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Endocrine Management of Ovotesticular DSD, an Index Case and Review of the Literature

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Abstract

Ovotesticular Differences in Sexual Development (OT-DSD) is a rare subset of DSD with great phenotypic variability characterized by the presence of both testicular and ovarian tissue in the same individual. Here, we describe the case of 46,XX, SRY-negative baby with ambiguous genitalia and ovotestis discovered during laparoscopy. As the family decided on female gender of rearing, the testicular component of the ovotestis was removed while the ovarian component was preserved. Stemming from this case, we review the clinical presentation of OT-DSD throughout ages, the role of genetics and risk for gonadal tumors when making decisions about prophylactic gonadectomy. Finally, we summarize the most recent information of the spontaneous endocrine function, with or without conservative therapy, and fertility potential of people with OT-DSD.

Keywords

Fertility; Gonadectomy; Gonadoblastoma; Ovotestis; Puberty

Introduction

OT-DSD is a rare subset of DSDs with incidence reports varying from 1:100,000,000 - 1:100,000 live births or in 2-10% of all DSD (1,2). It is characterized by the presence of both testicular and ovarian tissue in the same individual. The phenotype is variable (1,3-7). Patients usually present in infancy with differences in the appearance of external genitalia. However, there are multiple cases of affected individuals who present later in life, as phenotypical males or females (1,3-8). While most people with OT-DSD are hypogonadal, spontaneous puberty and fertility has been described (1,3,4). Gonadectomy is frequently advised because of the increased cancer risk in the dysgenetic gonad (9). Providing appropriate counseling for an individual patient with DSD is, therefore, complex and requires a multidisciplinary team approach. Furthermore, as OT-DSD is rare, long term outcome data to guide clinical practice are sparse. Decisions about gonadectomy vs. conservative surgery that preserves some gonadal tissue are challenging. In this paper, we present a baby with OT-DSD who underwent conservative gonadal surgery, review long

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The authors have no conflict to disclose.

term outcome data on gonadal function and fertility and highlight important aspects in the decision-making process for gonadal surgery in these patients.

Index Case

Our patient presented to Endocrinology shortly after birth due to clitoromegaly. The baby was born at term, after an uncomplicated pregnancy. Birth weight was normal. The genital examination was significant for a phallus-like structure measuring approximately 3.5 cm in length, mild posterior labial fusion, separate urethral and vaginal openings, and no palpable gonads. Chromosomes were 46,XX with a negative fluorescence *in situ* hybridization (FISH) for sex-determining region Y (SRY). Ultrasonography revealed a normal appearing uterus while the gonads were not clearly visualized. The clinical presentation along with the 46,XX karyotype, prompted investigation into the diagnosis of congenital adrenal hyperplasia (CAH). However, serum 17-hydroxyprogestrone levels were normal for age at 150ng/dL and did not rise significantly following a high dose cortrosyn test (260ng/dL). Furthermore, serum cortisol concentrations were normal at 18 mcg/dL. Normal baseline and stimulated deoxycorticosterone and 11-deoxycortisol levels ruled out 11-hydroxylase deficiency. The rest of the laboratory evaluation was significant for an elevated circulating testosterone level at 80 ng/dL during mini-puberty of infancy, along with anti-mullerian (AMH) hormone levels in the male range at 42 ng/dL. Serum gonadotropins were normal. This laboratory assessment raised the suspicion for presence of testicular tissue and the baby underwent an exploratory laparoscopy. During the procedure, what appeared to be a right streak gonad was removed; however, pathology revealed the presence of ovarian parenchyma with primordial and primary follicles. The left gonad had the appearance of an ovotestis, with clearly demarcated ovarian and testicular components, along with an associated fallopian tube. This gonad was biopsied and the pathology revealed dysgenetic testicular tissue with seminiferous tubules some of which contained few germ cells. No morphologic evidence of intratubular germ cell neoplasia was identified. Exploratory laparoscopy and cystoscopy confirmed normal uterus and vagina.

The family had the opportunity to express their wishes and concerns and received extensive counseling with Endocrinology, Urology, Genetics and Psychology about the diagnosis and anatomy. Discussion initially surrounded parental perception, prior thoughts on gender rearing, and perception given what was known about internal and external anatomy. Further conversation ensued regarding reproductive and fertility potential with the bipolar ovo-testis with clear demarcation and opportunity for conservative gonadal surgery. While no definitive information could be provided, female rearing was favored by the team and family from a fertility and sexual function standpoint given the presence of a separate vaginal orifice, possible functional ovarian tissue with follicles, and overall more reassuring ovarian function in 46 XX OT-DSD as outlined below. The family ultimately decided on a female gender of rearing. The baby underwent a repeat laparoscopy during which the testicular component of the left ovotestis was removed. In retrospect, the presumed "streak gonad" may have been biopsied and retained given the presence of ovarian parenchyma, although it would be have been challenging to determine the risk of gonadal cancer of this intra-abdominal dysgenetic gonad.

