Gynecologic Oncology 149 (2018) 33–42

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Review Article

Biological origins of sexual orientation and gender identity: Impact on health☆

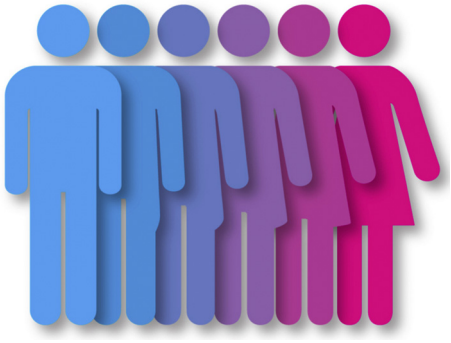
Katherine A. O'Hanlan [a,*], Jennifer C. Gordon [b], Mackenzie W. Sullivan [c]

[a] Laparoscopic Institute for Gynecology and Oncology (LIGO), 4370 Alpine Rd. Suite 104, Portola Valley, CA 94028, United States
[b] University of Tennessee Health Sciences Center, Memphis, TN, United States
[c] University of Virginia School of Medicine, Charlottesville, VA, United States

HIGHLIGHTS

- Sexual orientation is biologically conferred in the first trimester of pregnancy.
- Gender identity is biologically conferred during the middle trimester of pregnancy.
- Health risks are conferred by the social stigma of minority status.
- Gynecologic Oncologists can provide quality care to these minority individuals.

GRAPHICAL ABSTRACT



ARTICLE INFO

Article history:
Received 23 August 2017
Received in revised form 30 October 2017
Accepted 7 November 2017

Keywords:
Gender identity
Transgender
Transsexual
Sexual orientation
Homosexuality
Discrimination

ABSTRACT

Gynecologic Oncologists are sometimes consulted to care for patients who present with diverse gender identities or sexual orientations. Clinicians can create more helpful relationships with their patients if they understand the etiologies of these diverse expressions of sexual humanity. Multidisciplinary evidence reveals that a sexually dimorphic spectrum of somatic and neurologic anatomy, traits and abilities, including sexual orientation and gender identity, are conferred together during the first half of pregnancy due to genetics, epigenetics and the diversity of timing and function of sex chromosomes, sex-determining protein secretion, gonadal hormone secretion, receptor levels, adrenal function, maternally ingested dietary hormones, fetal health, and many other factors. Multiple layers of evidence confirm that sexual orientation and gender identity are as biological, innate and immutable as the other traits conferred during that critical time in gestation. Negative social responses to diverse orientations or gender identities have caused marginalization of these individuals with resultant alienation from medical care, reduced self-care and reduced access to medical care. The increased risks for many diseases, including gynecologic cancers are reviewed. Gynecologic Oncologists can potentially create more effective healthcare relationships with their patients if they have this information.

☆ The corresponding author is a surgeon in independent private practice. There are no conflicts of interest in the writing of this manuscript, but the author reports that she is a consultant and speaker for Baxter, Medtronic, BD and Cooper. There is no off-label use of any medical device in this manuscript. No financial support was received for any part of this manuscript.

* Corresponding author.
E-mail addresses: Kate.OHanlanMD@gmail.com (K.A. O'Hanlan), jgordo22@uthsc.edu (J.C. Gordon), mws2bn@virginia.edu (M.W. Sullivan).

https://doi.org/10.1016/j.ygyno.2017.11.014
0090-8258/

Contents

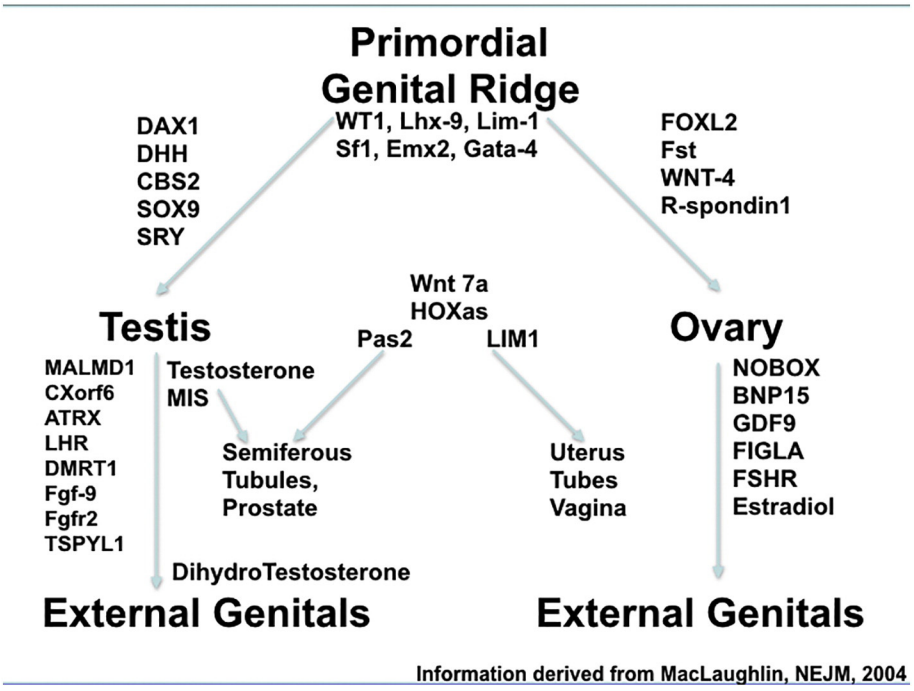


Fig. 1. Sex determination and gonadal differentiation require many proteins and endocrine stimulants to engender a fetus.[1] [1]MacLaughlin DT, Donahoe PK. Sex determination and differentiation. *N Engl J Med*. 2004;350 [4]:367–378.

1. Introduction

Gynecologic Oncologists sometimes care for patients with diverse sexual orientations and gender identities. Understanding the scientific basis of this diversity helps build the therapeutic relationship necessary to optimize patient health. This manuscript synthesizes the large body of published multidisciplinary evidence on sexual orientation and gender identity, from embryology, to endocrinology, genetics, genomics, anatomy, pediatrics, psychiatry, gynecology and neurobiology. Most of these findings have been replicated by others, but have not yet been collated into a singular report for clinicians.

1.1. Prenatal development

Both autosomal and sex genes variably express many proteins (WT1, Sf1 most notably) in the first trimester, which direct gonadal differentiation into ovaries (DAX1, Wnt4 from x chromosomes) or testes (SOX9, SRY, Fgf-9 from Y chromosomes). The gonads then begin their descent (Wnt 7a, Hox, among others), and variably release the hormones that permanently imprint the developing fetal brain, and confer physical attributes and physiologic abilities along a spectrum of "sexually dimorphic", e. g. female-typical or male-typical, patterns [1] (see Fig. 1).

Most typically, a female fetus secretes little or no testosterone. Their external genitals remain female-like and the genital tubercle stops enlarging after 12 weeks. They typically identify as female, exhibit girl-like play patterns, develop feminine bone structures and body motion, and exhibit increased empathy, verbal fluency, perceptual speed and accuracy, associative memory, and a sexual orientation toward men [1].

Most typically, a male fetus secretes testosterone, which is converted to dihydrotestosterone and estradiol, imprinting the brain and causing continued growth of the genital tubercle into a phallus and continued descent of the testis into the scrotum [2]. They identify as male, exhibit boy-like play patterns, develop masculine visuospatial abilities, bone structures and body motion, vocal range, math abilities, and an orientation toward women [1]. While these differences in gender are significant as measurable population means between the two ends of the spectrum, they do not indicate any generalizable limitations on an individual's capabilities or potentials.

Since the genitals differentiate in the first trimester, and the brain becomes imprinted in the latter half of gestation, it is possible for the fetal brain to be imprinted differently than the genitals [3]. As an experimental example, male rats treated *in utero* with a potent estrogen/testosterone inhibitor, demonstrate female-typical sexual behavior as adults but have normal male anatomy [4]. Many other biological correlates for transsexualism have been identified.

Most often, however, the fluctuating levels of hormones and proteins during early fetal development confer a set of sexually dimorphic features as continuous variables on a spectrum, between masculine and feminine. If only the thirty-seven proteins and two hormones mentioned above can vary from high to average to low, there are 3 to the thirty-seventh power, or over 450 quadrillion [11], possibilities of variation. As children mature, this innate imprinting expresses as genital anatomy, gender identity, sexual orientation and other physiologic capabilities and natural preferences along a continuum, between masculine and feminine. Thus, the concepts of binary heterosexual or homosexual, male or female, represent the furthest ends of the spectrum, with the vast majority of humans clustered near the heterosexual and gender-congruent ends of the spectrum, and a small percent falling in between, along the many mid-points of the spectrum [2].

1.2. Sexually dimorphic traits and skills

Prenatal hormone variations have been shown to correlate with many neurologic, physiologic and anatomic traits that typically express together and are congruent with sexual orientation and gender identity, demonstrating a mutual biological causality [1].

No evidence that orientation is learned

To my knowledge, no peer-reviewed published scientific studies support the hypotheses that life experience causes homosexuality, that sexual orientation is learned, that there is a psychological cause of homosexuality or that sexual orientation is chosen. On the other hand, a tremendous body of literature clearly demonstrates that gay, lesbian, and bisexual people experience their sexual orientation as being an innate quality of themselves, akin to race, hair color or height. In addition, attempts to change one's sexual orientation from homosexual to heterosexual through so-called "conversion therapy" consistently fail and can have a significantly negative impact on the individual's mental health.

