and fetal brain development interact to influence gender identity. Estrogen therapy has strong evidence for improving gender dysphoria and quality of life in many transgender women, the evidence therefore supports the hypothesis that inherited variation in these signaling pathways may contribute to prenatal brain development and later hormone responsiveness in trans-gender women, verses the reliance solely on testosterone. While the precise molecular mechanisms underlying differential hormone responsiveness remain an active area of investigation.

Selected Literature Themes

- Genetics and candidate-gene association studies
- Developmental neurobiology and fetal brain differentiation
- Neuroimaging studies before and after hormone therapy
- Clinical outcome studies of gender-affirming hormone therapy
- Endocrine and receptor signaling research

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