To follow up on the removal of the testicular components, 2 months post-operatively a laboratory evaluation and HCG stimulation test was performed. Serum testosterone level was low at 8ng/dL and did not rise after an HCG stimulation test (1,500IU intramuscular for 3 days) (post HCG serum testosterone at 10 ng/dL) confirming the absence of leydig cell tissue. An undetectable AMH level suggested that the seminiferous tubules had been successfully removed.

Clinical Presentation

We describe a baby with clitoral enlargement who was found to have a unilateral intraabdominal gonad with streak appearance but ovarian tissue on histology and a contralateral ovotestis, setting the diagnosis of OT-DSD. The case highlights the diagnostic importance of laparoscopy and gonadal biopsy. Most individuals with OT-DSD have an ovotestis, either bilaterally or unilaterally (1,3-7). The combination of an ovary and a testis on each side or presence of a streak gonad may also occur, although these findings are rather rare.

The baby in this vignette had a bipolar ovotestis that allowed the surgeon to identify and preserve the ovarian component of the gonad. This surgical approach that preserves the gonadal part of the ovotestis that conforms with the gender of rearing is referred to in the literature as a conservative gonadal surgery. Conservative surgery is not always feasible as the morphology of the ovotestis may vary (2,10). A histology review of 111 gonads of patients with OT-DSD from South Africa describes a mixed-type ovotestis that consists of an outer layer or mantle of ovarian tissue of various thickness that encapsulates either a defined core of testicular tissue or an admixture of ovarian and testicular tissue (10). A mixed-type ovotestis precludes conservative gonadal surgery.

The appearance of external and internal genitalia reflects the ability of the testicular component to secrete testosterone and AMH during fetal life. The external genitalia may, therefore, vary in their degree of virilization from ambiguous to phenotypically male or to phenotypically female (4). AMH, secreted by the Sertoli cells of the fetal testis, acts in a paracrine fashion to suppress the ipsilateral differentiation of the Mullerian structures. As the testicular component of an ovotestis is frequently dysgenetic, the internal genitalia may vary in appearance and include remnants of Mullerian and Wolfian structures, a hemi-uterus or a normal uterus (1). Gonads can be the scrotal area or undescended (1,3,4).

Phenotypical males usually have a history of hypospadias or cryptorchidism. As these individuals progress in central puberty, the ovarian component may become hormonally active and undergo ovulatory changes (11-13). Indeed, cases of painful testicular enlargement caused by follicular changes or bleeding within the ovotestis have been described (11-13). Rare cases of periodic hematuria when there is a functional uterus opening into the urinary tract or periodic abdominal pain have also been reported (1,3,4). Finally, close to 90% of pubertal males with OT-DSD have some degree of gynecomastia as a result of increased circulating estrogens from the ovarian component of the ovotestis. Patients with female phenotype may present with clitoromegaly, amenorrhea or periodic abdominal pain (1,3-7).

Genetics: From Clinical Evaluation to Providing Insights in Gonadal Differentiation

Given the rarity of OT-DSD, identifying proportions of individuals with particular genetic etiology and genotype-phenotype correlations is challenging. Barseghyan *et al* (14), in a review of two older publications (1,15), which included a total of 400 individuals suggests that approximately 65% are 46,XX, 20% are mosaic and contain some Y-chromosome, and about 10% are 46,XY. These data were reported prior to 1993 and were restricted to karyotype. Among all 46,XX DSD, it is thought that 80-90% have a translocated SRY gene, the primary driver for testicular development (4). In contrast, in 46,XX OT-DSD, the specific rate of SRY positivity is difficult to assess and may range from 10% (16) to 35% (1). It is possible that some of these individuals are missed as they may be SRY-negative in the blood samples but do have SRY gene expression in the testicular component of the gonad (i.e. mosaic).