Ellen Haller, MD
Professor of Clinical Psychiatry
Interim Site Director, Parnassus Campus, Psychiatry Residency Training Program
UCSF Department of Psychiatry
San Francisco, CA
(approved 3/16/2017 by personal electronic communication)

1.2.1. Hand bone structures

Girls typically have slightly longer index fingers compared to their ring fingers (high 2D:4D ratio), and boys' index fingers are relatively shorter (lower 2D:4D) [5]. While many social factors may also influence childhood behaviors, there is a significant correlation between the 2D:4D ratio and gender role play, aggression-proneness, preferred toy types, as well as both color and subject choice in drawings [6–8]. In females, a lower 2D:4D ratio correlates with lesbian orientation [9] and female-to-male transgender status [10], along with many other male-typical sexually dimorphic skills and traits [11] [12]. The 2D:4D ratio is lower, or masculinized, in females with congenital adrenal hyperplasia (CAH) also suggesting a prenatal hormonal influence [11]. Many other bone measurements of female-to-male transsexuals are in the intermediate range between male and female typical [13]. Lesbian monozygotic twins have lower 2D:4D ratios than their respective heterosexual co-twins [14]. Lower 2D:4D is correlated with increased levels of fetal testosterone relative to estradiol and insulin-like factor 3 in second trimester amniocentesis fluid, suggesting prenatal Leydig cell testosterone secretion [5,15].

Gay male co-twins have higher 2D:4D than their heterosexual male co-twins, confirming that the digit effect was not genetic (since they are identical), but likely epigenetic, resulting in disparate internal prenatal hormonal milieus [16]. The 2D:4D ratio is higher, or feminized, in male-to-female transsexuals [17].

1.2.2. Hearing

Studies of spontaneous otoacoustic emissions (SOAEs) confirm that hearing is a sexually dimorphic trait. Control males, men with microphallus or similar disorders of sexual differentiation (DSD's), and women with CAH all produced fewer spontaneous SOAEs – the male typical pattern – than control females [18]. Women with Complete Androgen Insensitivity Syndrome (CAIS), having no androgen receptors, also have female-typical SOAEs [18]. The hearing of male homosexuals is less androgenized and female homosexuals more androgenized compared with heterosexual counterparts [19]. Females with opposite-sex co-twins also demonstrate masculinized hearing abilities suggesting cross-amniotic membrane transfer of amniotic fluid hormones [20]. These auditory differences correlate strongly with other sexually dimorphic traits such as aggression–proneness [6,21], spatial ability, sexual orientation, and gender nonconformity [22].

1.2.3. Other sexually dimorphic traits

Adult lesbians have more male-typical features such as spatial [23] and visuospatial skills [24], less body dissatisfaction [25] and lower rates of eating disorder [26], lower voice pitch [27], greater athletic and throwing skills [28], possibly lower pain thresholds [29], more

ambidexterity [30] or left-handedness [31], and a higher sex drive than heterosexual women [32]. Gay males have more feminine-typical traits such as fluid body movement [33], self-objectification [34], eating disorders [35], letter and verbal fluency [36], body dissatisfaction [35], speech patterns [37], and fingerprint patterns [38].

1.2.4. Brain structure and function

Sexual differentiation of the brain begins in the second trimester and likely completes postnatally [7]. Because brain differentiation occurs months after differentiation of genitals, the differentiation of the body in one direction does not necessarily reflect the direction of the differentiation of the brain [39].

In 1992, Allen reported a correlation between male sexual orientation and a female-shifted or larger anterior commissure size, among the first reports suggesting a neurobiological origin for sexual orientation [25,40,41]. Male-to-female transgender individuals, regardless of their hormone use, also have a female-shifted or smaller volume of the central subdivision of the bed nucleus of the stria terminals (BSTc), a region typically larger in males and essential for sexual behavior [42]. Diffusion-weighted magnetic resonance imaging shows widespread differences in white matter microstructure of transgender individuals measuring between that of gender-congruent males and female controls [43]. Corpus callosum asymmetry has been correlated with fetal testosterone excess and sexually dimorphic cognition and behavior [44]. Lower 2D:4D ratio is associated with masculinized reduced gray matter volume in the dorsal anterior cingulate cortex, the region of emotional regulation [6]. In functional brain studies, homosexual males and females demonstrate cerebral asymmetry and functional connections, known to be set by prenatal hormones, in more opposite-sex-typical patterns [45]. Female-to-male transgender individuals, who were not yet taking any androgenic hormones, also expressed male-typical cognitive function and cerebral lateralization [46].

1.3. High prenatal androgen and females

Congenital adrenal hyperplasia and polycystic ovarian syndrome can provide important clinical evidence about the effects of excess prenatal androgen exposure in females [47].

Compelling evidence for a contribution of prenatal hormones to the development of homosexual orientation

This is illustrated best by the syndrome of congenital adrenal hyperplasia (CAH), a genetic condition in which female fetuses are exposed to unusually high levels of androgens produced by their own adrenal glands. A number of studies have shown increased homosexual orientation in women with this condition compared to healthy controls. More specifically, my team has demonstrated that women with this syndrome show markedly increased masculinization of behavior in general as well as markedly increased homosexual attraction, both in (statistically significant) correlation with the degree of prenatal androgen excess. This finding strongly supports a causal contribution of hormones to the development of sexual orientation, presumably in interaction with one or several of the many hormone-sensitive genes involved in the sexual differentiation of the brain.

Heino F. L. Meyer-Bahlburg, Dr. rer. nat
Director, Program of Developmental Psychoendocrinology
Associate Director, Division of Gender, Sexuality, and Health
Professor of Clinical Psychology (in Psychiatry)
New York State Psychiatric Institute & Department of Psychiatry, Columbia University
1051 Riverside Drive, Unit 15
New York, NY 10032
USA
(approved April 24, 2017 by personal electronic communication)

1.3.1. Congenital adrenal hyperplasia (CAH)

CAH is an adrenal enzyme deficiency (C-21 hydroxylase) in the cortisone synthesis pathway, resulting in an excess of androgenic precursors in the blood [48]. It was historically called "adrenogenital syndrome", because female infants were born with large clitorises and more male-typical play patterns, voices, and some of the skeletal structure typical for boys [49]. Many later identified as lesbian or bisexual in adulthood, and about 5–10% were transgender, particularly if their CAH was the more severe, salt wasting type [50,51]. More recently, CAH females with prenatal androgen exposure have been confirmed to demonstrate more male-typical play behavior in childhood [8], virilized voice [27], and gynephilic dreams [52] or homosexuality in adulthood [50,51].

1.3.2. Polycystic ovarian syndrome (PCOS)

PCOS is an endocrine condition comprised of lifelong elevated levels of luteinizing hormone, testosterone, androstenedione and dehydroepiandrosterone sulphate [53]. Females with polycystic ovaries have been observed to have more hirsutism, virilized bone structures, intersex genitals [54], same-sex orientation and female-to-male transgender status than unaffected controls [55]. Studies of female-to-male transgender individuals reveal heightened serum levels of adult male hormones, and higher incidences of PCOS [55], and CAH [50].

1.3.3. Females with male co-twins

Females with a fraternal male co-twin can be exposed to excess prenatal androgen [56] due to testosterone from the male twin's amniotic fluid diffusing to the female's amniotic fluid [21]. This is associated with androgenized changes in play patterns [21], neuroacoustic functioning [46], bone structure [15], teeth structure [57], subsequent risk of increased alcoholism [58] and reduced eating disorders [26], brain anatomy [59], and sexual orientation [60]. In fact, males with opposite-sex co-twins have an increased chance of homosexual orientation, likely due to receptor competition through amniotic fluid crossover by estrogens from the female fetus [61].

1.3.4. Exogenous and Xenohormones

From 1940 to 1970, the endocrine disruptor diethylstilbestrol (DES) was prescribed for women in the first trimester of pregnancy to prevent miscarriage. It increased the chances of lesbian orientation in the female offspring [62]. Even exogenous estrogens can cause mounting behavior in female rats, likely due to aromatization of the excess estrogens in the brain into testosterone [63]. In human brain tissue culture, antiepileptic drugs have been shown to enhance estrogen receptors, and can affect the sexually dimorphic nuclei [64]. Prenatal exposure to phenobarbital and phenytoin has been linked to higher rates of undescended testes, genital anomalies, male homosexuality, and male to female transgenderism [65]. Exogenous sources of androgen-like substances have been identified in steroid-supplemented fish [66], poultry [67], or beef [68], and may have unknown effects on the sexually dimorphic traits if consumed in large quatities during gestation.

1.4. Low prenatal androgens and males

Fetal testosterone levels measured from amniotic fluid of children whose behavior was later studied at age 4 showed a strong inverse correlation with empathy scores in males [69]. Reduced prenatal testosterone may be one possible etiological factor in the development of male-to-female transsexualism [17].

