1. Introduction

Disorders of sex development (DSD) refer to a collection of congenital conditions in which atypical development of sex occurs at one or more levels (chromosomal, gonadal, anatomic). Genetic males with DSD (i.e., 46,XY DSD) can present with an external genital phenotype that is female, ambiguous, or male including a micropenis (stretched penile length <2.5 SD for age). Studies of 46,XY DSD have focused largely on aspects of gender development such as satisfaction with gender of rearing, sexual orientation, gender identity, and gender role (GI/R) [1]. Very few studies have reported on additional aspects of physical or mental health despite the fact that patients and families often inquire about such topics. Furthermore, few studies have addressed the question of if, or how, a DSD diagnosis and related treatment impact quality of life (QoL) for affected individuals. For the purpose of this review, QoL can be operationally defined as the amount of enjoyment a person experiences in the physical, psychological, social, and spiritual dimensions of their life [2].

Although much remains to be learned concerning psychosexual development as it relates to DSD, the purpose of this paper is to review what is known about aspects of physical and mental health that contribute to overall QoL beyond GI/R and sexual orientation. Topics reviewed include QoL and psychological well-being, cognition, general health, fertility, and sexual function. Additionally, the focus of this review is on individuals affected by 46,XY DSD due to androgen insensitivity syndromes (AIS), 5α-reductase-2 deficiency (5α-RD-2), or 17β-hydroxysteroid dehydrogenase-3 deficiency (17β-HSD-3)—reared male or
female. These conditions were chosen because while much has been written about gender development in affected individuals, less emphasis has been placed on other outcomes that may contribute to QoL, such as genital surgery or hormone therapy to induce and maintain pubertal development. Congenital micropenis was not included in the current review because too little information exists on outcomes aside from gender development in this DSD for meaningful interpretation of the data. Data on individuals with micropenis is further confused by the incorrect practice of some authors of describing individuals with a small phallus including hypospadias as having a micropenis.

2. Methods

A search of the databases Medline and Psyc INFO was performed using the terms disorders of sex development, DSD, intersex, hermaphrodite, male pseudohermaphrodite, ambiguous genitalia, androgen insensitivity, 5-α reductase-2 deficiency, and 17β-hydroxysteroid dehydrogenase-3 deficiency. Peer-reviewed articles published in English since 1955 were considered if they referred to adults with DSD grouped and analyzed according to the above-mentioned etiologies. The year 1955 was chosen because this was when John Money started to publish extensively on DSD in peer-reviewed scientific journals [3, 4].

To be considered for inclusion in the current review, articles must report on mental or physical health outcomes other than, or in addition to, GI/R and sexual orientation. Articles were excluded if they provided outcome information about GI/R or sexual orientation only, or when data from study participants could not be attributed to one of the specific DSD diagnoses referred to earlier. A total of 35 articles were located and reviewed according to these criteria.

3. Androgen Insensitivity Syndromes (AISs)

AISs in either the complete (CAIS) or partial (PAIS) form represent a relatively common presentation of 46,XY DSD [5–7]. CAIS and PAIS result in complete or partial end organ insensitivity to androgens, respectively. The majority of mutations of the human androgen receptor gene are base substitutions, although base and gene deletions, base insertions, and premature terminations occur. While it is well established that androgens bind to intracellular androgen receptors to alter gene expression in target tissues, evidence for nongenomic actions of androgens is accumulating [8]. The degree of androgen insensitivity of target tissues is usually inferred by the extent of under-masculinization of the external genitalia at birth coupled with the degree of under-virilization at puberty.

The clinical presentation of CAIS in adulthood is typically that of a tall woman with a female distribution of adipose tissue, female breasts and external genital development, and little or no sexual hair. Infants can present with testes that descend into the inguinal canals or labia, and adolescents can present with absent menses and sexual hair in conjunction with normal breast development. Due to the female external genital phenotype associated with CAIS, affected individuals are always assigned and reared as girls despite their possession of a 46,XY chromosomal complement and testes. Individuals with PAIS typically present as newborns with varying degrees of genital ambiguity. Thus, male or female sex of rearing occurs, depending on the degree of under-masculinization of the genitalia.