All individuals with DSDs should have thorough genetic testing as part of their multidisciplinary evaluation (17). Practically, the presence of OT-DSD is often not known at the time of genetic testing. Determination of the chromosomal compliment via standard karyotype is often undertaken first, given that it is both relatively inexpensive and faster than some other tests; however, the genomic resolution is not high. Small but clinically relevant deletions can be missed, the size of which depends on the testing laboratory and their standards; for example, an individual with 46,XY and a small intragenic SRY deletion would be missed. Karyotype can also miss mosaicism, which is particularly relevant in OT-DSD. A karyotype to rule out mosaicism involves counting of additional cells, and could include FISH, so including the indication for the test is critical for communication with the testing laboratory. Depending on the laboratory, a genomewide SNP array may be more or less sensitive to low level mosaicism than a karyotype. Even a typical karyotype and SNP array does not fully rule out mosaicism, given that mosaicism can be absent in the peripheral blood but present in other tissues such as gonads. In the case of individuals with non-mosaic 46,XX or 46,XY OT-DSD, whole exome (WES) or next-generation sequencing (NGS) panels can be used to identify the specific molecular diagnosis (18,19). 46,XX OT-DSD and 46,XY OT-DSD are no longer “complete” molecular diagnoses, in the absence of further genetic testing. Interpretation of this testing can be challenging, and involvement of a clinical genetics professional (physician or genetic counselor) is advised.

The recent advancement in genetic testing has helped with the diagnosis and management of individual patients but has also shed light in the biology of gonadal differentiation. The timely expression of multiple transcription factors enables the progressive development of the initial undifferentiated, bipotential gonad into a testis or ovary (18). The identification of the mammalian testis-determining gene SRY a quarter of a century ago provided an entry point to our understanding of testicular development. Since then, a “pro-testis” cascade of molecular events that involves expression of multiple members of the SOX family, such as SOX 9, SOX 3, SOX10 and SOX 13, has been described (18). Genes involved in ovarian differentiation were described later, and briefly, include the activation of WNT4 and RSPO1, that stabilize β-catenin to then promote the expression of ovarian genes such as follistatin

(FST) and FOXL2 (18). Studies of SRY-negative 46,XX OT-DSD individuals reveals either an increased expression of pro-testis genes or insufficient expression of pro-ovarian genes or genes that suppress testicular differentiation (20). SOX9 duplication, overexpression of SOX3 and SOX10, loss-of -function mutations of WNT4 and RSPO1 have all been described in SRY-negative 46,XX OT-DSD (20). More recently NR5A1 and NRF2F2 have been described as novel candidate genes in XX OT-DSD (21).

Risk for Gonadal Tumors and Considerations about Prophylactic Gonadectomy

Individuals with DSD are at increased risk for the development of germ cell tumors or cancer (GCC) (9,19). Risk factors that predispose to malignancy include the presence of a dysgenetic gonad, an intraabdominal location of the gonad and the presence of the Y chromosome (19). The gonadoblastoma locus (GBY), mapped at the proximal part of the short and long arm of the Y, is the only oncogenic locus on the human Y chromosome (22). Expression of the GBY locus is considered to render the developmentally-arrested germ cells of a dysgenetic gonad susceptible to malignancy. The main GBY candidate gene is the testis-specific protein Y (TSPY) gene located in the proximal part of the short Y arm, which encodes a protein that is involved in testicular germ cell proliferation and differentiation during fetal life. TSPY is overexpressed in germ cells of DSD patients and is thought to disrupt normal cell cycle regulation and predispose them to malignancy (22,23). Beyond TSPY expression, immunohistochemical characterization of the gonad for certain embryonic germ cell markers has been proposed as a way to better assess the individual risk for GCC development and guide management (19,22). The POU transcription factor Oct-3/4 has been shown to be critical for maintaining embryonic stem (ES) cell character. Absence of a positive staining for Oct-3/4 in the biopsy sample indicates that no such cells are present. In contrast, prolonged expression of Oct-3/4 is thought to play a role in the development and proliferation of precursors of GCC such as gonadoblastoma or carcinoma -*in situ* (CIS). In case of a positive staining for Oct-3/4, further immunohistochemistry for KITLG might be helpful in identifying GCC. A positive KITLG staining indicates truly neoplastic germ cells (CIS and gonadoblastoma) allowing for better decision making regarding prophylactic gonadectomy (23,24).