1.4.1. The fraternal birth order effect

It is well established that the greater number of older brothers a male has, the more likely he will have been gender-atypical as a child [70], have an adult sexual orientation toward men [71], or recognize an adult androphilic transsexual identity [72]. One prevailing theory is transplacental antibody formation that accumulates an effect over

time. Proteins, such as SRY, encoded from the fetal Y chromosome, cross the placenta and are believed to stimulate formation of maternal antibody directed against "foreign" male proteins [71]. With each successive male pregnancy, more antibodies are induced that ultimately reach the male fetus' circulation, blunting the serum levels or effect of androgens. In research on heterosexual men, among the 20% who reported "some" homosexual feelings, a significantly greater number of older brothers was observed [73]. More recently, some studies have suggested that a maternal immune response may also cause low fetal weight, possibly influencing sexual orientation and gender-atypical behavior and identity among males [74].

Prenatal Factors Impact Development of Sexual Orientations in Humans

The most broadly established finding in the area of etiological research on homosexuality is that biological older brothers increase the odds of homosexuality in later-born males, even if they were reared in different households.
In contrast, sisters, stepbrothers or adoptive brothers have no effect on sexual orientation. This result argues against various family environment explanations that have been advanced, for example, the notion that younger brothers are more likely to be gay because they are conditioned by sex play with older brothers.
The main connection between older brothers and younger brothers reared separately is the fact that they successively occupied the same uterus.
Older brothers affect the probability of homosexuality in later-born males while they themselves are still fetuses by stimulating, in some mothers, antibodies to male-specific cell-surface proteins—antibodies that can influence the brain development of male fetuses in subsequent pregnancies.
This fraternal birth order effect has been demonstrated in studies conducted in the United States, Canada, the United Kingdom, the Netherlands, Spain,

Italy, Turkey, Brazil, Iran, and Independent Samoa, in subjects born over a 130-period (1860 to c. 2000).
Two studies have estimated the proportion of gay men who owe their sexual orientation to prenatal, immunologic mechanisms at 15–29%.
The available evidence suggests that
the remaining percentage of gay men (probably including all those with no older brothers) owe their sexual orientation to other biological causes such as inherited genes.
There is also a mysterious connection between homosexuality and left-handedness in both men and women. Although there is no agreement on what gives rise to this connection, it clearly arises during prenatal life, because handedness is established during the first trimester.

Ray Blanchard, Ph.D.
Department of Psychiatry
University of Toronto
(approved April 24, 2017, by personal electronic communication)

The fraternal birth order effect

"The most consistent biodemographic correlate of sexual orientation in men is the number of older brothers (fraternal birth order). The mechanism underlying this effect remains unknown. Only number of biological older brothers, and not any other sibling characteristic, including non-biological older brothers, predicted men's sexual orientation, regardless of the amount of time reared with these siblings. These results strongly suggest a prenatal origin to the fraternal birth order effect."1-35

Anthony F. Bogaert, PhD
Professor, Dept. of Community Health Sciences and Psychology,
Brock University, St. Catharines, Canada L2S 3A1
(approved 3/20/2017 by personal electronic communication)

1.5. Genetics of orientation and identity

1.5.1. Identical twin studies

Twin studies confirm that gender identity and sexual orientation have a genetic link [75]. When a monozygotic twin is lesbian, 48% of the co-twins were also lesbian, as compared to 16% orientation concordance in dizygotic co-twins, 14% of non-twin sisters, and 6% of adopted sisters [76,77]. Similarly, more monozygotic than dizygotic twin boys express concordance in homosexual orientation [78,79]. In a study of 96 monozygotic pairs and 61 dizygotic pairs, gender identity dysphoria was shown to have clear hereditary correlates and no environmental correlates [80].

1.5.2. Epigenetics

Epigenetic differences, the modulation of gene expression by chemical binding of inherited DNA, can account for the discordant expressions of traits in monozygotic twins [16]. Modulating the effects of excess androgens on female fetuses, and enhancing androgen sensitivity in male fetuses "canalizes" fetal development in a sex-typical fashion, reducing concordance of monozygotic twins' expression of sexual orientation [81]. Sexually dimorphic expression of certain microRNAs has been tied to sexual orientation. Androgen genes and the miRNAs involved in their regulation have been shown to have a sexuality-concordant effect [82]. These epigenetic modifications and the variability in the degree of their expression/modulation contribute to the non-binary, "spectrum" effect of sexually dimorphic traits and orientations.

1.5.3. Chromosomal evidence

Many gay males have a gay maternal uncle, suggesting some association with the maternally inherited X chromosome. Homosexual orientation among males has been correlated with the gene Xq28, on the long arm of the X chromosome [83]. A recent study of over 700 men, half of whom were gay, showed a significant correlation between a gene in the 7q36 region with sexual orientation [84]. Other X chromosome mutations, as well as 47XYY and 47XXX, have also been correlated with gender identity dyssynchrony [85,86,87].

1.5.4. Complete androgen insensitivity syndrome (CAIS)

In CAIS, 46XY males have functioning undescended testes and normal testosterone levels, but a defective or absent gene for the androgen receptor. Males born with CAIS can have a micropenis [88], with partial to phenotypically complete bodily feminization [89] and are usually psychosocially female and oriented toward men [90]. Individuals with CAIS can report more gender identity dyssynchrony [91] and have a higher, more feminized, 2D:4D digit ratio [11].

Genetic and biological etiology

Recent biological and psychological research suggests that genetic and biological factors, including prenatal hormones, influence gender-related traits that predict adult sexual orientation. For example, developmental psychology studies show that childhood gender nonconformity is strongly associated with later adult homosexuality. Boys who display more "feminine" interests and behaviors than typical boys, and girls who display more "masculine" interests and behaviors than typical girls are statistically more likely to become homosexual adults. Such findings suggest that early biological factors mold childhood gender-related behaviors and later adult sexual orientation.
Twin studies reveal a significant genetic component to variations in sexual orientation, and many animal studies show that mating behaviors targeted at males or females are influenced by prenatal hormonal factors and linked to subsequent variations in brain structures."

Richard A. Lippa, PhD
Professor of Psychology
California State University, Fullerton
Fullerton, CA 92834
(approved June 15, 2017 by personal electronic communication)

1.5.5. 5 alpha-reductase deficiency syndrome (5ARDS)

5ARDS is a rare autosomal recessive condition with 33 possible mutations whereby testosterone cannot be converted to its most active form, dihydrotestosterone, essential for the formation of fetal male external genitalia [92]. Family lines with recurring offspring with 5ARDS have been identified in the Dominican Republic, Papua New Guinea, Turkey, and Egypt. An XY baby born with 5ARDS often has ambiguous or more female-typical genitals and is raised as a girl. Many have male-typical play patterns and develop a male gender identity as children [93]. Then, at puberty, with surging levels of androgens, their bodies and genitals masculinize and they will typically then identify as male [94]. This condition has been unrecognized in some individuals until long after removal of their testes and surgical reduction of their phallus into a clitoris, a practice now discouraged.

1.6. Differences of sexual development (DSD's)

Some children are born with genitals appearing between male- and female-typical, precluding confident sex assignment at birth [90]. DSD (formerly "intersexed") can be idiopathic, or later attributed to excessive androgen exposure in females (as with congenital adrenal hyperplasia) and lower androgens in males from genetic aberrations of the sex chromosomes, hypothalamic or gonadal dysfunction, CAIS, or 5ARDS, above.

The historical approach to ablatio penis [95], or penile agenesis [96], or to children with ambiguous genitals (small phallus or macroclitoris) was to surgically shorten the glans, remove the testes and assign the child to be a girl. Prepubertal surgery to shape the ambiguous female genitalia into a clitoris has resulted in gross adult genital disfigurement, arousal and orgasmic dysfunction, and permanent psychologic injury [97]. The more ethical modern approach is support and education of the concerned family, allowing the child to mature and express their gender identity, and offer surgical modification only to the consenting adolescent or adult [49,98].

1.7. Social influences

While genetics, epigenetics and prenatal hormones begin to explain the diversity of sexual orientation and gender identity, the underlying causes are unknown for the vast majority of homosexuals, gender nonconforming persons and individuals with DSD.

Heterosexual, homosexual and transsexual individuals report that they are certain they were "born that way", and prefer their status [99]. Bisexual individuals are born with an orientation nearer the center of the spectrum, attracted to both men and women, though not necessarily equally, or always. To date, no social, or environmental effect has been significantly correlated with orientation or identity. From neuroanatomist Simon Levay in the April 2011 issue of Frontiers of Neuroendocrinology, "The book on social influences [on sexual orientation and gender identity] is not closed, so much as it is blank" [75]. From neuroscientist D. F. Swaab in Functional Neurology: "There is no proof that social environment after birth has an effect on gender identity or sexual orientation" [3]. The American Psychiatric Association removed homosexuality from a psychopathological designation in 1973 [100]. In the 2013 DSM-5, the American Psychiatric Association affirmed that "gender nonconformity is not in itself a mental disorder, but a discontent with the assigned gender and the apparent gender of their bodies" [101]. Since then, sexual orientation and gender identity have gradually become protected as statuses that should not endure discrimination or lack of accommodation by state and federal laws [102].

Convenience survey data from the 1980's revealed that lesbians frequently experienced ostracism, rough treatment, and disdain from their medical practitioners [103]. As a result, many lesbians did not disclose their orientation to their physician, and withdrew from routine health maintenance visits [104]. A survey of California physicians in 1986 revealed that about 23% had significantly negative attitudes toward their homosexual patients [105]. At that time, most medical schools provided under three hours training about issues of orientation and none on transgender status [106].

