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Article

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On Gender, Gender Incongruence, and Gender-Affirming Care

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As the number of transgender individuals continues to rise, there is an urgent need to understand the nature of gender and the evidence supporting gender-affirming care. This article proposes the hypothesis that one's gender is a perception, influenced by biological and social factors. Early-onset gender incongruence seems to be influenced but not wholly determined by the prenatal hormonal environment, while late-onset gender incongruence is associated with comorbidities, suggesting that one's sense of gender can be impacted by a variety of psychological and social conditions that affect the mind-body connection. Puberty blockers have been used on children to buy time for them to decide whether to continue with their transition. However, most gender dysphoria desists at puberty, but this is prevented by puberty blockers. Moreover, puberty blockers have negative psychological and physiological consequences, and studies of puberty blockers and cross-sex hormones have not shown long-term improvements in mental health outcomes. Thus, while some gender incongruence does not resolve upon puberty and may be best treated by transitioning, the preponderance of evidence does not support a medicalized gender-affirming approach for children and adolescents.

Keywords: puberty blockers, luteinizing hormone, gonadotropin-releasing hormone, desistance, comorbidity, social construct, dysphoria, own-body perception, detransitioning, hypothalamus, pituitary, Dutch Protocol

The controversy surrounding gender identity and gender-affirming care shows no sign of diminishing. A US study using data from 2017–2020 found that 1.3 million individuals aged 13 and older identified as transgender, with youth aged 13–17 significantly more likely to identify as transgender than adults (1.4% vs. 0.3%).¹ As progress is being made in understanding gender and gender-affirming care, much remains to be determined.

This article builds on a previous review of the literature on gender incongruence,² with particular focus upon the nature of

gender perception and the evidence surrounding aspects of gender-affirming care. Although much of the debate on this topic involves philosophical and theological arguments, this review focuses primarily on the biology, but it will also include a discussion of possible Christian responses.

This article is organized into two main sections. The first section deals with gender, its relationship to sex, and possible causes of gender incongruence. It also addresses identity development and suggests that gender incongruence may be due to abnormal self-perception. The second section covers aspects of gender-affirming care and the evidence supporting this care. This section includes a discussion of the quality of evidence in clinical studies and concludes that the evidence does not unequivocally support

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gender-affirming care. Regret and detransitioning are also discussed, along with Christian perspectives on gender incongruence and some unresolved questions.

What Is Gender?

Perspectives on the Nature of Gender

Gender or gender identity is the internal sense of whether one is male or female (or neither for non-binary individuals), as opposed to one's sex, which is genetically determined and involves the bodily manifestations of one's sex. Although gender is popularly used as a synonym for biological sex, the two are not equivalent. A diverse and often conflicting collection of views on the nature, origin, and stability of sex underlies discussions about gender dysphoria and transgender healthcare. As will be described in more detail later, gender incongruence can be apparent at different stages in development: in childhood or in adolescence. It is not clear to what degree these two forms have a shared etiology, but this article will propose differences in their context, which can affect their sense of gender.

One view of gender is the biology-based essentialist view, which argues that gender is identical to sex and wholly derived from it.³ However, this view cannot account for the fact that sex and gender are incongruent for some people.

A second view is that gender is influenced, but not completely determined, by testosterone (some of which is converted to estrogen) present in the male but not in the female fetal brain.⁴ This hormonal milieu is thought to cause the brain to develop sex-specific characteristics. For example, fetal testosterone corresponds with male-typical play in children⁵ and rodents.⁶ While a definitive biological mechanism cannot be identified,⁷ there may be genetic and epigenetic (environmental) contributions to gender incongruence. Higher frequencies of gender incongruence are seen in congenital adrenal hyperplasia,⁸ partial androgen insensitivity,⁹ polycystic ovary syndrome,¹⁰ exposure to diethylstilbestrol,¹¹ and genetic variants of androgen receptors¹² and estrogen signaling pathways.¹³

A study of 32 transgender individuals found differences in epigenetic profiles (DNA methylation patterns) between transgender and cisgender populations, although these findings are preliminary as they did not account for other conditions that affect DNA

methylation.¹⁴ Nevertheless, some of the affected genes are known to be involved in neural development, although their role in gender development is unknown. Curiously, most of these differences were seen in male-to-female transgender individuals (87 differences) but only two were seen in female-to-male individuals. These differences were seen before gender-affirming hormone therapy (GAHT); consequently, GAHT caused changes in methylation patterns.¹⁵ It should be noted that each of these conditions, whether genetic or epigenetic, only partially contributes to an increase in the frequency of gender incongruence. Thus, other factors must play a role in one's gender perception.

A striking example of the role of hormones in gender perception is the case of Greg Eilers.¹⁶ Eilers suffered from gender dysphoria, which intensified in adulthood, to the point where he was forced to retire from the ministry in order to transition to Gina. The transitioning process included bottom surgery and estrogen treatments. The absence of testosterone and the higher levels of estrogen resolved his dysphoria. Counterintuitively, as long as he remains on estrogen, he senses his gender as male.

While the Eilers case also provides an example of gender not being fixed, Jack Turban, a child and adolescent psychiatrist and prominent advocate for gender-affirming care and author of *Free to Be: Understanding Kids & Gender Identity*, suggests that gender is invariant, one's "authentic self."¹⁷ For Turban, it is not that one's gender changes, it is one's understanding of their gender that might evolve.¹⁸

Another factor to consider is the stability of gender perception over time. If one's gender is one's "true self" and cannot change, that would strengthen the argument for treating gender incongruence via body modification. However, 60–90% of early-onset gender incongruence has been reported to desist at puberty.¹⁹ Further evidence for a biological component to gender perception involves individuals with a deficiency of the enzyme 5-alpha reductase-2, which converts testosterone to dihydrotestosterone. Testosterone is thought to be involved in masculinization of the fetal brain, but dihydrotestosterone is needed for development of male genitalia. Individuals lacking 5-alpha reductase-2 have abnormal genitals at birth and are often raised as girls. However, when testosterone levels increase at puberty, there are changes in the genitals and other secondary sex characteristics. In one study, roughly half of these individuals changed

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from female to male.²⁰ That not everyone changed their gender indicates that other factors are involved, and one cannot exclude the possibility that the gender incongruence existed in childhood but was not manifest until puberty. The author of the study noted that there was no correlation between the degree of external masculinization and gender changes, so it remains unclear why some people changed their gender and not others.

Nonbiological perspectives on gender are also influential. One involves the Vrije (Free) University Medical Center (VUMC) in Amsterdam, in the forefront of treatments for gender dysphoria since the 1960s. The VUMC is a (Reformed) Christian institution and the stated motivation for the surgeons performing the sex change operations was explicitly Christian²¹ and, in the case of the surgeon Freerk Bouman, grounded in a dualist conception in which treatment of the body functioned as service to the soul. Bouman states,

To me [performing these surgeries] is proof of Christian compassion. These people are in need; they are kind of the wretched of this earth. From a Christian point of view the soul, the psyche, should be considered more important than the body. So, if the soul is so disturbed that it makes people feel totally unhappy and get into trouble, it is allowed to help them in this way. I can justify that. Jesus is the Good Samaritan. He looks after the outcasts. I think that is beautiful.²²

While Bouman's ethic of compassion and service is commendable, it should not automatically be taken as the normative Christian perspective. Felipe de la Torre in his book *Gender as Love: A Theological Account of Human Identity, Embodied Desire, and Our Social Worlds* argues that prioritizing soul over body (or in Bouman's case, gender over biological sex) runs the risk of falling into Gnosticism, treating the body as evil and temporal.²³ Moreover, such a position is incompatible with the monistic perspective, held by some Christians, that body and soul are unified.