Gonadoblastomas, dysgerminomas, seminomas and yolk sac carcinomas have been reported in OT-DSD (25,26). The risk for gonadal tumors in OT-DSD is considered low compared to other DSD. Rates around 2.5-4% have been reported (1,3,4). These low numbers likely reflect the fact that most of the OT-DSD individuals have a 46,XX karyotype and lack SRY. Although gonadoblastoma has been reported in 46,XX non-DSD individuals, these cases are exceedingly rare (27). The exact risk of gonadal malignancy in OT-DSD persons is likely to vary considerably according to the chromosomal make up and the location of the gonad. Gonadal biopsy at the time of diagnosis can give information on how immature or poorly differentiated the gonadal tissue is and whether there are precursors of malignancy, such as carcinoma-in-situ (CIS) or gonadoblastoma. In general, a poorly differentiated or dysgenetic gonad is at higher risk for malignancy. Presence of an intra-abdominal streak gonad in an individual with a Y chromosome is associated with increased risk for

malignancy and requires surgical removal. In contrast, the cancer risk of a phenotypical male with OT-DSD and a descended gonad may be quite different even in the presence of a Y chromosome. Counseling in such cases is hindered by the rarity of the disorder and sparse disease-specific data. Management may be similar to individuals with 46,XY or 45X/46,XY gonadal dysgenesis and involve regular self-examination of the descended gonad and annual ultrasounds after puberty (19,23). Overall, discussions with patients and families about prophylactic gonadectomy in OT-DSD should be individualized taking into account the specific cancer risk in each case but also gender assignment and the potential endocrine function of the gonad.

Endocrine and Sexual Function

The endocrine function is variable in OT-DSD ranging from normal to gonadal failure (1,3-7). In neonates, normal for age serum testosterone concentrations during the mini-puberty of infancy or after stimulation with HCG have been reported (1,3-7). AMH levels are variable and can frequently fall within the low male range (1,3-7).

Long term endocrine function in OT-DSD is presented in few outcome studies coming from various parts of the world (1,3-7,28,29). Unless the child undergoes bilateral gonadectomy in infancy, onset of puberty can be normal. The same is true for individuals who underwent conservative gonadal surgery. The number of patients who enter puberty spontaneously varies according to the report and can be close to 50% in certain series (1,3-7). However, progressive gonadal failure is frequent, and as a result, some patients require hormonal replacement to complete puberty or to maintain sexual function later on in life (1,3-7). Gonadal failure involves more frequently the testicular component, which is typically dysgenetic and shows progressing germ cell loss and fibrosis with advancing age (1,4). On the contrary, the ovarian component can be normal and contain multiple follicles that undergo ovulatory changes during puberty. Spontaneous menarche and regular menstruation has been reported in phenotypic females who have an intact uterus (1,3,4). Premature ovarian failure has also been reported (1,3,4).

Little is known about the sexual function of people with OT-DSD. Beyond endocrine concerns and need for hormonal replacement, sexual function can be affected by previous genital surgery. Individuals raised as males may require multiple surgeries and suffer complication such as urethra fistula (3). Sexual function and activity can be normal, and a number of individuals report being married or in a relationship (1,3,4). The exact rates, however, are uncertain. In a series of 33 individuals with OT-DSD, information on sexual satisfaction was collected in 9 individuals (5 males and 4 females). In this series, more males expressed satisfaction with their sexual life and neither group expressed gender dysphoria (4). These findings certainly need to be validated with additional studies.

Rates of gender dysphoria are unknown and this lack of information may render the decision for gender assignment challenging in a baby with ambiguous genitalia due to OT-DSD. Elevated serum testosterone levels during neonatal period (18) raise the concern of brain masculinization and imprinting (18). While prenatal androgen exposure is associated with “masculine” behaviors such as toy preference, its role on gender dysphoria and sexual

orientation remains less certain. Zucker reported a child who was assigned to the male sex at birth, was reassigned to the female sex at age two months and developed gender dysphoria later on (30). A series of 20 Brazilian patients with OT-DSD, with two-thirds assigned as male, reported re-assignment of three females to males (3). Among 64 South African individuals with OT-DSD, also with two-thirds assigned male, gender dysphoria was noted in 8 subjects (11%), all initially assigned female gender. Five of these subjects underwent reassignment (31). In contrast to the Brazilian and South African cohorts, 3 of 7 Thai children with OT-DSD changed gender assignment: 2 from male to female and 1 from female to male (28). Finally, in a Japanese cohort of 8 individuals, half reared female and half male, 6 had long-term (median 8.4 yr) follow up and none had gender dysphoria (5). With the small sample sizes, it is challenging to make broad conclusions regarding gender dysphoria but the published cohorts seem to suggest that, despite a greater percentage assigned male, a large component of those with gender dysphoria were initially assigned female. The debate is ongoing whether patients should have early surgery based on the decision of the family with the guidance of the medical team (5,6,32) or the “watch and wait” approach advocated for by the intersex community and certain medical and legislative bodies (33). With time and investigation, we may gain some insight into the differences of gender identity differences and gender dysphoria between these groups.