In 1995, presentations of snowball survey data were made to members of the Department of Health and Human Services which revealed that lesbians appeared to have more risk factors for heart diseases and cancers than heterosexual women. Presenters requested that more valid health information of this minority group be provided through ongoing nationally-funded probability surveys by including a question about sexual orientation [107]. The Institute of Medicine (IOM) convened a committee in 1997 which confirmed that lesbians as a minority population did deserve research focus by the National Institutes of Health (NIH) [108]. Three years later, with no national probability studies reporting any demographic information about lesbian citizens, the Office of Research on Women's Health in the NIH convened the Scientific Workshop on Lesbian Health to study how the IOM Report could finally be implemented [109]. In 2001, the NIH requested that all ongoing NIH-funded national probability projects stratify their demographic data by sexual orientation, especially those focusing on HIV, cancer, cardiovascular diseases, infectious diseases, life-span development, and mental health [110]. The Women's Health Initiative (WHI) subsequently piloted a question of sexual orientation to some of its participants. Upon finding the very question inoffensive to their research participants, the WHI included a question of sexual orientation in its final survey instrument [111]. The Nurses' Health Survey (NHS) similarly included a question of sexual orientation, with both surveys providing a high-quality demographic of lesbians' health issues in the new millennium [112].

2. Health impact

2.1. Social issues through the lifespan

Children as young as 10 years old can recognize their burgeoning attraction to a particular gender [113]. By high school, about 10% of Minnesota girls say they are unsure about their orientation, with 4.5% reporting lesbian attraction and 1% having engaged in lesbian behavior [114]. The Committee on Adolescence of the American Academy of Pediatrics states that while homosexual youth are attempting to reconcile their feelings with some of the negative societal attitudes, they still must then confront a "lack of accurate knowledge, [a] scarcity of positive role models, and an absence of opportunity for open discussion. Youth who self-identify as lesbian or gay during high school report higher rates of unintended pregnancy, victimization, sexually risky behaviors, substance use and all at an earlier age than their peers" [115]. Rejection by family and peers based on common misconceptions about homosexuality may lead to isolation, domestic violence, depression, school or job failure, run-away behavior, homelessness, and suicide [116]. In a CDC health questionnaire administered in Massachusetts to all students in grades 7–12, 10.5% reported bisexual behavior and were at significantly increased risk for having had unprotected sex at last encounter, a history of forced/unwanted sex, past-year depression and past month drug use [117]. Among 3816 Minnesota high school girls surveyed, the 1% who identified as lesbian, bisexual, or questioning had a significantly higher prevalence of pregnancy (12%) and physical or sexual abuse than heterosexual adolescents [118]. In one study 30% of lesbians and 19% of heterosexual women experienced abuse as a youth [119], while 19% of lesbian adults and 9% of heterosexual women reported sexual abuse or rape [119]. Multiple other reports suggest that lesbians may have experienced more physical and sexual abuse as children by their male relatives, and physical abuse as adults from male strangers [120–122]. Such abuses are a risk factor for suicide [123,124]. Gay, lesbian, bisexual, or questioning youth were 3.41 times more likely to report a suicide attempt [125], particularly in the setting of severe peer and family harassment [126]. Victimization of young transgender

individuals is also positively associated with depressive symptomology and suicide [127].

The American Psychological Association, American Psychiatric Association, National Education Association, American Academy of Pediatrics and many other mental health, child health and education groups report the "unanimity of the health and mental health professions on the normality of homosexuality" [128]. They endorse age-appropriate education about family diversity (same-gender, grandparent, etc) for all children in elementary school, school-supported after-school clubs such as gay-straight alliances, and counseling to help lesbian youth navigate their teens without smoking, drug abuse, sexual risk-taking, unintended pregnancy, or social alienation. Cultural and familial relaxation of social pressures on girls to conform to rigid gender roles will also reduce alienation, risk of suicidal symptoms, and improve peer acceptance and support. Thus far, there have been no national probability studies that stratify by transgender status—these are needed.

2.2. Gynecologic issues

While the overall incidence of vaginitis and sexually transmitted diseases appears quite low in the lesbian population, all types of STD's have been diagnosed [129]. Therefore standard STD surveillance and testing should be similarly applied to all females, especially if symptomatic with pelvic pain and vaginal discharge [130].

The two national probability surveys of women have offered high-quality data on lesbian health in middle age and post-menopause. The NHS-II respondents were between ages 31 and 49 [112], and the WHI respondents were between ages 50 and 79 [111]. The Nurses' Health Study and the Women's Health Initiative both report that the women who identify as lesbian or who have sex with women have higher rates of alcohol use, self-reported abuse histories, and higher rates of cigarette smoking, depression, and antidepressant use [111,112]. Both NHS-II and WHI studies demonstrated significantly lower parity among lesbians and bisexuals, with nulligravidity rates of 51–76% for lesbians and 19–49% for bisexuals, compared with 8–22% for heterosexuals [111,112]. Based on their sexual behaviors and family histories, male to female transgender individuals will need pap smears of their neovaginas, HPV vaccinations, and screening mammograms similar to biological females, as they can develop vaginal dysplasia/cancer, and breast cancer [131].

2.3. Fertility issues

Serum hormone levels of testosterone, androstenedione, estradiol and progesterone of lifelong lesbians, lesbians who realized their orientation at a later age, and heterosexual women were measured at the same points in the menstrual cycle and revealed no differences [132], Fertility workup and treatments should be similar in lesbians and heterosexual women [133]. Conception rates among lesbians should be similar to heterosexual women using donated sperm [134].

Transgender female-to-male individuals will typically initiate testosterone therapy following the World Professional Association for Transgender Health Standards of Care. They can conceive and deliver children if they temporarily discontinue their androgens or they can use their preserved oocytes if harvested prior to gender-confirming surgery. Most will undergo bilateral mastectomy, hysterectomy and salpingoophorectomy [135]. Few will have phalloplasty, which is insensate, as their clitoris typically substantially increases in size from the testosterone, and remains sensitive and functional.

2.4. Cardiovascular disease and obesity

Lesbian women weigh more, eat slightly fewer fruits and vegetables, exercise similarly, have similar rates of hypertension, and higher reported rates of heart attacks and smoke more than heterosexual women [111,112]. Lesbians with higher BMI were more likely to have a lower socioeconomic status, and exercise less [136]. They had accurate perceptions of being overweight, and often reported a health condition that limited their exercise [111,112]. Transgender female-to-male individuals can be assumed to have similar risk demographics for heart disease and cancers as aging men, in general, given that they are taking testosterone with levels in the normal male range [137]. Transgender male-to-females should use transdermal estrogen to avoid the risk of thrombus formation from oral estrogens [137].

2.5. Ovarian, endometrial and cervical cancers

In general, preventive health screening for gay, lesbian, and transgender patients should be consistent with the standards for the organs they possess. Lower parity and less use of oral contraceptives, combined with higher rates of obesity [111,112] may give rise to a higher rate of tubal/ovarian/peritoneal carcinoma and endometrial carcinoma in the lesbian population [138] [111, 112],. Although hysterectomy rates appear similar between lesbians and heterosexual women in the WHI [111], stigma may inhibit lesbians from obtaining routine care [139], resulting in higher risk of more advanced disease and lower cure. Culturally sensitive interventions are needed to both prevent obesity and decrease BMI in older lesbians [140]. Any vaginal bleeding or abdominal symptomatology in transgender individuals should be thoroughly addressed based on the organs that are *in situ*, as ovarian carcinoma and uterine carcinoma have been missed in the transgender population.

The same Pap smear guidelines should be applied to all patients with a cervix, but many lesbians do not comply with these standards [141]. Although most lesbians have had sex with men at some time in their lives as a source of Human Papilloma Virus (HPV) [111,112] HPV has been transmitted by exclusively lesbian sexual contact from a bisexual women to her exclusively lesbian partner [142]. Lesbians and bisexuals also have higher smoking rates and lower pap smear compliance [111,112], additional risk factors for cervical carcinoma. Carcinoma of the neovagina in a male-to-female transgender individuals can be diagnosed late [143]. All transgender individuals are at similar risk to biological females for sexually transmitted diseases based on the organs they posess and the sexual behaviors they employ, and thus require similar screening pap smears and vaccinations against HPV [144].

2.6. Breast cancer

Lesbians have more risk factors for breast cancer than heterosexual women, including nulliparity, alcohol and cigarette abuse, and obesity [111], compounded by evidence that they may get fewer mammograms than the general population [145]. Lesbians had significantly fewer pregnancies, children, abortions and miscarriages as well as significantly more breast biopsies when compared with their heterosexual sisters [146]. Among the WHI population, lesbians and bisexual women had more breast cancers than heterosexual women, despite similar mammography screening rates as study protocol participants [111,112].

Clinicians should be aware that some lesbians diagnosed with breast cancer may be more comfortable with bilateral mastectomy without reconstruction as a means to simplify their future lives and reduce risk maximally [147]. Male-to-female transgender individuals typically take estrogen in doses that can induce breast formation and can develop breast cancer, although it is rare and often many years after estrogen initiation [131]. Female-to-male transgender individuals can also develop breast cancer even after mastectomy [148]. All transgender individuals with recognizeable breast tissue should have screening mammograms.