3.1. Health-Related Quality of Life, Psychological Well-Being, and Affective Disorders in CAIS. While psychosexual evaluations of girls and women affected by CAIS unequivocally reveal female GI/R [9–11], outcomes of other aspects of mental health vary greatly across studies. For example, psychological distress as assessed by the Brief Symptom Inventory (BSI), self-harming behavior, and suicidal tendencies are prevalent in some samples of women with CAIS recruited from physicians or support groups [12–14]. In a study of women with CAIS recruited from subspecialty clinics at a University Hospital, participants affected by CAIS reported better QoL scores and fewer depressive symptoms than women with other types of DSD or unaffected control women when assessed with the Danish version of the Quality of Life-Assessment of Growth Hormone Deficiency in Adults (QoL-AGHDA) questionnaire [15]. In yet another study of women with CAIS recruited from both a clinic sample and a support group, affected individuals did not differ from controls on measures of self-esteem, assessed by the Self-Esteem Scale, or psychological well-being, measured by responses to the Psychological General Well-Being Scale (PGWBS) [12]. While it is surprising that some studies of women with CAIS report equal or better QoL than unaffected women, this may be due to small sample sizes and participation bias. Additional QoL studies including larger sample sizes and greater participant diversity are needed in this population to better understand the impact of having a 46,XY chromosomal complement and being born with testes on overall psychological well-being in this group of women. Recently, the German Network of Disorders of Sex Development published clinical evaluation data on 439 individuals with DSD [16]. QoL information from this study sample will prove extremely valuable when published. Furthermore, a study that assesses potential differences in long-term QoL among women with CAIS whose testes were removed during infancy, compared to those who consented to gonadectomy later in their development, would provide very useful information for optimizing medical and surgical treatment for this group.

3.2. Cognition in CAIS. Mice with androgen receptor gene mutations (testicular feminization mutant or tfmr) exhibit a more pronounced impairment on spatial recognition and memory retention tasks when considered in conjunction with the epsilon4 allele of theapolipoprotein E gene (apoE4) [17]. This subclass of apolipoprotein plays an important role in cholesterol metabolism and is associated with Alzheimer’s disease, impaired cognition, and reduced neurite growth [18]. The implication is that androgen insensitivity may
impact cognition in women affected by AIS who also express the epsilon 4 allele of the APOE gene.

Only two studies of cognitive performance in girls and women affected by CAIS exist in the peer-reviewed literature. The first employed standardized, age-appropriate intelligence testing for participants ranging in age from 5 to 28 years and observed normal scores for all of the girls and women who participated [19]. A second intelligence assessment was performed in women with CAIS and revealed no group differences in overall IQ between CAIS participants, unaffected men, and unaffected women [20]. However, unaffected women and those with CAIS performed worse than men on visuospatial components of the IQ measure. Taken together, these data reveal that girls and women with CAIS exhibit similar IQ scores and cognitive performance patterns as unaffected women who possess a 46,XX chromosomal complement and end organ responsiveness to androgens. Whether or not cognitive differences would be detected on measures of spatial recognition and memory for women affected by CAIS when apoE4 is considered is not known at this time. Future studies should consider the potential interaction of end organ unresponsiveness to androgens with apoE4 in this population. Additionally, more refined neuropsychological testing, regardless of apoE4 status, might reveal important cognitive differences in girls and women affected by this type of DSD.