Another view is that gender is a social construct. As the child develops, they respond to cues from their own bodies and how they are conditioned by others to develop a sense of gender.²⁴ Proponents of this view are motivated by a concern to avoid defined (and potentially discriminatory) gender roles. For instance, the transgender journalist Andrea Long Chu, following Judith Butler, claims that we must rid ourselves of the idea that any necessary relationship exists between sex and gender.²⁵ She argues

for the right to change one's biological sex without appealing to gender and the right to assume a gender that is not determined by one's sexual biology. The transgender law professor Florence Ashley also uses the social constructivist perspective to bolster moral claims when she argues for gender self-determination and medical transitioning as a medical right.²⁶

Partly because of the difficulty in determining a definitive cause for gender incongruence, this article proposes the hypothesis that gender is not so much an *entity* as a *process*, one of perception or interpretation, which develops over time. Specifically, it proposes that one's sense of gender is emergent, influenced by but not reducible to biological sex. A fertilized egg has a biological sex but no gender. As the embryo, the fetus, and then the child develops, that person is influenced by biological and social factors—for example, the hormonal environment of their brain, their awareness of their body, how they are treated by others, and role models and perceived gender roles that they encounter. They then incorporate all of this as their sense of gender develops. Generally, one's gender aligns with one's biological sex, but various factors could affect this process, resulting in gender incongruence. Once established, one's sense of gender can be remarkably resistant to change. Some sufferers of gender incongruence simply cannot escape their dysphoria. However, as will be shown later, in other contexts, one's sense of gender is not as stable as one might think, especially during adolescence.

Gender incongruence is thought to come in two general categories. The early-onset form arises before puberty, usually between ages 3 and 7,²⁷ while the late-onset form arises in adolescence. Most early-onset cases desist upon puberty. A recent general population study of 2,772 individuals in the Netherlands found a decrease in gender non-contentedness over the course of adolescence from 11% at age 10 to 4% by age 26. In contrast, just 2% experienced increasing gender non-contentedness over time and, associated with that, a poorer self-concept and mental health.²⁸ Those experiencing increased gender nonconformity were ten times more likely to be same-sex attracted or bisexual; this is similar to findings in other studies.²⁹ This correlation raises the possibility that these individuals mistook same-sex attraction for gender incongruence and/or that there is a shared etiology between the two conditions. However, for those in whom the incongruence persists, the dysphoria intensifies and causes extreme distress, in part due

to the development of unwanted secondary sex characteristics.

While the relationship between early- and late-onset gender incongruence is unknown, the proportion of the late-onset form is increasing in the overall population and, unlike the early-onset form which primarily affects natal males, primarily involves natal females.³⁰ The late-onset population also presents with considerable psychiatric comorbidity.³¹ Little is understood about the nature and causes of this form of gender incongruence. This article proposes the hypothesis that late-onset gender incongruity is not biologically determined, as in early-onset gender dysphoria, although there still could be a biological contribution; rather, it is a disorder of perception, facilitated by the associated psychiatric comorbidities.

In hypothesizing that late-onset gender dysphoria is a disorder, it must be acknowledged that the American Psychological Association,³² the Endocrine Society,³³ and the World Professional Association for Transgender Health (WPATH)³⁴ strongly disagree with the characterization of gender incongruence as a disorder and thus object to any efforts to “treat” the incongruence in any way except by gender-affirming care. However, despite the commendable desire to avoid stigmatization embodied in the gender-affirming approaches offered by these organizations, a major purpose of this article is to consider the possibility that gender incongruence is a disorder of perception. Thus, the term disorder will be retained, although in so doing there is no intent to denigrate those with gender incongruence or prejudice the cause of their condition.

Perception of Self

The scientific question of how one experiences one’s gender, let alone how that experience can change, is difficult to address, as one’s sense of gender cannot be objectively measured. The nature of perception was introduced in the previous review,³⁵ but needs to be elaborated here. In addition to the work of Anil Seth, the neuroscientists Gregory Berns³⁶ and Andy Clark³⁷ have also elaborated on the process of perception. Berns summarizes the neuroscience thus:

... the question of self-identity boils down to one of self-perception, namely how a person thinks about themselves. Take gender, for instance, which not so long ago was thought to be a fixed, objective feature of someone’s identity. The argument went, you can look in the mirror and see for yourself the shape of your body, the genitals you were born with (or

not). But we now understand that *what you do with that information*, your own sense of gender identity, whether congruent or not with the physical expression of your sex, is a matter of perception – and that is a process that occurs in the brain.³⁸ (italics added)

All three authors describe the process of perception as making inferences, using incomplete sensory information, and those inferences are updated as more data come in. The brain receives a variety of inputs, including chemical and electrical signals, and, by trial and error, uses those signals to try and make sense of its surroundings. This process can readily be seen in babies, who gradually become aware of their surroundings and learn how to interact with them in a process that Joshua Rule and colleagues describe as hacking.³⁹ This approach leads to more rapid perception, improvements in perception with learning, and selective attention in the presence of distractors.⁴⁰

In addition, there is also interoceptive inference, in which the brain receives inputs from the body – for example, pH, blood pressure, electrical signals, hormones, inflammatory molecules – and uses those signals, in a process known as allostasis, to construct a guess about one’s physiological state and to respond accordingly.⁴¹ Usually, this guess is correct or can be modified with further information, but disorders of allostasis – misinterpretations – can occur. Conditions like anxiety and depression may involve such.⁴² Seth and Manos Tsakiris apply the concept of interoceptive inference to self-perception.⁴³ If one’s sense of self is based on inference, that inference may not necessarily be correct. As Seth and Tsakiris explain,

On the view we propose, the function of perception is not to recover a “veridical,” action-independent representation of the external environment or body. Instead, predictive perception, in any modality, is ultimately geared towards driving actions that preserve physiological integrity of the organism. In other words, we do not perceive the world (and self) as it is, but as it is useful to do so. This may involve systematically “misperceiving” the environment, by criteria of veridicality.⁴⁴

Seth and Tsakiris go on to explain that perception remains relatively stable because we do not expect our “selves” to change significantly over time, although they acknowledge the possibility of breakdowns in cases such as schizophrenia, dementia, delirium, and multiple personality disorder.

Although Seth and Tsakiris do not discuss it, the subjectivity of perception may also apply to gender. This

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possibility was proposed by the clinical psychologist Jaco van Zyl, who describes gender dysphoria as an affective-perceptual disturbance involving the body.⁴⁵ Under certain circumstances (e.g., the comorbidities that are common in gender incongruence), one's gender perception might be affected.

The nature of own-body perception in gender incongruence was investigated by Jamie Feusner et al., who carried out an fMRI study and found weaker functional connections within the self-body identification network in (adult) transgender persons than in controls.⁴⁶ They suggest that the connection between body perception and self-identification might be more reflective than reflexive, that is, gender identity might be a conclusion rather than a genetic or developmentally determined feature; such a conclusion supports the hypothesis of perception described above.

A striking example of the role of (mis)perception in gender identity was described by V.S. Ramachandran and Paul McGeoch, who examined the existence of phantom penises (the sense of having a penis when there isn't one) in transgender individuals.⁴⁷ Transgender males experienced phantom penises *before* they acquired a penis through surgery while transgender females experienced a lower incidence of phantom penises after surgery than would be experienced by people whose penis was removed for other reasons, for example, cancer. This further supports the idea that gender incongruence might involve misperception.⁴⁸

Though attributing gender incongruence to misperception, it needs to be clear that this is not meant to diminish or discount how real it is to those suffering from gender dysphoria, just as other body dysmorphias, such as phantom appendages and anorexia, are very real. Furthermore, once formed, it may be difficult to change one's perception, since one's perception shapes how subsequent information is received and indeed may result in a "rewired" brain. The (mis)perception hypothesis may help explain why various biological contributions only cause a relatively low frequency of gender incongruence.