2.7. Lung cancer

Smoking rates of adolescent, middle age, and older lesbians, bisexuals and transgender people are higher than their heterosexual counterparts, placing them at higher risk of lung cancer [111,112,149]. Culturally sensitive interventions are needed to both prevent smoking and promote quitting [150].

2.8. Colorectal cancer

Smoking, obesity and high alcohol intake have been shown to increase rates of colon and gastric cancer, though per the WHI and the NHS-II, lesbians were shown to develop colon cancer at similar rates to heterosexuals and bisexuals [111,112].

2.9. Mental health and aging

Age, poverty, and health issues can render older lesbians invisible [151]. Historically, many lesbian seniors forfeited their gay identity to meld into senior and retirement communities in a generation that was still predominantly homophobic [152]. Integration into a broader community with other lesbians results in higher levels of senior life satisfaction [153]. Toward this end there have been a few retirement communities created and advertised in the lesbian, gay, bisexual and transgender (LGBT) media specifically to enable residents to maintain their identities as they age. LGBT older adults had higher risk of disability, poorer mental health, and higher rates of smoking and excessive drinking than did heterosexuals among the 97,000 survey respondents of the Washington State Behavioral Risk Factor Surveillance System [154].

3. Conclusion

The evidence shows that both orientation and identity are biologic features that co-vary with a very large number of other biologic sexually dimorphic traits. All of these sexually dimorphic traits are innate, immutable and innocent human features with cultural impacts that may result in disparate health maintenance and higher risk for cancer and heart disease. Gender-atypia or homosexuality do not themselves lead to social pathology, drug abuse, suicide, sex-work or HIV infection; rather, the pervasive societal misconceptions and negative social attitudes unnecessarily alienate and marginalize individuals from their families, their communities, and from medical care, causing preventable injury [126]. With this understanding, Gynecologic Oncologists can facilitate the greater health of the individuals they serve.

All orientations are biologically conferred

"It is clear from the peer-reviewed published scientific literature, including our own studies, that homosexuality has, just like heterosexuality, an early developmental cause that is partly genetic and partly based upon other factors influencing - in a permanent way – brain development before birth. Homosexuality is an innate property of our brain and is not a choice, in the same way as heterosexuality is an innate property of our brain and not a choice. The same holds for the entire spectrum of sexual orientations, from hetero- to homosexuality. Homosexuality is thus a biological property and has also been observed in many animal species. The below references reveal the evidence of this statement and also contain the references to our own work."

Dick F. Swaab, MD, PhD
Prof. of Neurobiology, Univ. of Amsterdam
Netherlands Institute for Neuroscience, KNAW
Meibergdreef 47
1105 BA Amsterdam
(approved 3/19/2017, by personal electronic communication)

Conflicts of interest

The authors have no conflicts to declare.

References

[1] Q. Rahman, The neurodevelopment of human sexual orientation, Neurosci. Biobehav. Rev. 29 (7) (2005) 1057–1066.
[2] S. Bocklandt, E. Vilain, Sex differences in brain and behavior: hormones versus genes, Adv. Genet. 59 (2007) 245–266.
[3] D.F. Swaab, A. Garcia-Falgueras, Sexual differentiation of the human brain in relation to gender identity and sexual orientation, Funct. Neurol. 24 (1) (2009) 17–28.
[4] W.W. Beatty, Gonadal hormones and sex differences in nonreproductive behaviors in rodents: organizational and activational influences, Horm. Behav. 12 (2) (1979) 112–163.
[5] T. Mitsui, A. Araki, A. Imai, et al., Effects of prenatal Leydig cell function on the ratio of the second to fourth digit lengths in school-aged children, PLoS One 10 (3) (2015), e0120636.
[6] A.X. Gorka, R.E. Norman, S.R. Radtke, J.M. Carre, A.R. Hariri, Anterior cingulate cortex gray matter volume mediates an association between 2D:4D ratio and trait aggression in women but not men, Psychoneuroendocrinology 56 (2015) 148–156.
[7] E. Hampson, C.L. Ellis, C.M. Tenk, On the relation between 2D:4D and sex-dimorphic personality traits, Arch. Sex. Behav. 37 (1) (2008) 133–144.
[8] J. Valla, S.J. Ceci, Can sex differences in science be tied to the long reach of prenatal hormones? Brain organization theory, digit ratio (2D/4D), and sex differences in preferences and cognition, Perspect. Psychol. Sci. 6 (2) (2011) 134–136.
[9] Q. Rahman, G.D. Wilson, Sexual orientation and the 2nd to 4th finger length ratio: evidence for organising effects of sex hormones or developmental instability? Psychoneuroendocrinology 28 (3) (2003) 288–303.
[10] M.S. Wallien, K.J. Zucker, T.D. Steensma, P.T. Cohen-Kettenis, 2D:4D finger-length ratios in children and adults with gender identity disorder, Horm. Behav. 54 (3) (2008) 450–454.
[11] S.M. Breedlove, Minireview: organizational hypothesis: instances of the fingerpost, Endocrinology 151 (9) (2010) 4116–4122.
[12] S. Hisasue, S. Sasaki, T. Tsukamoto, S. Horie, The relationship between second-to-fourth digit ratio and female gender identity, J. Sex. Med. 9 (11) (2012) 2903–2910.
[13] H.A. Bosinski, I. Schroder, M. Peter, R. Arndt, R. Wille, W.G. Sippell, Anthropometrical measurements and androgen levels in males, females, and hormonally untreated female-to-male transsexuals, Arch. Sex. Behav. 26 (2) (1997) 143–157.
[14] L.S. Hall, C.T. Love, Finger-length ratios in female monozygotic twins discordant for sexual orientation, Arch. Sex. Behav. 32 (1) (2003) 23–28.
[15] S. Lutchmaya, S. Baron-Cohen, P. Raggatt, R. Knickmeyer, J.T. Manning, 2nd to 4th digit ratios, fetal testosterone and estradiol, Early Hum. Dev. 77 (1–2) (2004) 23–28.
[16] W.R. Rice, U. Friberg, S. Gavrilets, Homosexuality as a consequence of epigenetically canalized sexual development, Q. Rev. Biol. 87 (4) (2012) 343–368.
[17] B. Kraemer, T. Noll, A. Delsignore, G. Milos, U. Schnyder, U. Hepp, Finger Length Ratio (2D:4D) in Adults with Gender Identity Disorder, Arch. Sex. Behav. 38 (3) (2009) 359–363.
[18] A.B. Wisniewski, B. Espinoza-Varas, C.E. Aston, et al., Otoacoustic emissions, auditory evoked potentials and self-reported gender in people affected by disorders of sex development (DSD), Horm. Behav. 66 (3) (2014) 467–474.
[19] D. McFadden, Sexual orientation and the auditory system, Front. Neuroendocrinol. 32 (2) (2011) 201–213.
[20] C.C. Cohen-Bendahan, J.K. Buitelaar, S.H. van Goozen, P.T. Cohen-Kettenis, Prenatal exposure to testosterone and functional cerebral lateralization: a study in same-sex and opposite-sex twin girls, Psychoneuroendocrinology 29 (7) (2004) 911–916.
[21] C.C. Cohen-Bendahan, J.K. Buitelaar, S.H. van Goozen, J.F. Orlebeke, P.T. Cohen-Kettenis, Is there an effect of prenatal testosterone on aggression and other behavioral traits? A study comparing same-sex and opposite-sex twin girls, Horm. Behav. 47 (2) (2005) 230–237.
[22] J.C. Loehlin, D. McFadden, Otoacoustic emissions, auditory evoked potentials, and traits related to sex and sexual orientation, Arch. Sex. Behav. 32 (2) (2003) 115–127.
[23] R. Bull, P.J. Benson, Digit ratio (2D:4D) and the spatial representation of magnitude, Horm. Behav. 50 (2) (2006) 194–199.
[24] M.L. Collaer, S. Reimers, J.T. Manning, Visuospatial performance on an internet line judgment task and potential hormonal markers: sex, sexual orientation, and 2D:4D, Arch. Sex. Behav. 36 (2) (2007) 177–192.
[25] S.E. Beren, H.A. Hayden, D.E. Wilfley, C.M. Grilo, The influence of sexual orientation on body dissatisfaction in adult men and women, Int. J. Eat. Disord. 20 (2) (1996) 135–141.
[26] K.M. Culbert, S.M. Breedlove, S.A. Burt, K.L. Klump, Prenatal hormone exposure and risk for eating disorders: a comparison of opposite-sex and same-sex twins, Arch. Gen. Psychiatry 65 (3) (2008) 329–336.
[27] U. Nygren, M. Sodersten, H. Falhammar, M. Thoren, K. Hagenfeldt, A. Nordenskjold, Voice characteristics in women with congenital adrenal hyperplasia due to 21-hydroxylase deficiency, Clin. Endocrinol. 70 (1) (2009) 18–25.
[28] J.A. Hall, D. Kimura, Sexual orientation and performance on sexually dimorphic motor tasks, Arch. Sex. Behav. 24 (4) (1995) 395–407.
[29] E. Keogh, C. Mounce, M. Brosnan, Can a sexually dimorphic index of prenatal hormonal exposure be used to examine cold pressor pain perception in men and women? Eur. J. Pain 11 (2) (2007) 231–236.
[30] L. Ellis, M.N. Skorska, A.F. Bogaert, Handedness, sexual orientation, and somatic markers for prenatal androgens: are southpaws really that gay? Laterality 22 (2) (2017) 157–180.