3.4. Fertility and Sexual Function in CAIS. As women with CAIS possess neither ovaries nor a uterus, fertility is not possible in this group at the present time. While vaginal lengthening is needed for penile penetration in some women with CAIS [29, 30], others have a normal vaginal length and report satisfactory intercourse despite never having received dilatation or surgery [10, 31]. Three studies of orgasmic function report that women with CAIS can reach sexual climax [10, 32, 33], indicating that androgens are not necessary for this aspect of sexuality in this group. Low libido, or hyposexual function, is reported by some women with CAIS [33, 34]. Interestingly, even when women report sexual dysfunction, they also report sexual satisfaction at levels that equal unaffected women [34]. Perhaps hyposexual function associated with CAIS is secondary to vaginal hypoplasia, the need for androgens to support libido (but not orgasm), or sexual avoidance by women who feel stigmatized by their medical condition. Further research that includes unaffected women as control subjects is needed to understand the extent, and underlying causes, of hyposexual function in women affected by this 46,XY DSD. Additionally, future studies would benefit from considering the impact of the type and timing of vaginoplasty on sexual satisfaction—an important component of QoL.

3.5. Health-Related Quality of Life, Psychological Well-Being, and Affective Disorders in PAIS. Self-reported psychological distress as determined by responses to the BSI, self-harming behavior, suicidal tendencies, and suicidal attempts is observed in people affected by PAIS—whether reared male or female [12–14]. In a long-term followup study of adults with PAIS, psychological counseling for problems such as difficulty with family members, depression, and substance abuse was commonly reported during interviews—once again regardless of male or female rearing [35]. However, some studies of men and women affected by PAIS fail to observe significant problems with mental health [36, 37]. Furthermore, QoL as determined by responses to the SF-36 Health Survey exceeded normative data in one case series of 3 women affected by PAIS [38]. While it is clear that some individuals with PAIS experience mental health obstacles, both the extent and type of these obstacles in this patient population remain to be elucidated. The potential impact of clinical decisions such as the type and timing of genital surgeries on QoL in affected people, regardless of their gender assignment, is important information that is missing from our knowledge base at this time.

3.6. General Health and Cognition in PAIS. Based on studies of 24 patients, people with PAIS are thought to be at high risk (~50%) for developing germ cell tumors if the testes are not located in the scrotum. For this group, gonadectomy is recommended at the time of diagnosis [23]. 46,XY women affected by PAIS do not appear to be at risk for developing prostate cancer, despite their possession of prostate tissue, as determined by PSA levels and digital rectal exam. Presumably this is due to the fact that these women are gonadectomized, and thus protected from androgenic actions on the prostate.
In contrast, men with PAIS have PSA levels comparable to unaffected men matched for age and race [28]. Therefore, when individuals with PAIS are reared male, screening for prostate disease is recommended in a manner that is similar to the general male population. No other published reports on general health outcome in 46,XY individuals with PAIS, reared male or female, were located. Additionally, no studies on cognition in this group were found.

3.7. Fertility and Sexual Function in PAIS. At the present time fertility is challenging, but not impossible, for individuals with PAIS raised male [39, 40]. In contrast, fertility is not possible for individuals raised female. A study of 15 adults reared male found that none had ever engaged in penile-vaginal intercourse and all experienced severe sexual dysfunction [41]. In a second study of 21 men and 18 women with 46,XY DSD due to PAIS, most had participated in sexual relationships. Dissatisfaction with sexual function was common but not universal, and this dissatisfaction was similar for those reared male or female [35]. Smaller investigations of sexual function in women with PAIS reveal that, for those who participated in sexual relations with a partner, those experiences were rated as both satisfactory [37] and unsatisfactory [29, 37]. The great variability in outcome measures across studies indicates the need to study larger sample sizes [16] as well as employ standardized, validated measures of sexual function when examining men and women with PAIS.

4. 5α-Reductase-2 Deficiency

5α-reductase-2 (5α-RD-2) deficiency can result in female external genitalia (with a normal sized or enlarged clitoris) and male internal sex ducts in people with a 46,XY chromosomal complement. This occurs because the enzyme 5α-RD-2 is needed to convert testosterone to dihydrotestosterone (DHT). DHT has a greater affinity for the androgen receptor than testosterone and is required to masculinize the external genitalia, but not the internal male sex ducts, during fetal development. Testosterone alone is sufficient to support somatic virilization postnatally [42, 43].