Development of a Sense of Self in Adolescence

How would adolescence be a time of susceptibility to gender incongruence? Erik Erikson's eight stages of identity development throughout an individual's lifespan provides a possible explanation.⁴⁹

These stages are marked by a psychosocial crisis, which the individual must navigate to continue their development. The fifth stage, which occurs during adolescence, is a crisis of identity. Rapid body changes accompanied by sexual awakening force the individual to seek a sense of belonging. If this stage is not successfully navigated, the individual is susceptible to identity confusion. The overreaction to this lack of identity includes over-identifying with a particular group and becoming intolerant of others. Erikson wrote,

*It is difficult to be tolerant if deep down you are not quite sure that you are a man (or a woman), that you will ever grow again and be attractive, that you will be able to master your drives, that you really know who you are ...*⁵⁰ (italics added)

James Marcia further develops Erikson's identity stage, describing two categories of individuals with identity confusion. Those who have not experienced the crisis of identity are foreclosed, retaining their parents' identity and possibly being threatened if their childhood beliefs are challenged. By contrast, those still in the crisis period are preoccupied and struggle to make commitments.⁵¹ While Marcia does not address gender, the latter group may be particularly susceptible to gender incongruence.

Anatomical changes in brain development during adolescence may affect one's sense of gender. A study by Nienke Nota et al. found functional brain connectivity differences between transgender adults and controls but not between prepubescent children with gender dysphoria and controls.⁵² This suggests that anatomical changes associated with incongruent perception are not early-onset but develop over time. In childhood, subcortical areas such as the amygdala and striatum are associated with cue-driven impulsivity. As the child enters adolescence, the brain matures rapidly as the neocortical (conscious) area continues to develop (it is not complete until well into one's twenties⁵³), providing better cognitive processing of emotional cues—that is, the adult thinks things through before responding.⁵⁴ This may allow adults to be more resistant to stimuli that may trigger late-onset gender incongruence.

Accompanying the cognitive aspects of brain maturation in adolescents is the development of the mind-body connection and one's sense of self. Ivanka Savic and coworkers demonstrated a correlation between self-body perception and gender dysphoria. Using fMRI, they found that transgender men and

women showed weaker structural and functional connections in the anterior cingulate-precuneus and right occipito-parietal cortex, regions known to process self-body perception.⁵⁵ In contrast, homosexuals exhibited intermediate connectivity between heterosexual cisgender and transgender. In another study, they found that maturation of the cerebral cortex of transgender individuals is reduced in the occipito-parietal cortex and sensory motor cortex, which are regions thought to encode one's own body image and body ownership.⁵⁶ One possible implication of these findings is that a less-developed mind-body connection weakens the sex-gender connection and makes the individual more susceptible to factors that lead to gender incongruence.

Jennifer Pfeifer and coworkers used functional magnetic resonance imaging (fMRI) to compare regions of the brain that were active when children and adults were asked questions related to their self-knowledge (e.g., does a particular feature describe themselves or someone else).⁵⁷ In children, this activity preferentially activated the (immature) prefrontal cortex, while in adults the temporal lobes were preferentially activated. The authors interpreted this to mean that the children in this study relied more on active self-reflection and less on stored self-knowledge than adults when responding to these cues, again making adults more resistant to gender incongruence.

As individuals reach puberty, it appears that they can be susceptible to gender incongruence if the development of their mind-body connection is impaired. This can occur in several ways, including mental stress such as anxiety, depression, or social isolation. It can also occur in the context of autism. These factors will be discussed next.

Social Isolation, Touch, and the Mind-Body Connection

Social context and social interactions play important roles in the development of an individual's mental development and beliefs.⁵⁸ An abnormal social context could affect one's sense of self and gender. The mind-body connection is harmed by social isolation and the lack of physical contact. Consider touch perception, in which different types of receptors present in the skin provide information about temperature, pain, light touch, stretching, et cetera, to the sensory homunculus, which "maps out" the body to allow the individual to know what part of the body has been stimulated, and how. However, there is another

type of touch sensation, which was discovered in two patients who, due to neuropathy, lacked the primary touch sensations but retained a different kind of touch receptor, called C-tactile fibers.⁵⁹ These receptors respond to gentle touch, particularly slow stroking on hairy skin, and provide a pleasant but nonlocalized sensation. Rather than activating the sensory cortex, these fibers activate the insular cortex, which is thought to be important for body ownership.⁶⁰

This type of touch is thought to be important for social development and in the construction of a sense of self and body ownership.⁶¹ It can be illustrated by the rubber hand illusion. In this illusion, the experimenter gently strokes both the participant's hand, which is hidden from view, and an adjacent rubber hand, which is in view. Over time, the participant transfers the sense of ownership from their real hand to the rubber hand.⁶² Notably, Pawel Tacikowski et al. used the same stroking approach on participants wearing virtual reality goggles while lying on a table. If the goggles portrayed a person of the opposite sex while their bodies were being stroked (in a nonsexual way), their sense of gender also shifted to the opposite sex,⁶³ suggesting that, under certain conditions, one's sense of gender could be somewhat fluid.

Physical contact between friends is frequent in both boys and girls, although expressed differently, and is important for the development of body ownership and development of mind-body ownership. That contact can be lacking in adolescents who are socially isolated, particularly if the cause of their social isolation is anxiety or depression or not fitting in with their peer group. It is difficult to distinguish cause and effect, but a recent study found that transgender and gender-questioning adolescents spent an astounding 4.5 and 3.4 more hours respectively of total recreational screen time per day than their peers!⁶⁴

Autism and Gender Incongruence

Differences in brain development can also have an effect on the development of one's sense of gender. Emily Thrower et al. reviewed studies that looked at the correlation between autism and gender dysphoria⁶⁵ and found that the proportions of people with gender incongruence on the autism spectrum ranges from 6–26%, higher than the 2.47% frequency found in the general population.⁶⁶ Similarly, the frequency of gender incongruence among those with autism is over four times higher than in the general population.⁶⁷

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The basis for this increased co-occurrence is unclear, though it has been extensively studied. A review of the literature by Juliette Bouzy et al. considered elevated fetal testosterone, less internalization of gender roles and identification with a gender group, and cognitive differences that might affect one's awareness of social pressures for gender conformity.⁶⁸ Assia Riccioni et al. described shared features between autism and gender incongruence, including impaired social behavior and theory of mind, repetitive thoughts/obsessions, cognitive inflexibility, and altered sensory processing.⁶⁹ People on the autism spectrum tend to display a reduced gender self-concept.⁷⁰ There is a diminished mind-body connection⁷¹ and processing of social touch by C-tactile fibers in people with autism.⁷² The effect of the latter on development is compounded by the fact that autistic people tend to avoid social touch, likely due to a hyper- or hypo-sensitivity.⁷³

Comorbidities, Mind-Body Connection, and Gender Perception

There is a higher incidence of comorbidities associated with gender incongruence, which this article will argue affects gender stability. The result of gender minority stress on the mental health and suicidal ideation of transgender people has been established.⁷⁴ One study of college students found a 4.3-fold higher incidence of mental health problems in those with gender incongruence.⁷⁵ Other studies had similar findings.⁷⁶ A survey of children at a clinic in Australia found the comorbidities listed in Table 1.⁷⁷

Family conflict	66%
Parental mental illness	63%
Separation from important figures	60%
Bullying	54%
Depression	62%
Anxiety	63%
Behavior disorders	35%