[31] B.S. Mustanski, J.M. Bailey, S. Kaspar, Dermatoglyphics, handedness, sex, and sexual orientation, Arch. Sex. Behav. 31 (1) (2002) 113–122.
[32] R.A. Lippa, The relation between sex drive and sexual attraction to men and women: a cross-national study of heterosexual, bisexual, and homosexual men and women, Arch. Sex. Behav. 36 (2) (2007) 209–222.
[33] K.L. Johnson, S. Gill, V. Reichman, L.G. Tassinary, Swagger, sway, and sexuality: judging sexual orientation from body motion and morphology, J. Pers. Soc. Psychol. 93 (3) (2007) 321–334.
[34] Y. Martins, M. Tiggemann, A. Kirkbride, Those speedos become them: the role of self-objectification in gay and heterosexual men's body image, Personal. Soc. Psychol. Bull. 33 (5) (2007) 634–647.
[35] A.J. Blashill, Gender roles, eating pathology, and body dissatisfaction in men: a meta-analysis, Body Image 8 (1) (2011) 1–11.
[36] Q. Rahman, S. Abrahams, G.D. Wilson, Sexual-orientation-related differences in verbal fluency, Neuropsychology 17 (2) (2003) 240–246.
[37] S.E. Linville, Acoustic correlates of perceived versus actual sexual orientation in men's speech, Folia Phoniatr. Logop. 50 (1) (1998) 35–48.
[38] J.A. Hall, D. Kimura, Dermatoglyphic asymmetry and sexual orientation in men, Behav. Neurosci. 108 (6) (1994) 1203–1206.
[39] A.M. Bao, D.F. Swaab, Sexual differentiation of the human brain: relation to gender identity, sexual orientation and neuropsychiatric disorders, Front. Neuroendocrinol. 32 (2) (2011) 214–226.
[40] S.A. French, M. Story, G. Remafedi, M.D. Resnick, R.W. Blum, Sexual orientation and prevalence of body dissatisfaction and eating disordered behaviors: a population-based study of adolescents, Int. J. Eat. Disord. 19 (2) (1996) 119–126.
[41] L.S. Allen, R.A. Gorski, Sexual orientation and the size of the anterior commissure in the human brain, Proc. Natl. Acad. Sci. U. S. A. 89 (15) (1992) 7199–7202.
[42] F.P. Kruijver, J.N. Zhou, C.W. Pool, M.A. Hofman, L.J. Gooren, D.F. Swaab, Male-to-female transsexuals have female neuron numbers in a limbic nucleus, J. Clin. Endocrinol. Metab. 85 (5) (2000) 2034–2041.
[43] G.S. Kranz, A. Hahn, U. Kaufmann, et al., White matter microstructure in transsexuals and controls investigated by diffusion tensor imaging, J. Neurosci. 34 (46) (2014) 15466–15475.
[44] L.R. Chura, M.V. Lombardo, E. Ashwin, et al., Organizational effects of fetal testosterone on human corpus callosum size and asymmetry, Psychoneuroendocrinology 35 (1) (2010) 122–132.
[45] I. Savic, P. Lindstrom, PET and MRI show differences in cerebral asymmetry and functional connectivity between homo- and heterosexual subjects, Proc. Natl. Acad. Sci. U. S. A. 105 (27) (2008) 9403–9408.
[46] P.T. Cohen-Kettenis, S.H. van Goozen, C.D. Doorn, L.J. Gooren, Cognitive ability and cerebral lateralisation in transsexuals, Psychoneuroendocrinology 23 (6) (1998) 631–641.
[47] S.M. Breedlove, Prenatal influences on human sexual orientation: expectations versus data, Arch. Sex. Behav. 46 (6) (2017) 1583–1592.
[48] J. Money, V.G. Lewis, Bisexually concordant, heterosexually and homosexually discordant: a matched-pair comparison of male and female adrenogenital syndrome, Psychiatry 50 (2) (1987) 97–111.
[49] R. Gonzalez, B.M. Ludwikowski, Should CAH in females be classified as DSD? Front. Pediatr. 4 (2016) 48.
[50] A.B. Dessens, F.M. Slijper, S.L. Drop, Gender dysphoria and gender change in chromosomal females with congenital adrenal hyperplasia, Arch. Sex. Behav. 34 (4) (2005) 389–397.
[51] H.F. Meyer-Bahlburg, C. Dolezal, S.W. Baker, M.I. New, Sexual orientation in women with classical or non-classical congenital adrenal hyperplasia as a function of degree of prenatal androgen excess, Arch. Sex. Behav. 37 (1) (2008) 85–99.
[52] B.S. Khorashad, G.M. Roshan, A.G. Reid, et al., Sexual orientation and medical history among Iranian people with complete androgen insensitivity syndrome and congenital adrenal hyperplasia, J. Psychosom. Res. 92 (2017) 55–62.
[53] P.L. Chang, S.R. Lindheim, C. Lowre, et al., Normal ovulatory women with polycystic ovaries have hyperandrogenic pituitary-ovarian responses to gonadotropin-releasing hormone-agonist testing, J. Clin. Endocrinol. Metab. 85 (3) (2000) 995–1000.
[54] H.A. Bosinski, M. Peter, G. Bonatz, et al., A higher rate of hyperandrogenic disorders in female-to-male transsexuals, Psychoneuroendocrinology 22 (5) (1997) 361–380.
[55] T. Baba, T. Endo, H. Honnma, et al., Association between polycystic ovary syndrome and female-to-male transsexuality, Hum. Reprod. 22 (4) (2007) 1011–1016.
[56] V. Lummaa, J.E. Pettay, A.F. Russell, Male twins reduce fitness of female co-twins in humans, Proc. Natl. Acad. Sci. U. S. A. 104 (26) (2007) 10915–10920.
[57] P.J. Dempsey, G.C. Townsend, L.C. Richards, Increased tooth crown size in females with twin brothers: evidence for hormonal diffusion between human twins in utero, Am. J. Hum. Biol. 11 (5) (1999) 577–586.
[58] J.M. Ellingson, W.S. Slutske, L.S. Richmond-Rakerd, N.G. Martin, Investigating the influence of prenatal androgen exposure and sibling effects on alcohol use and alcohol use disorder in females from opposite-sex twin pairs, Alcohol. Clin. Exp. Res. 37 (5) (2013) 868–876.
[59] J.S. Peper, R.M. Brouwer, G.C. Van Baal, et al., Does having a twin-brother make for a bigger brain? Eur. J. Endocrinol. 160 (5) (2009) 739–746.
[60] C.C. Cohen-Bendahan, C. van de Beek, S.A. Berenbaum, Prenatal sex hormone effects on child and adult sex-typed behavior: methods and findings, Neurosci. Biobehav. Rev. 29 (2) (2005) 353–384.
[61] P.S. Bearman, H. Brückner, Opposite-sex Twins and Adolescent Same-sex Attraction, 107, Columbia University Academic Commons, 2002.
[62] A.A. Ehrhardt, H.F. Meyer-Bahlburg, L.R. Rosen, et al., The development of gender-related behavior in females following prenatal exposure to diethylstilbestrol (DES), Horm. Behav. 23 (4) (1989) 526–541.
[63] M.V. Wu, D.S. Manoli, E.J. Fraser, et al., Estrogen masculinizes neural pathways and sex-specific behaviors, Cell 139 (1) (2009) 61–72.