4.1. Health-Related Quality of Life, Psychological Well-Being, and General Health in 5α-RD-2 Deficiency. Clinical distress, determined by responses to the BSI and suicidal ideation, is observed in 46,XY women affected by 5α-RD-2 deficiency, although studies of larger sample sizes are needed to determine the generalizability of this finding [14]. Whether this distress is due to female assignment, feminizing surgeries, or both is unknown at this time. A bone health investigation of affected adults (none of whom had been gonadectomized nor given exogenous hormone replacement) revealed that bone mineral density did not differ from unaffected men [22]. A second bone density study concluded that DHT is not needed to maintain normal bone health [44]. No other studies on general health outcomes were located for review for this particular group of DSD. Of particular concern is the lack of knowledge pertaining to germ cell tumor [23] or prostate cancer [28] risk for this group. Additionally, no studies of cognitive performance were located.

4.2. Fertility and Sexual Function in 5α-RD-2 Deficiency.

Both sperm production and paternity have been documented in men affected by 5α-RD-2 deficiency [43, 45–48]. High-dose androgen therapy improves virilization, erectile response and ejaculatory volume in individuals reared male [45]. For those who identify as women, sexual activity is reported to be satisfactory following vaginal dilatation [44]. Similar to AIS, it is not clear how sexual function in people with 5α-RD-2 deficiency, reared male or female, contributes to QoL.

5. 17β-Hydroxysteroid Dehydrogenase-3 Deficiency

17β-HSD-3 deficiency results in impaired testicular conversion of androstenedione to testosterone [49]. The clinical presentation of 17β-HSD-3 deficiency can be confused with CAIS as affected individuals often present with female external genitalia prior to puberty [50, 51]. If the testes remain in situ, virilization at puberty occurs in a manner that is similar to what is observed in 5α-RD-2 deficiency [50, 52].

5.1. Health-Related Quality of Life, Psychological Well-Being, and General Health in 17β-HSD-3 Deficiency. Clinical distress as determined by the BSI and suicidal ideation is observed in 46,XY women affected by 17β-HSD-3 deficiency, but interpretation of these data is limited by the small sample size studied [14]. Once again, how gender assignment and the medical and surgical treatment that accompanies such assignment impact QoL for this group is unknown. Germ cell tumor risk is estimated to be intermediate (≈28%) [23, 50]. No other studies of general health or cognition conducted in this category of 46,XY DSD were located for review.

5.2. Sexual Function and Fertility in 17β-HSD-3 Deficiency. Case reports of 46,XY women with 17β-HSD-3 deficiency indicate satisfactory sexual function [44, 53], but available information is too incomplete to draw conclusions with confidence. Case reports of affected individuals living as men also indicate satisfactory sexual function [50, 53], although dissatisfaction attributed to having a small phallus appears in the literature [51].

6. Summary and Conclusions

Of the 35 studies reviewed that included outcomes information apart from gender, 24 included information about CAIS, 9 about PAIS, 11 about 5α-RD-2 deficiency, and 5 about 17β-HSD-3 deficiency. Possibly, greater emphasis has been placed on studying CAIS apart from gender because female rearing in this particular DSD is undisputed. In contrast, male or female rearing occurs in people affected by PAIS, 5α-RD-2, and 17β-HSD-3 deficiencies. Perhaps GI/R and sexual orientation have been the focus of studies in these conditions in response to the clinical challenges of assigning gender in
affected individuals. Finally, because CAIS has an animal model (tfm) associated with it, this condition may lend itself more easily to scientific investigation.