It is difficult to disentangle cause and effect in this phenomenon. The presence of gender dysphoria may contribute to or result from these mental health comorbidities. The latter may be the case in this study, in which children first sensed their incongruence before age 10. Even in these cases, however, the comorbidities may hinder the resolution of gender dysphoria in adolescence by impeding the development of the mind-body connection. Because of the

uncertain relationship between the dysphoria and comorbidities, Mark Yarhouse and Julia Sadusky encourage counselors to first address comorbidities and see if the dysphoria resolves.⁷⁸

Gender-Affirming Care

Medical care for those with gender incongruence should ideally be evidence based, accessible, and offered by knowledgeable and culturally sensitive medical providers.⁷⁹ The present standard of care is transitioning. It involves three phases: social transition, which allows the individual to present as the opposite sex without surgical or pharmacological treatment, puberty blockers (for children) and cross-sex hormones, and surgery. The latter might involve some combination of mastectomy, metoidioplasty, or phalloplasty (construction of a penis by two different means), or vaginoplasty (construction of a vagina) in addition to cosmetic surgeries to help the individual "pass" as the opposite sex. This review focuses primarily on the first two phases.

Transitioning in Children and Adolescents

There is a debate about the ethics of treatment of children and adolescents with gender dysphoria, primarily because their brains have not fully developed and the evidence suggests that they cannot fully grasp the consequences of transitioning: lifelong dependence on hormones, loss of fertility, numerous surgeries with frequent complications, and loss of sexual function. A small qualitative study of 14 individuals considering puberty suppression and their parents found that most of the parents, clinicians, and adolescents did not fully understand puberty suppression and its consequences.⁸⁰ A second small study found that only 24% of transgender youth expressed a wish to have their own biological child.⁸¹ A third small study found that transgender adolescents had lower rates of romantic relationships and sexual experiences than the general population, which may affect their valuation of sexual relationships.⁸²

Social Transition

Social transition involves efforts to disguise one's sex or resemble the other sex. Initial practices include changing one's name and pronouns, dressing androgynously, altering one's hair style, and changing one's voice to sound more like the desired sex. As puberty develops, further measures may be taken, though not without deleterious physical consequences. One study of chest binding to flatten the

breasts found over 97% incidence of pain, shortness of breath, bad posture, and/or skin problems.⁸³ The practice of tucking to disguise male genitalia involves bringing the testes up into the inguinal canal and pushing the penis back toward the rectum, and can lead to infection, testicular pain, issues with urinary flow, and lowered sperm count.⁸⁴

Although the long-term effects of social transition are uncertain,⁸⁵ Mark Yarhouse and Julia Sadusky propose social transition as a way of allowing the patient to manage their dysphoria.⁸⁶ Yet James Morandini et al. examined the effect of social transition in over 200 children and adolescents but found no significant effects on their mental health status.⁸⁷ Social transitioning also does not appear to affect long-term outcomes. James Rae et al. compared children who socially transitioned earlier (due to more intense dysphoria) with those who transitioned later and found no difference in gender identification and preferences between earlier- and later-transitioning individuals.⁸⁸

Puberty Blockers and the Dutch Protocol

Gender-dysphoric children face a dilemma when reaching puberty. Development of secondary sex characteristics could intensify the dysphoria but as described earlier, in most cases, the incongruence desists. The puberty blocker treatment was proposed to buy time to see if the incongruence would desist, without the added stress of the development of secondary sex characteristics.⁸⁹ If the incongruence persists, then the child would take cross-sex hormones. The evidence is now clear that this approach, while well-intended, is problematic.

The regulation of sex hormones involves the hypothalamus, anterior pituitary, and the gonads (fig. 1). Neurons in the hypothalamus release gonadotropin-releasing hormone (GnRH) to the anterior lobe of the pituitary, where it activates cells called gonadotropes, which release luteinizing hormone (LH) and follicle-stimulating hormone (FSH) into the bloodstream. This occurs in both males and females. These two hormones regulate reproductive functions in the testes or ovaries, including the production of sex steroids such as testosterone, estrogen, and progesterone. In males, constant levels of testosterone are maintained through a negative feedback system, in which the sex steroids and the protein inhibin suppress the production of GnRH, LH, and FSH. In females of reproductive age, increased estrogen production by developing ovarian follicles overrides this negative feedback, resulting in ovulation. Thus, in

females, the levels of estrogen and progesterone rise and fall over the course of the menstrual cycle.

The extent of hormone production can vary over time. For instance, there is also a prenatal wave of GnRH production, which causes a surge in testosterone production in baby boys. This testosterone enters the brain where it is involved in masculinization of the brain.⁹⁰ When someone reaches puberty, GnRH levels increase, stimulating the release of LH and FSH, and the sex steroids. The age at which this occurs is affected by external and internal factors, occasionally resulting in delayed or precocious puberty.

Puberty can be suppressed pharmaceutically by the GnRH *agonists* (GnRHa) leuprorelin/leuprolide or triptorelin, colloquially known as puberty blockers.⁹¹ GnRH is normally released in pulses and acts on gonadotropes in the anterior pituitary to cause them to release LH and FSH. However, overstimulation by constant (rather than pulsatile) levels of GnRHa downregulates GnRH receptors on these cells, which in turn decreases LH and FSH, and then sex steroid hormone production by the gonads. GnRHa is not needed for female-to-male transitioning, as testosterone overrides any effect of estrogen. The combination of GnRHa and estrogen can be used off-label in adolescent or adult biological males to suppress testosterone production as part of their transition to a female identity. It is also used in children to suppress the development of puberty in the Dutch protocol.

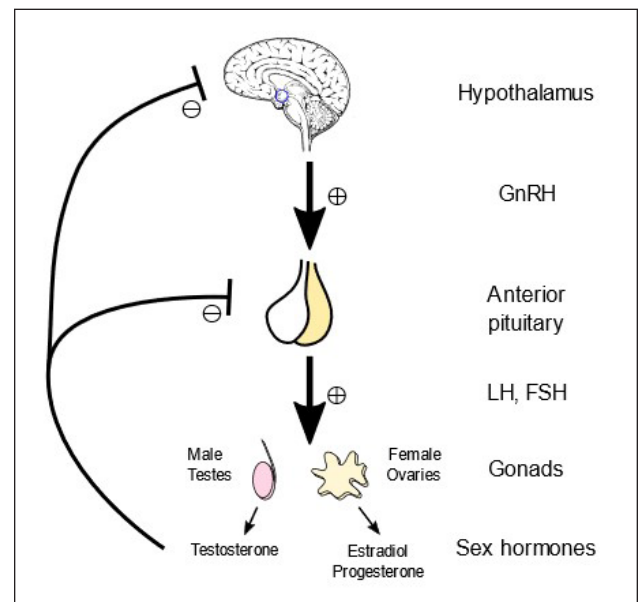


Figure 1. Simplified diagram of regulation of the hypothalamus-pituitary-gonad (HPG) axis. See text for details. By Artoria2e5 – Own work, CC BY 3.0, <https://commons.wikimedia.org/w/index.php?curid=81460023>.

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Because individuals with gender dysphoria may experience intensified distress as secondary sex characteristics develop during puberty, GnRHa may be used to suppress puberty in order to buy time to see if the incongruence persists. The use of puberty suppression for this purpose was first reported in the Netherlands.⁹² A female with gender dysphoria was treated with puberty suppression starting at age 13 and testosterone treatments at 18, followed by several sex-reassignment surgeries over the course of several years, including mastectomy, hysterectomy, and metoidioplasty (construction of a small penis). Overall, the patient was satisfied with the transition, although they suffered some depression due to an inability to function sexually. The patient also was of above average intelligence (and later became a physician), had no other serious psychopathology, and concomitantly received extensive counseling.