[64] N. Killer, M. Hock, M. Gehlhaus, et al., Modulation of androgen and estrogen receptor expression by antiepileptic drugs and steroids in hippocampus of patients with temporal lobe epilepsy, Epilepsia 50 (8) (2009) 1875–1890.
[65] A.B. Dessens, P.T. Cohen-Kettenis, G.J. Mellenbergh, J.G. Koppe, N.E. Poll, K. Boer, Association of prenatal phenobarbital and phenytoin exposure with genital anomalies and menstrual disorders, Teratology 64 (4) (2001) 181–188.
[66] M.F. Shue, T.C. Chen, L.M. Bellotindos, M.C. Lu, Tributyltin distribution and producing androgenic activity in water, sediment, and fish muscle, J. Environ. Sci. Health B 49 (6) (2014) 432–438.
[67] M.J. Fennell, C.G. Scanes, Effects of androgen (testosterone, 5 alpha-dihydrotestosterone, 19-nortestosterone) administration on growth in turkeys, Poult. Sci. 71 (3) (1992) 539–547.
[68] J. Scarth, C. Akre, L. van Ginkel, et al., Presence and metabolism of endogenous androgenic-anabolic steroid hormones in meat-producing animals: a review, Food Addit. Contam. Part A Chem. Anal. Control Expo. Risk Assess. 26 (5) (2009) 640–671.
[69] R. Knickmeyer, S. Baron-Cohen, P. Raggatt, K. Taylor, G. Hackett, Fetal testosterone and empathy, Horm. Behav. 49 (3) (2006) 282–292.
[70] R. Blanchard, K.J. Zucker, A. Cavacas, S. Allin, S.J. Bradley, D.C. Schachter, Fraternal birth order and birth weight in probably prehomosexual feminine boys, Horm. Behav. 41 (3) (2002) 321–327.
[71] A.F. Bogaert, M. Skorska, Sexual orientation, fraternal birth order, and the maternal immune hypothesis: a review, Front. Neuroendocrinol. 32 (2) (2011) 247–254.
[72] D.P. Vanderlaan, R. Blanchard, K.J. Zucker, et al., Birth order and Androphilic male-to-female transsexualism in Brazil, J. Biosoc. Sci. (2016) 1–10.
[73] N. McConaghy, D. Hadzi-Pavlovic, C. Stevens, V. Manicavasagar, N. Buhrich, U. Vollmer-Conna, Fraternal birth order and ratio of heterosexual/homosexual feelings in women and men, J. Homosex. 51 (4) (2006) 161–174.
[74] M.N. Skorska, R. Blanchard, D.P. VanderLaan, K.J. Zucker, A.F. Bogaert, Gay male only-children: evidence for low birth weight and high maternal miscarriage rates, Arch. Sex. Behav. 46 (1) (2017) 205–215.
[75] S. LeVay, From mice to men: biological factors in the development of sexuality, Front. Neuroendocrinol. 32 (2) (2011) 110–113.
[76] F.L. Whitam, M. Diamond, J. Martin, Homosexual orientation in twins: a report on 61 pairs and three triplet sets, Arch. Sex. Behav. 22 (3) (1993) 187–206.
[77] J.M. Bailey, R.C. Pillard, M.C. Neale, Y. Agyei, Heritable factors influence sexual orientation in women, Arch. Gen. Psychiatry 50 (3) (1993) 217–223.
[78] N. Buhrich, J.M. Bailey, N.G. Martin, Sexual orientation, sexual identity, and sex-dimorphic behaviors in male twins, Behav. Genet. 21 (1) (1991) 75–96.
[79] K.S. Kendler, L.M. Thornton, S.E. Gilman, R.C. Kessler, Sexual orientation in a U.S. national sample of twin and nontwin sibling pairs, Am. J. Psychiatry 157 (11) (2000) 1843–1846.
[80] F.L. Coolidge, L.L. Thede, S.E. Young, The heritability of gender identity disorder in a child and adolescent twin sample, Behav. Genet. 32 (4) (2002) 251–257.
[81] W.R. Rice, U. Friberg, S. Gavrilets, Sexually antagonistic epigenetic marks that canalize sexually dimorphic development, Mol. Ecol. 25 (8) (2016) 1812–1822.
[82] C.P. Morgan, T.L. Bale, Sex differences in microRNA-mRNA networks: examination of novel epigenetic programming mechanisms in the sexually dimorphic neonatal hypothalamus, Biol. Sex Differ. 8 (1) (2017) 27.
[83] A.R. Sanders, E.R. Martin, G.W. Beecham, et al., Genome-wide scan demonstrates significant linkage for male sexual orientation, Psychol. Med. 45 (7) (2015) 1379–1388.
[84] B. Wang, S. Zhou, F. Hong, et al., Association analysis between the tag SNP for sonic hedgehog rs9333613 polymorphism and male sexual orientation, J. Androl. 33 (5) (2012) 951–954.
[85] R. Green, E.B. Keverne, The disparate maternal aunt-uncle ratio in male transsexuals: an explanation invoking genomic imprinting, J. Theor. Biol. 202 (1) (2000) 55–63.
[86] N. Taneja, A.C. Ammini, I. Mohapatra, S. Saxena, K. Kucheria, A transsexual male with 47,XYY karyotype, Br. J. Psychiatry 161 (1992) 698–699.
[87] M.T. Turan, E. Esel, M. Dundar, et al., Female-to-male transsexual with 47,XXX karyotype, Biol. Psychiatry 48 (11) (2000) 1116–1117.
[88] A. Bhangoo, F. Paris, P. Philibert, F. Audran, S. Ten, C. Sultan, Isolated micropenis reveals partial androgen insensitivity syndrome confirmed by molecular analysis, Asian J. Androl. 12 (4) (2010) 561–566.
[89] H.T. Hooper, B.C. Figueiredo, C.C. Pavan-Senn, et al., Concordance of phenotypic expression and gender identity in a large kindred with a mutation in the androgen receptor, Clin. Genet. 65 (3) (2004) 183–190.
[90] A.B. Wisniewski, T. Mazur, 46,XY DSD with female or ambiguous external genitalia at birth due to androgen insensitivity syndrome, 5alpha-reductase-2 deficiency, or 17beta-hydroxysteroid dehydrogenase deficiency: a review of quality of life outcomes, Int. J. Pediatr. Endocrinol. 2009 (2009) 567430.
[91] G. T'Sjoen, G. De Cuypere, S. Monstrey, et al., Male gender identity in complete androgen insensitivity syndrome, Arch. Sex. Behav. 40 (3) (2011) 635–638.
[92] L. Maimoun, P. Philibert, B. Cammas, et al., Phenotypical, biological, and molecular heterogeneity of 5{alpha}-reductase deficiency: an extensive international experience of 55 patients, J. Clin. Endocrinol. Metab. 96 (2) (2011) 296–307.
[93] C.K. Cheon, Practical approach to steroid 5alpha-reductase type 2 deficiency, Eur. J. Pediatr. 170 (1) (2011) 1–8.
[94] E.P. Praveen, A.K. Desai, M.L. Khurana, et al., Gender identity of children and young adults with 5alpha-reductase deficiency, J. Pediatr. Endocrinol. Metab. 21 (2) (2008) 173–179.
[95] S.J. Bradley, G.D. Oliver, A.B. Chernick, K.J. Zucker, Experiment of nurture: ablatio penis at 2 months, sex reassignment at 7 months, and a psychosexual follow-up in young adulthood, Pediatrics 102 (1) (1998), e9.
[96] H.F. Meyer-Bahlburg, Gender identity outcome in female-raised 46,XY persons with penile agenesis, cloacal exstrophy of the bladder, or penile ablation, Arch. Sex. Behav. 34 (4) (2005) 423–438.