Results from studies of psychological well-being in the specific 46,XY DSD categories considered here vary greatly across investigations. This is likely due to the fact that these include only a handful of participants, interviewed only once, in no particular relation to developmental stage or medical/surgical event. Future studies should include larger samples and take into account developmental stages as well as the potential impact of corresponding medical and surgical procedures associated with these stages [16]. Additionally, for those who have access to mental health services, it is critical to determine the effectiveness of these services on psychological well-being within specific categories of DSD.

No systematic studies of IQ or cognition have been conducted in people affected by 46,XY DSD due PAIS or androgen biosynthetic defects due to 5α-RD-2 or 17β-HSD-3 deficiencies. Unlike tfm rodent models, it is unknown if women with CAIS are more likely to develop spatial memory problems if they also express the epsilon 4 allele of the APOE gene. As individuals with 46,XY DSD are generally expected to live a full lifespan, a more complete understanding of the potential for their DSD to impact neuropsychological development, particularly later in development, is needed.

General health outcome studies in people affected by AIS, 5α-RD-2 deficiency, and 17β-HSD-3 deficiency are few and have been limited to gonadal tumors, and bone and prostate health. Further health outcome studies, particularly in conditions that exhibit clear sex differences or influences of sex steroid action, are needed. For example, whether or not possession of a Y chromosome places 46,XY women at risk for developing a male-typical presentation and course of cardiovascular disease, independent of androgen action, is not known. Alternatively, it is currently unknown if under-masculinized genetic males have an elevated risk for developing female-typical medical conditions such as autoimmune diseases or depression. As our understanding of DSD broadens to include physical and mental health outcomes apart from gender development, it is anticipated that QoL will improve for affected individuals.

Fertility and sexual function can be important components to living a fulfilled life and maintaining relationships; yet we know very little about such topics. We do know from patient populations affected by conditions other than DSD that infertility [54] sexual dysfunction [55] and surgeries to the reproductive organs [56] negatively impact health-related QoL. Such information, as it pertains specifically to DSD, is crucial in optimizing treatment and supporting affected individuals.

Knowledge about the physical and mental health outcomes in DSD throughout the life cycle is important for improving or maintaining health in affected individuals and the population overall. For example, the few studies of bone health that have been conducted in AIS and 5α-RD-2 deficiency imply that testosterone, but not DHT, is necessary for optimizing bone density. Such information may be useful for developing treatments for conditions such as osteopenia and osteoporosis.

It is important to focus on QoL factors for persons with a DSD diagnosis because parents ask questions such as How will my child perform in school? Will my child establish friendships? Will my child have a career? Will my child fall in love? Parents also want to know how their children will feel about their DSD diagnosis. In short, parents want information about their affected child’s future QoL. Only through systematic investigation of such questions will answers be obtained, and appropriate interventions developed.

We could find no data pertaining to individual adjustment to the categories of DSD discussed in the current review. Additionally, very little is known about how family members respond to a child’s diagnosis of DSD. While we know that parents of children affected by CAIS or PAIS report feelings of shock, grief, anger, and shame when they learn of their child’s condition [57], more studies of parents are needed as their attitudes surely exert a significant impact on subsequent child health and well-being [58]. Finally, the definition for QoL presented earlier includes social and spiritual components—neither of which were investigated systematically in any of the papers reviewed.

In conditions in which GI/R does not always develop in concordance with sex of rearing—such as PAIS, 5α-RD-2 deficiency, and 17β-HSD-3 deficiency—a better understanding of factors that influence QoL may help to explain the developmental trajectory of GI/R in people for whom GI/R development does not match their initial gender assignment [11]. We still have a long way to go in understanding why some people with these conditions change gender while others do not. Importantly, approximately a third of people with DSD other than AIS, 5α-RD-2 deficiency, or 17β-HSD-3 deficiency are born with malformations that likely affect QoL [59]. Future studies must consider those individuals as well. This review has attempted to show that we also have a long way to go before we have a full appreciation of the mental, physical, social, and spiritual domains that contribute to QoL of people affected by 46,XY DSD who are born with either female or ambiguous external genitalia.

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