This single case was followed by a larger trial, now known as the Dutch Protocol,⁹³ which reported some success. This protocol was soon adopted in many other countries as a treatment for gender dysphoria, though the trial was critiqued as producing data of limited reliability.⁹⁴

Critique of Puberty Blocker Studies

Given that so much of gender-affirming care is based on the Dutch Protocol, which is a single study, it is important to review this study, in order to evaluate the quality of the evidence that was presented, particularly in the use of this protocol in other clinical settings. The Dutch Protocol study suffers from many weaknesses, which are summarized in table 2. First, this was just a single study, comprising 70 individuals. Although one needs to start somewhere, this single study was undertaken to establish the Dutch protocol—yet other studies did not show the same success. A study of 324 sex-reassigned persons in Sweden found that, although patients' dysphoria was alleviated, there was still a high risk of mortality, suicidal behavior, and psychiatric morbidity.⁹⁵

Small sample size
Lack of a control group
Counseling support adds confounding variables
Loss of patients to follow-up
Short study duration
Defective assessment tool

A similar study conducted in Finland involving 3,665 individuals seeking gender reassignment found that gender reassignment did not change the risk of needing subsequent psychiatric assessment,⁹⁶ and a follow-up study of 2,083 gender-referred patients did not find a correlation between gender dysphoria and suicide mortalities, but they did find a correlation with psychiatric morbidity (note the use of objective measurements and the larger patient numbers than those reported in the Dutch Protocol study).⁹⁷ Finally, a smaller study in the UK on 47 individuals with gender dysphoria found rates of deterioration and improvement over a period of 36 months similar to the rates found in larger studies.⁹⁸

A second critique of the Dutch study was that all the patients remained gender dysphoric and went on to cross-sex hormone treatments.⁹⁹ This contrasts with gender dysphoric children not on puberty blockers, who experience a frequency of desistance ranging from 61 to 90%,¹⁰⁰ the majority of whom are same-sex attracted. Indeed, almost ninety percent of this study group reported attraction to their natal sex; that is, they were same-sex attracted and not transgender.¹⁰¹

While the authors of this study noted but did not attempt to explain the connection, Kelley Drummond et al., in a separate study of biological females, noted a high (88%) desistance rate; in addition, they found a positive correlation between the severity of the childhood dysphoria and the probability of same-sex attraction.¹⁰² Subsequent studies with puberty blockers have found a similarly high, but not complete, persistence of gender incongruence.¹⁰³ A long-term follow-up study of 307 transgender youth by Kristina Olson et al., found just 2.5% desistance after five years.¹⁰⁴ These participants had undergone a complete social transition and received puberty blockers during the course of the study.

The authors of the Dutch study argued that the persistence they observed was due to the careful selection of patients who had genuine gender dysphoria.¹⁰⁵ While it may be possible that these researchers were exceptionally adept at identifying those whose gender incongruence would persist, it could be argued that the reorganization of the brain that occurs at puberty due to sex hormones is a more likely explanation for the desistance, which had been prevented by the puberty blockers used in the Dutch study. Indeed, the administration of puberty blockers did not ameliorate the dysphoria, a result that was expected by the authors of this study.¹⁰⁶ If the likely

cause of the incongruence was related to the hormonal milieu *in utero*, it is possible that the reactivation of the hypothalamus-pituitary-gonadal axis at puberty could reset the brain to resolve the incongruence. The influence of pubertal testosterone in gender perception was described earlier in this paper in a study of genetic males who had female or ambiguous genitalia due to a deficiency in the conversion of testosterone to dihydrotestosterone (the latter is required for male genital development). These individuals were raised as females but roughly half of them changed to a male gender as their testosterone levels increased in adolescence or early adulthood.¹⁰⁷

A third critique of this study was that there was no control group. This was an observational study, following the patients after treatment. Other studies acknowledge the lack of a control group but state that this is for “obvious ethical reasons”: withholding treatment would be unethical.¹⁰⁸ However, this reasoning begs the question by assuming the very hypothesis they are testing. An additional concern is that since all participants in this study received puberty blockers, one cannot discount the placebo effect.¹⁰⁹ Not only did these patients receive treatment, which would improve their hope for relief, but changes in hormone levels have profound effects on psychological function and brain anatomy, possibly giving the impression that their dysphoria is resolving.¹¹⁰ The effects of treatments on the person’s mood is a phenomenon described by Jack Turban as gender euphoria.¹¹¹

Another concern about this study is that participants in this trial received extensive counseling support to address any psychological or social problems. Such support is obviously a good thing, but it prevents one from distinguishing the benefit of puberty blockers from the benefit of counseling support. This is an important point because it may account for the fact that when the Dutch protocol was adopted in the UK, the patients did not receive a similar level of counseling support¹¹² and the Dutch results were not replicated.¹¹³

Yet another weakness of the Dutch study and many other studies is the loss of participants to follow-up. Provided that the reason for the attrition is unrelated to the treatment received, this would not be a concern. However, in this case, those not satisfied with the treatment would be less likely to persist in the trial and thus attrition could skew the data. In a follow-up to the original Dutch study, 55 of the original

70 patients one year after cross-sex hormone treatment found good overall psychological function.¹¹⁴ Six of the remaining fifteen original patients were not yet eligible for surgery and thus were not included,¹¹⁵ but no reasons were listed for the remaining nine. While an attrition rate of 13% is reasonable, other studies that claim success of puberty blockers have higher attrition rates. For example, one study lost 65% of its participants over the 18 months of their trial.¹¹⁶

One of the greatest concerns with this original study is the assessment tool that was used. Participants filled out a survey that, in part, assessed the participants’ degree of gender dysphoria and perception of their body image at three times during the trial: before puberty suppression (T0), upon initiation of cross-sex hormones (T1), and one year after gender-reassignment surgery (T2). There were two versions of the survey, one for males and one for females, but patients at time T2 used the opposite survey that they used at T0 and T1. Consequently, the sex-specific nature of the survey made it impossible to compare conditions before and after treatment.

Another part of this survey assessed psychological functioning, including depressive symptoms, anger, anxiety, and behavior and emotional problems. Many measures on this portion of the assessment showed statistically significant improvement from T0 to T2. The authors did not show a statistical comparison between T0 and T1 vs. T1 to T2; however, an examination of the relevant table in their paper (table 3) shows approximately half of this improvement occurring between T0 and T1, even though the gender dysphoria had not abated nor was there any physical change, since cross-sex hormones had only just been administered and there wasn’t time to have effects.¹¹⁷ Although it is impossible to know for certain in the absence of a control group, this improvement in subjective measures suggests that much of the improvement could be attributed to the placebo effect. Moreover, measures of depression, anger, and anxiety did not change over the course of the study.

All this criticism is not to fault the authors of the Dutch Protocol study, as the scientific community was interested in preliminary findings, and this research group intends to publish a longer-term study when the data become available. As senior author Peggy Cohen-Kettenis noted, “A truly proper follow-up needs to span a minimum period of 20 years.”¹¹⁸ Whether such a study will be feasible, given the challenges in keeping track of participants for so long, is

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an open question. Nevertheless, at this time, the evidence does not support the use of puberty blockers to improve the plight of those suffering from gender incongruence.