[97] A. Nordenskjold, G. Holmdahl, L. Frisen, et al., Type of mutation and surgical procedure affect long-term quality of life for women with congenital adrenal hyperplasia, J. Clin. Endocrinol. Metab. 93 (2) (2008) 380–386.
[98] J.H. Yang, L.S. Baskin, M. DiSandro, Gender identity in disorders of sex development: review article, Urology 75 (1) (2010) 153–159.
[99] N. Dickson, C. Paul, P. Herbison, Same-sex attraction in a birth cohort: prevalence and persistence in early adulthood, Soc. Sci. Med. 56 (8) (2003) 1607–1615.
[100] J. Drescher, Out of DSM: depathologizing homosexuality, Behav. Sci. 5 (4) (2015) 565–575.
[101] K.J. Zucker, P.T. Cohen-Kettenis, J. Drescher, H.F. Meyer-Bahlburg, F. Pfafflin, W.M. Womack, Memo outlining evidence for change for gender identity disorder in the DSM-5, Arch. Sex. Behav. 42 (5) (2013) 901–914.
[102] K.A. O'Hanlan, Health policy considerations for our sexual minority patients, Obstet. Gynecol. 107 (3) (2006) 709–714.
[103] K.A. O'Hanlan, S.L. Dibble, H.J. Hagan, R. Davids, Advocacy for women's health should include lesbian health, J. Women's Health (Larchmt) 13 (2) (2004) 227–234.
[104] S.D. Cochran, V.M. Mays, Disclosure of sexual preference to physicians by black lesbian and bisexual women, West. J. Med. 149 (5) (1988) 616–619.
[105] W.C. Mathews, M.W. Booth, J.D. Turner, L. Kessler, Physicians' attitudes toward homosexuality–survey of a California County Medical Society, West. J. Med. 144 (1) (1986) 106–110.
[106] C.M. Tesar, S.L. Rovi, Survey of curriculum on homosexuality/bisexuality in departments of family medicine, Fam. Med. 30 (4) (1998) 283–287.
[107] K.A. O'Hanlan, Recruitment and retention of lesbians in health research trials, in: Office of the Director of the National Institutes of Health of the United States Department of Health and Human Services (Ed.), Recruitment and Retention of Women in Clinical Studies, vol. 95–3756, Office of Research on Women's Health of the National Institutes of Health, Bethesda, Maryland 1995, pp. 101–104.
[108] A. Solarz, Lesbian Health: Current Assessment and Directions for the Future, Institute of Medicine, National Institutes of Health, United States Department of Health and Human Services, National Academy Press, Washington, DC, 1999.
[109] S.G. Haynes, Scientific Workshop on Lesbian Health 2000: Steps for Implementing the IOM Report, Department of Health and Human Services, Washington, DC, 2000.
[110] National Institutes of Health (NIH), in: Human National Institute of Child Human Department NIoAAaA, National Institute of Mental Health (Eds.), Research on Social Networks and HIV Risk Prevention, Department of Health and Human Services (HHS), 2001https://grants.nih.gov/grants/guide/pa-files/PAS-01-068.html:.
[111] B.G. Valanis, D.J. Bowen, T. Bassford, E. Whitlock, P. Charney, R.A. Carter, Sexual orientation and health: comparisons in the Women's Health Initiative sample, Arch. Fam. Med. 9 (9) (2000) 843–853.
[112] P. Case, S.B. Austin, D.J. Hunter, et al., Sexual orientation, health risk factors, and physical functioning in the Nurses' health study II, J. Women's Health (Larchmt) 13 (9) (2004) 1033–1047.
[113] G. Herdt, M. McClintock, The magical age of 10, Arch. Sex. Behav. 29 (6) (2000) 587–606.
[114] G. Remafedi, M. Resnick, R. Blum, L. Harris, Demography of sexual orientation in adolescents, Pediatrics 89 (4 Pt 2) (1992) 714–721.
[115] American Academy of Pediatrics: Committee on Adolescence, Homosexuality and adolescence, Pediatrics 92 (4) (1993) 631–634.
[116] R. Garofalo, R.C. Wolf, S. Kessel, S.J. Palfrey, R.H. DuRant, The association between health risk behaviors and sexual orientation among a school-based sample of adolescents, Pediatrics 101 (5) (1998) 895–902.
[117] J.M. White Hughto, K.B. Biello, S.L. Reisner, A. Perez-Brumer, K.J. Heflin, M.J. Mimiaga, Health risk behaviors in a representative sample of bisexual and heterosexual female high school students in Massachusetts, J. Sch. Health 86 (1) (2016) 61–71.
[118] E.M. Saewyc, L.H. Bearinger, R.W. Blum, M.D. Resnick, Sexual intercourse, abuse and pregnancy among adolescent women: does sexual orientation make a difference? Fam. Plan. Perspect. 31 (3) (1999) 127–131.
[119] S.B. Austin, H.J. Jun, B. Jackson, et al., Disparities in child abuse victimization in lesbian, bisexual, and heterosexual women in the Nurses' Health Study II, J. Women's Health (Larchmt) 17 (4) (2008) 597–606.
[120] P. Tjaden, N. Thoennes, C.J. Allison, Comparing violence over the life span in samples of same-sex and opposite-sex cohabitants, Violence Vict. 14 (4) (1999) 413–425.
[121] K.F. Balsam, E.D. Rothblum, T.P. Beauchaine, Victimization over the life span: a comparison of lesbian, gay, bisexual, and heterosexual siblings, J. Consult. Clin. Psychol. 73 (3) (2005) 477–487.
[122] J.P. Stoddard, S.L. Dibble, N. Fineman, Sexual and physical abuse: a comparison between lesbians and their heterosexual sisters, J. Homosex. 56 (4) (2009) 407–420.
[123] A.H. Faulkner, K. Cranston, Correlates of same-sex sexual behavior in a random sample of Massachusetts high school students, Am. J. Public Health 88 (2) (1998) 262–266.
[124] M.L. Hatzenbuehler, The social environment and suicide attempts in lesbian, gay, and bisexual youth, Pediatrics 127 (5) (2011) 896–903.
[125] R. Garofalo, R.C. Wolf, L.S. Wissow, E.R. Woods, E. Goodman, Sexual orientation and risk of suicide attempts among a representative sample of youth, Arch. Pediatr. Adolesc. Med. 153 (5) (1999) 487–493.
[126] C. Ryan, D. Huebner, R.M. Diaz, J. Sanchez, Family rejection as a predictor of negative health outcomes in white and Latino lesbian, gay, and bisexual young adults, Pediatrics 123 (1) (2009) 346–352.
[127] J.M. White Hughto, J.E. Pachankis, T.C. Willie, S.L. Reisner, Victimization and depressive symptomology in transgender adults: the mediating role of avoidant coping, J. Couns. Psychol. 64 (1) (2017) 41–51.
[128] American Psychological Association, Just the Facts About Sexual Orientation & Youth: a Primer for Principals, Educators and School Personnel, American Academy of Pediatrics, American Counseling Association, American Association of School Administrators, American Federation of Teachers, American Psychological Association, American School Health Association, Interfaith Alliance Foundation, National Association of School Psychologists, National Association of Social Workers, National Education Association, Washington, DC, 2000.
[129] J.M. Marrazzo, P. Coffey, M.N. Elliott, Sexual practices, risk perception and knowledge of sexually transmitted disease risk among lesbian and bisexual women, Perspect. Sex. Reprod. Health 37 (1) (2005) 6–12.
[130] A.S. Koh, C.A. Gomez, S. Shade, E. Rowley, Sexual risk factors among self-identified lesbians, bisexual women, and heterosexual women accessing primary care settings, Sex. Transm. Dis. 32 (9) (2005) 563–569.
[131] G.R. Brown, Breast cancer in transgender veterans: a ten-case series, LGBT Health 2 (1) (2015) 77–80.
[132] C. Dancey, Sexual orientation in women: an investigation of hormonal and personality variables, Biol. Psychol. 30 (3) (1990) 251–264.
[133] L.S. Steele, H. Stratmann, Counseling lesbian patients about getting pregnant, Can. Fam. Physician 52 (2006) 605–611.
[134] S. Nordqvist, G. Sydsjo, C. Lampic, H. Akerud, E. Elenis, A. Skoog Svanberg, Sexual orientation of women does not affect outcome of fertility treatment with donated sperm, Hum. Reprod. 29 (4) (2014) 704–711.
[135] K.A. O'Hanlan, S.L. Dibble, M. Young-Spint, Total laparoscopic hysterectomy for female-to-male transsexuals, Obstet. Gynecol. 110 (5) (2007) 1096–1101.
[136] A.K. Yancey, S.D. Cochran, H.L. Corliss, V.M. Mays, Correlates of overweight and obesity among lesbian and bisexual women, Prev. Med. 36 (6) (2003) 676–683.
[137] L.J. Gooren, K. Wierckx, E.J. Giltay, Cardiovascular disease in transsexual persons treated with cross-sex hormones: reversal of the traditional sex difference in cardiovascular disease pattern, Eur. J. Endocrinol. 170 (6) (2014) 809–819.
[138] S.L. Dibble, S.A. Roberts, P.A. Robertson, S.M. Paul, Risk factors for ovarian cancer: lesbian and heterosexual women, Oncol. Nurs. Forum 29 (1) (2002) E1–7.
[139] A. Brenick, K. Romano, C. Kegler, L.A. Eaton, Understanding the influence of stigma and medical mistrust on engagement in routine healthcare among black women who have sex with women, LGBT Health 4 (1) (2017) 4–10.
[140] A. Tomisek, B. Flinn, T. Balsky, C. Gruman, A.M. Rizer, Strong, healthy, energized: striving for a healthy weight in an older lesbian population, J. Women Aging 29 (3) (2017) 230–242.
[141] C. Curmi, K. Peters, Y. Salamonson, Lesbians' attitudes and practices of cervical cancer screening: a qualitative study, BMC Womens Health 14 (2014) 153.
[142] K.A. O'Hanlan, C.P. Crum, Human papillomavirus-associated cervical intraepithelial neoplasia following lesbian sex, Obstet. Gynecol. 88 (4 Pt. 2) (1996) 702–703.
[143] H.M. Fernandes, T.P. Manolitsas, T.W. Jobling, Carcinoma of the neovagina after male-to-female reassignment, J. Low. Genit. Tract Dis. 18 (2) (2014) E43–45.
[144] Committee on Adolescent Health C, Committee opinion no. 685: care for transgender adolescents, Obstet. Gynecol. 129 (1) (2017) e11–e16.
[145] K.N. Barefoot, J.C. Warren, K.B. Smalley, Women's health care: the experiences and behaviors of rural and urban lesbians in the USA, Rural Remote Health 17 (1) (2017) 3875.
[146] S.L. Dibble, S.A. Roberts, B. Nussey, Comparing breast cancer risk between lesbians and their heterosexual sisters, Womens Health Issues 14 (2) (2004) 60–68.
[147] M.T. Brown, J.A. McElroy, Sexual and gender minority breast cancer patients choosing bilateral mastectomy without reconstruction: "I now have a body that fits me", Women Health (2017) 1–16.
[148] D.V. Nikolic, M.L. Djordjevic, M. Granic, et al., Importance of revealing a rare case of breast cancer in a female to male transsexual after bilateral mastectomy, World J. Surg. Oncol. 10 (2012) 280.
[149] H. Dai, Tobacco product use among lesbian, gay, and bisexual adolescents, Pediatrics 139 (4) (2017), e20163276.
[150] N.G. Smith, K. Winderman, B. King, E.M. Obasi, L.R. Reitzel, The association of lesbian, gay, and bisexual identity facets with smoking dependence motives, Nicotine Tob. Res. (2017) ntx061, https://doi.org/10.1093/ntr/ntx061.
[151] E.M. Fullmer, D. Shenk, L.J. Eastland, Negating identity: a feminist analysis of the social invisibility of older lesbians, J. Women Aging 11 (2–3) (1999) 131–148.
[152] J.K. Quam, G.S. Whitford, Adaptation and age-related expectations of older gay and lesbian adults, Gerontologist 32 (3) (1992) 367–374.
[153] H.J. Kim, K.I. Fredriksen-Goldsen, A.E. Bryan, A. Muraco, Social network types and mental health among LGBT older adults, Gerontologist 57 (Suppl. 1) (2017) S84–S94.
[154] K.I. Fredriksen-Goldsen, H.J. Kim, S.E. Barkan, A. Muraco, C.P. Hoy-Ellis, Health disparities among lesbian, gay, and bisexual older adults: results from a population-based study, Am. J. Public Health 103 (10) (2013) 1802–1809.