The GRADE Criteria for Evaluating Evidence

The quality of current evidence for transgender healthcare may be assessed using the GRADE approach developed by Gordon Guyatt et al., which employs evaluation criteria to arrive at a reliable objective assessment of the quality of evidence for medical procedures.¹¹⁹ One component of this assessment is the kind of data that is being collected, whether it is objective or subjective. Reporting on patients' perceptions is less reliable than objective measurements of things such as mortality, fertility, and other physiological measurements. The seriousness of the outcomes also contributes to the quality of evidence; for example, changes in the number of suicides constitute stronger evidence than measurements of suicidality, which may be temporary and not lead to actual suicide. Similarly, the seriousness of the side effects of treatment needs to be considered. Mortality and the loss of fertility are more serious than weight gain or social anxiety. One also needs to consider all the possible side effects of a treatment.

The GRADE criteria also consider study design. Randomized trials (with negative controls and blinding of researchers) provide stronger evidence than observational studies. In randomized trials, the data to be collected are decided upon beforehand, whereas in observational studies, researchers record findings after the fact; this method can result in biased data analysis. Observational studies, in turn, are stronger than individual case studies, which have no control and are more susceptible to confounding variables. Moreover, a greater number of participants generates more confidence in the findings. Finally, a longer study duration will detect effects that may be missed in shorter studies.

In transition studies, longitudinal studies of at least five years' duration are important to assess the long-term impacts of transitioning. Loss of participants during follow-up can skew the data, especially in studies of gender transition (those with negative outcomes are less likely to be willing to respond to further requests to participate). Wide confidence intervals, due to small sample sizes or wide variability in results, and small effect sizes also weaken confidence in one's conclusions. Finally, possible conflict of interest and publication bias can call into

question the objectivity of the study (negative results are often not published or accepted by journals).

While there are many studies that claim to support the use of gender-affirming care, whether puberty blockers or for medical transition,¹²⁰ the above weaknesses consistently arise.¹²¹ Using the GRADE criteria, Guyatt concluded that the evidence supporting puberty blockers was very weak.¹²²

More recently, the Cass Review commissioned by the UK National Health Service (NHS) under the direction of Dr. Hilary Cass, a pediatric endocrinologist, reported that the evidence for gender-affirming treatments was weak.¹²³ It cited the low quality of evidence and equivocal findings in the available studies. In response, the NHS has indefinitely banned the use of puberty blockers for gender incongruence in children under the age of 18.¹²⁴ This decision parallels similar legislation in the Canadian province of Alberta, roughly half of the US states, and several European countries. In response, WPATH (World Professional Association for Transgender Health), an organization that publishes standards of care for professionals working in gender health,¹²⁵ issued a critical response to the Cass Review, arguing that Cass lacks personal experience in transgender healthcare, the report contains no new research, several countries disagree with the findings of the review,¹²⁶ and the double-blinded clinical trials called for by the review would be unethical because the control group is withheld from receiving beneficial treatments.¹²⁷

Cass responded to these criticisms, pointing out that the team carrying out the review met with over 1,000 individuals, some in one-to-one meetings, others in groups, interviewing both people with lived experience of gender dysphoria and organizations working with LGBTQ+ children.¹²⁸ Moreover, this review was not intended to contain new research but a survey of existing studies. Finally, claiming that double-blinded clinical trials withhold beneficial treatments is a circular argument because trials are needed to determine whether the treatments are beneficial in the first place.

Cognitive Effects of Puberty Blockers

The effect of puberty blockers on the brain has been reviewed by Vincent Prévot et al.¹²⁹ and Nimmi Wickramasuriya et al.¹³⁰ In rams, suppression of testosterone reduces emotional reactivity, hampers adjustment to environmental change, and delays maturation of cognitive processes (e.g., information

processing, which affects the motivation to approach and avoid objects).¹³¹ In male mice, puberty blockers “increase hyperlocomotion, change social preference, and increase neuroendocrine stress responses. In female mice, they increase hyponeophagia (a measure of anxiety) and despair-like behavior.”¹³² In female macaques, puberty blockers make the monkeys more submissive and less affiliative but also less anxious.¹³³

Although weakened by small studies and overreliance on case studies, the available evidence suggests that puberty blockers also have cognitive and emotional effects in humans. There are GnRH receptors in the amygdala (emotion processing), hippocampus (memory function), and olfactory system (smell processing).¹³⁴ When puberty blockers were used to treat 15 girls with precocious puberty, their IQ decreased by approximately 7 points,¹³⁵ consistent with a decrease of 9 IQ points reported in a transgender patient.¹³⁶ Other studies indicate adverse effects on visual working memory,¹³⁷ executive function,¹³⁸ and mood.¹³⁹ GnRHa administration has been shown to increase depression and alter reward processing, although it is not clear from this particular study whether this results from the decrease in GnRH effectiveness or from altered sex steroid hormone levels.¹⁴⁰ Adult Down syndrome patients experience improved cognition and brain connectivity when their reduced levels of GnRH were treated with pulsatile GnRH therapy.¹⁴¹ This agrees with the correlation between decreased cognition (and olfaction) and reduced levels of GnRH in a mouse model of Down syndrome. The decreased cognition is abolished by restoring normal GnRH levels. That treatment rescues cognitive deficits suggests that the cognitive effects of puberty blockers might be reversible.

Luteinizing hormone (LH) receptors are also expressed in several regions of the brain involved in cognition, including the hippocampus and cortex.¹⁴² One review suggests that elevated levels of LH in the blood of older men and women (due to the lack of negative feedback because of reduced levels of estrogen or testosterone; see fig. 1) may contribute to cognitive decline in Alzheimer’s disease.¹⁴³

It may seem contradictory that *decreased* GnRH and *increased* LH have similar cognitive effects, since the former induces the latter. However, Jeffrey Blair et al. reconciled this apparent discrepancy by showing that circulating LH levels in the *bloodstream* inversely correlate with LH levels in the *brain*.¹⁴⁴ This is con-

sistent with a study indicating that removal of the ovaries with or without a hysterectomy increases the risk of dementia.¹⁴⁵ This correlation is consistent with the removal of negative feedback on GnRH and LH levels upon loss of estrogen, increasing LH levels in the blood. There are also receptors for FSH in the brain¹⁴⁶ and, although there is no direct evidence in humans, the perturbation of FSH signaling in mice results in depression-like behaviors¹⁴⁷ and affective disorders.¹⁴⁸

Other Physiological Effects of Puberty Blockers

Puberty is an important physiological developmental stage, which can be missed by suppressing puberty.¹⁴⁹ However, the limited studies (reviewed by Jo Taylor et al. as part of the Cass Review¹⁵⁰) of the physiological effects of puberty blockers used for gender dysphoria documented relatively minor effects, although a few may be cause for concern.

The first involves bone mineral density. The growth spurt that occurs during puberty is largely driven by rising levels of sex steroids, primarily estrogen (testosterone in males is converted to estrogen by the enzyme aromatase). Puberty blockers prevent this upregulation and therefore result in reduced bone density.¹⁵¹ When sex steroid levels increase again upon transition, with cross-sex hormones or by stopping puberty blockers, the bone density does not fully recover to normal levels.¹⁵² Reduced height is one consequence.¹⁵³ This effect on bone density is compounded by the fact that bone density in transgender youth is low even before treatment.¹⁵⁴ It is not clear why this is the case, but possible reasons include decreased physical activity and a poor diet, which are common in these individuals.¹⁵⁵

The second adverse effect involves future reproductive function, although this has not been well studied in humans, as only a minority of gender-incongruent children feel that future fertility is important.¹⁵⁶ Therefore, few preserve their sperm or eggs before treatment.¹⁵⁷

Female mice treated with puberty blockers and testosterone can still produce fertilizable eggs that develop into normal looking pups, suggesting that female fertility is not jeopardized by puberty blockers.¹⁵⁸ However, a recent study (available as a preprint) found a dramatic change in human testicular cell populations in response to puberty blockers over a two-year timeframe.¹⁵⁹ This includes the expected

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drastic reduction of germ cells, which develop into mature sperm, and a dramatic reduction in the number of Sertoli cells, which are important for sperm development as they regulate the sperm production process in response to signals from the pituitary. As the samples were obtained from biopsies, it is unclear if sperm production would recover when puberty blocker treatment ceases. However, the authors state that “gland atrophy and abnormalities from the histology data raise a potential concern regarding the complete ‘reversibility’ and reproductive fitness of spermatogonial stem cells.”¹⁶⁰

Cross-Sex Hormone Treatments

The transitioning process itself also involves alteration of the hormonal environment. The intended effect is to cause development of the desired secondary sex characteristics, but the hormonal treatment also affects brain structure and function.¹⁶¹

There are several cross-sex hormone options for biological males, which differ in cost (government subsidies differ among countries), accessibility, and prescriber preference.¹⁶² The options include puberty blockers to block testosterone production for adolescents and children beginning puberty (Tanner stage 2) and in adolescence. As puberty blockers are considerably more expensive than the other options, they are unlikely to be used unless covered by health insurance. Much cheaper and safe to use, provided fluid intake is maintained, is spironolactone. It is normally used as a diuretic since it acts in the kidney to reduce sodium reuptake and thus water retention, but spironolactone, at higher doses, also blocks the binding of testosterone to its receptor. Spironolactone may be taken in combination with estrogen since negative feedback from estrogen suppresses LH production, thus further reducing the levels/action of testosterone (fig. 1). An even more effective cross-sex hormone, not licensed in the US but used in much of the rest of the world, is cyproterone acetate. It can be used in combination with estrogen as it inhibits testosterone and stimulates progesterone. It also elevates levels of the hormone prolactin (with negative consequences on sexual function and bone mass¹⁶³) and is associated with a worse cardiovascular risk profile.¹⁶⁴

Cross-sex hormone treatment for biological females is simpler. Testosterone administration overrides the effects of estrogen and suppresses the production of LH and thus estrogen by negative feedback (fig. 1).

Both male-to-female and female-to-male treatments are associated with a variety of adverse drug reactions,¹⁶⁵ including elevated intracranial pressure,¹⁶⁶ erythrocytosis (excess red blood cells),¹⁶⁷ pelvic pain,¹⁶⁸ and pelvic floor and sexual dysfunction.¹⁶⁹

Given that hormonal treatments for transitioning have irreversible anatomical and physiological effects, there should be clear, evidence-based guidelines to direct care. However, a systematic review of guidelines used for these treatments (undertaken as part of the Cass Review) found this not to be the case.¹⁷⁰ Most guidelines did not systematically review empirical evidence or offer evidence-based recommendations, and they did not make it clear how the treatment should be implemented. A companion review assessed the associated guidelines for psychological and medical interventions and found that guidance for psychological care should be provided and management of the overall healthcare of prepubertal children should be limited, among other concerns.¹⁷¹

Surgical Treatments

Genital surgeries such as vaginoplasty and phalloplasty, colloquially known as bottom surgeries, were discussed in the previous article in this journal,¹⁷² so will only be briefly reviewed here. Vaginoplasties are the formation of a vagina, primarily by inversion of skin from the penis or using intestinal tissue.¹⁷³ Complications include a lack of depth of the neovagina and reduced sensitivity and desire. Carmen Kloer et al. reviewed studies on the success of vaginoplasties using the female sexual function index (FSFI), a multidimensional self-report instrument to measure sexual satisfaction in which scores range from 2 to 36, and a score of 26.5 or less indicates sexual dysfunction.¹⁷⁴ Out of 17 studies measuring FSFI in vaginoplasty recipients, only two had scores above 26.5.

Phalloplasty is the formation of a penis, either from existing genital tissue (metoidioplasty), or from elsewhere (flap-based phalloplasty).¹⁷⁵ Metoidioplasty is more straightforward and results in an undersized penis with good sensitivity. Flap-based phalloplasty uses skin from different locations, is more complicated, and results in an anatomically sized penis, but which lacks sensitivity. Depending on the technique used, roughly a third of the surgeries experience complications, primarily to urethral reconstruction.¹⁷⁶

Most transgender individuals do not undergo bottom surgery. Bitá Tristani-Firouzi et al. in 2022 surveyed preferences for and barriers to gender affirming surgeries in the US.¹⁷⁷ Only 20% of trans women underwent bottom surgery, while an additional 67% were interested in it. Only 4% of trans men underwent bottom surgery, although a further 50% expressed interest in it. By contrast, almost half of trans men had a mastectomy, with almost everyone else in this survey expressing an interest in having one. The primary barriers to surgery were potential complications, cost, and not feeling ready.

Mental Health Outcomes After Gender-Affirming Care

Many studies indicate improved mental health after gender affirmation treatments, although a recent meta-analysis of longitudinal studies found no consistent improvements in depression or suicidality.¹⁷⁸ Unfortunately, the available studies also suffer from small sample sizes, subjective measures of benefits, lack of controls, comorbidities, high dropout rate, and short study durations.¹⁷⁹

For example, Rikke Simonsen et al. evaluated 104 adult individuals from the Danish national registry (ages >30 years, 56 MtF, 48 FtM) who underwent sex reassignment surgery from 1978–2010.¹⁸⁰ Of these, 7 had psychiatric morbidity before and after surgery, 23 had morbidity before but not after, and 17 had morbidity after but not before surgery, although the reasons for psychiatric morbidity may differ before vs. after surgery. There were also two suicides, but their clinical significance was unclear due to the small sample size. The strengths of this study include its longer time frame (>10 years after surgery) and the fact that the participants were adults who likely experienced persistent gender dysphoria for many years.

Anthony Almazan and Alex Keuroghlian analyzed data from a large 2015 US Transgender Survey of over 27,000 adults.¹⁸¹ Of this group, 3,559 had undergone at least one type of gender-affirming surgery at least two years prior, while a further 16,401 endorsed a desire for surgery but had not yet received it. As the latter also received other gender-affirming care, such as counseling, puberty blockers, and hormone therapy, they served as controls to reduce the impacts of these confounding variables. They found significant decreases in psychological distress and suicidal ideation within the month prior to the survey. In contrast, *lifetime* mental health (suicidal ideation, suicide attempts, smoking, and alcohol use) was

not affected by gender-affirming surgery. Despite the large sample size and exemplary control group, the study is limited by its use of data from survey responders, who might not be representative of the overall population. A similar phenomenon may be at play in a recent US study by Wilson Lee et al., which found an increase in suicide attempts after the implementation of laws restricting gender-affirming care to minors.¹⁸² Because of the study design (a survey recruiting participants through social media), this study could not measure actual suicides.

In contrast, Diana Tordoff et al. conducted a short time-frame (< 3 months) survey of 104 13-to-20-year-olds (63 FtM, 27 MtF, 14 nonbinary or unknown).¹⁸³ Though there was high variance in the results, they found 60% (95% CI: 0.17–0.95) lower odds of depression and 73% (95% CI: 0.41–2.51) lower odds of suicidality but no change in anxiety (95% CI: 0.41–2.51) twelve months after surgery. Nevertheless, this study was limited by its short time frame, low participation (only two-thirds of those invited chose to participate), and high attrition (37.5%) in the study.

Finally, Amy Green et al. collected data from a large 2020 US online survey of LGBTQ youth aged 13–24, including 11,914 who identified as transgender or nonbinary.¹⁸⁴ Within this sample, they compared youth who would like to receive gender-affirming hormone treatment (4,537 individuals) with those who were receiving this therapy (1,216 individuals). Those receiving hormone therapy showed reduced depression over the previous two weeks (61% vs. 75%), exhibited reduced suicidality in the past year (44% vs. 57%), and made fewer suicide attempts in the past year (15% vs. 23%). The large sample size points to the validity of these differences, although the authors acknowledged that they were unable to determine whether hormonal treatment caused the improvements in mental health, in that those with more suicidal ideation may have been less able to obtain hormone treatment in the first place.

Regret and Detransitioning

The incidence and experiences of those who decide not to continue with their transition is a difficult topic to assess, and detransitioners are not well studied.¹⁸⁵ One may feel regret but choose not to detransition, as they have invested so much in the process that they do not want to go through the biological and social ordeals of detransitioning.

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Reasons for regret and/or detransitioning include discrimination, discomfort with one's new sex, medical complications, or realizing that there was a different cause for their distress than gender dysphoria—for example, that an individual is gay and not trans.¹⁸⁶ In any case, the transition procedures are not easily reversible. Estrogen stimulates breast development and testosterone, a deeper voice, facial hair, bone remodeling, and vaginal atrophy, which makes intercourse painful. These changes do not regress upon detransitioning. Both sexes may have difficulty passing (that is, it is obvious that a person is transgender), due to the secondary sex characteristics that developed before transitioning. Mastectomy produces scars.

It is difficult to determine the incidence of regret or of detransitioning.¹⁸⁷ Many clinics do not carry out follow-up studies on their patients after treatment.¹⁸⁸ Because of dissatisfaction with the results of their transition, detransitioners are unlikely to return to the clinic where they received their initial treatments and thus would be lost to follow-up. However, some work has been done in this area. Riittakerttu Kaltiala et al. followed the national medical records in Finland from 1996–2019, using individuals who discontinued cross-sex hormones as a proxy for detransitioning.¹⁸⁹ They found a 7.9% discontinuation rate overall, with a higher rate among more recent transitioners. Christina Roberts et al. examined hormone treatments in the US Military Health System from 2009 to 2018 and found a hormone continuation rate of 70.2%, that is, a discontinuation rate of 29.8% at four years.¹⁹⁰ These discontinuation rates contrast with a meta-analysis done by Valeria Bustos et al., who found just 77 out of 7,928 patients (~1%) expressed regret after surgery. The reasons for the large differences between the different studies are unclear but may involve the different criteria used to determine regret. The studies reviewed by Bustos et al. address regret directly using patients' responses, while the studies by Kaltiala et al. and Roberts et al. assumed that cessation of hormone treatments was equivalent to desistance.

Christian Perspectives on Gender Incongruence

It should not be surprising that the debate over gender has not left the church unaffected. Christians suffering from gender incongruence may feel isolated and unable to discuss their condition with others. They may be exposed to hurtful comments from well-

meaning but uninformed pastors and other church leaders, which may lead them to reject the Christian faith. Thus, it is important for Christian leaders to be knowledgeable about this topic in order to effectively serve these members of the body of Christ.

As in the secular culture, there is a variety of views on gender incongruence in the church. Mark Yarhouse, a clinical psychologist specializing in gender, describes three frameworks for conceptualizing gender incongruence: the integrity, disability, and diversity frameworks.¹⁹¹ This was described in more detail in the earlier review¹⁹² and is summarized here.

The *integrity position*, most familiar to theologically conservative Christians, is essentialist. Using various scripture passages, it roots gender in sex and sexual complementarity between males and females. As with homosexuality, any expression of gender incongruence is viewed as sinful and a rejection of how we were created male and female.

The *disability position* likewise roots gender in creational norms (biological sex) but recognizes that in this fallen world there is disorder, which can include gender incongruence. This view differs from the integrity view in that the incongruence is not viewed as immoral but as a disorder, deserving of compassion rather than judgment. Like other psychological conditions, the possibility of a biological contribution to gender incongruence affects the degree of (but does not eliminate) responsibility that the individual bears for navigating their condition. They may try to minimize its influence on their lives. However, if an individual cannot function in their biological sex, this view would allow transition to alleviate the suffering.

The *diversity position* holds to the view that the biblical accounts of the creation of humans as male and female are descriptive but not prescriptive. They do not indicate that gender is binary but rather a spectrum. Consequently, differential gender expression, whether due to biological causes or a choice rooted in one's personal autonomy, may be celebrated.

Final Comments

Numerous questions about the biological and cognitive bases of gender dysphoria and transgender healthcare persist; these are not likely to be answered soon. Similarly, among the diverse range of views on the nature and causes of gender, none of them clearly articulates its exact nature. This article proposes the

hypothesis that one's sense of gender is a perception that develops over time in a top-down process that is dependent on the development of one's mind-body connection. If that development is hampered—either by prenatal hormonal influences or by conditions such as autism, social isolation, depression, or anxiety—that person may be susceptible to gender incongruence. Alternatively, these comorbidities that result from pre-existing gender incongruence could hinder the development of the mind-body connection. In either case, the mind-body connection strengthens in adolescence, sometimes leading to desistance.

The application of animal studies to the human experience of gender is limited but the prenatal hormonal milieu may play a role as well. This is illustrated by the case of Greg Eilers's adult gender incongruence, which was resolved using cross-sex hormones.¹⁹³ Nevertheless, such cases are rare. Genetic¹⁹⁴ and epigenetic¹⁹⁵ studies have identified genes associated with gender incongruence, but we do not know how they affect gender.

While most agree that early-onset and adolescent-onset gender incongruence are different, some argue that the two are the same, and that those who experience the so-called late-onset variant simply come to an understanding of their condition at a later stage in their life. However, the differences between early- and adolescent-onset gender incongruence (which include different sex ratios) suggest that different mechanisms are involved. Considering that the early-onset variant resolves in most cases, to resolve a child's dysphoria without undergoing the various steps of transition would be a desirable goal, not to mention preventing the need for possible detransitioning afterward. However, it is possible for some transgender people to live fulfilled lives after transitioning, as may be seen from the examples of the Christian theologian Austen Hartke¹⁹⁶ and the musician Kristina Rizzotto.¹⁹⁷

Defining gender incongruence as a misperception doesn't tell us what to do when it occurs. While it is beyond the scope of this article, counseling is obviously a vital component of treatment for gender dysphoria, including reducing suicidal ideation,¹⁹⁸ and there are new approaches that could help resolve one's dysphoria without resorting to the invalidated methods and harmful effects of conversion therapy.¹⁹⁹ One approach is to address the comorbidities that may hamper the development of one's mind-

brain connection. Another approach, psychodynamic psychotherapy, encourages the patient to explore their gender before proceeding with gender-affirming care.²⁰⁰ Florence Ashley contends this approach is tantamount to conversion therapy because, like conversion therapy, it sees gender incongruence as a disorder and seeks to resolve it without altering the body.²⁰¹ In contrast, Robert D'Angelo maintains that psychotherapy empowers young people to develop creative solutions to their difficulties and promotes agency and autonomy, although this is complicated when working with minors.²⁰² Until further clarity is reached on the benefits of psychotherapy, well-meaning but ill-informed people should demonstrate extreme caution and refrain from asserting that counseling is all that is needed to "fix the problem."

Currently, the evidence surrounding gender-affirming care is weak. The variability between studies, including the use of different criteria, makes comparisons and meta-analyses difficult, and some data, like the longer-term cognitive effects of puberty blockers, still need to be collected. People are individuals and differ one from another, so the causes and possible treatments will vary. Newer studies, and especially long-term studies, are needed to strengthen the evidence and provide best practice protocols.

In the interim, there is a danger of oversimplifying when trying to gain an understanding of this complex issue. Disagreements will persist, but we need to be united in the goal of acting in the best interests of those who suffer from this condition.

Notes

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