Fertility

Fertility is markedly reduced in OT-DSD due to multiple factors. First of all, many patients may undergo gonadectomy because of risk for malignancy. There may be anatomical barriers because of abnormalities in Mullerian or Wolfian structures. Some of these individuals may avoid intimate relationships or sexual activity because of dissatisfaction with genital appearance or function (3). Finally, the gonad may be dysgenetic. Histologically, the ovarian component of ovotestis is typically normal, while the testicular tissue is mostly dysgenetic (1). In contrast, spermatogenesis has been reported in solitary testis of individuals with OT-DSD (34).

OT-DSD is a rare condition with only few studies reporting on long term outcomes including fertility (1,3,4,8). Risk for infertility is, therefore, hard to determine. Spontaneous pregnancies have been reported in women with OT-DSD as early as 1988 (8). In a series of 283 cases of OT-DSD (1), 21 pregnancies were carried by 10 women, who had either ovotestis at the time of delivery or had undergone prior removal of the testicular component of the ovotestis. All of them had a 46XX karyotype except one with a mixed 46XX/46 XY karyotype. In contrast, only one male fathered a child. In a smaller series of 33 individuals (4), no fertility was reported. Azoospermia was observed in a single patient who had sperm analysis.

New reproductive technologies may now offer additional fertility options for individuals with OT-DSD. In 2005, Sugawara *et al* reported a case of successful pregnancy fathered by a 46,XX/46,XY individual with OT-DSD and azoospermia (35). Sperm was retrieved by testicular biopsy and pregnancy was achieved by intracytoplasmatic sperm injection (ICSI). A second successful delivery was later reported involving the same individual and using a refrozen thawed specimen from the initial testicular biopsy (35). Another successful

pregnancy by ICSI using ejaculate sperm from a 46,XX/46, XY man with OT-DSD was recently reported by another group (36). Further, patients with intact Mullerian structures may be able to carry a baby to term either via *in vitro* fertilization with partner, self and/or donor gametes (37). As reproductive techniques improve and become more accessible, one is likely to expect that an increasing number of individuals with OT-DSD would be able to achieve fertility.

Future directions may include efforts around fertility preservation. A recent study showed that most patients with DSD, including OT-DSD, have the potential for fertility as germ cells are found in the DSD gonad. Further research is needed to determine the viability of these cells and whether they can mature *in vitro* (38). Currently, no data are available to assess the value of cryopreservation of surgically removed gonadal tissue for later fertility attempts or whether this approach is safe for patients with a precursor lesion for GCC.

Conclusions

OT-DSD presents with great phenotypic variability, which influences decisions about gender assignment and counseling about genital and gonadal surgery. Individuals who are phenotypically males or females usually present later on in life, when they have likely established a gender identity. In such cases, decisions about gonadal surgery are driven primarily by concerns for gonadal malignancy. Conservative therapy, whenever feasible, is desirable because these individuals may maintain endocrine gonadal function and perhaps fertility. Decisions in infancy can be more complex. These babies usually present with sexual ambiguity. Decisions about gender assignment can be particularly challenging as gender dysphoria and/or patient-initiated gender changes have been described in this group, and disease-specific guidelines to direct management are lacking. In such settings, watchful waiting to allow for the child to participate in the decision needs to be discussed with family. During this difficult time, families may also reach a decision about the gender of rearing based on genital appearance, the available surgical options, and their own personal beliefs and social environment. In this context, conservative gonadal surgery can be performed after considering the needs of each individual case. The role of the endocrinologist, as part of a multidisciplinary team, is crucial not only during diagnosis and initial counseling but also for long term hormonal monitoring and treatment of these individuals.

References

1. Krob G, Braun A, Kuhnle U. True hermaphroditism: geographical distribution, clinical findings, chromosomes and gonadal histology. Eur J Pediatr 1994;153:2–10 [PubMed: 8313919]
2. Nistal M, Paniagua R, Gonzalez-Peramato P, Reyes-Mugica M. Perspectives in Pediatric Pathology, Chapter 7. Ovotesticular DSD (True Hermaphroditism). Pediatr Dev Pathol 2015;18:345–352 [PubMed: 25105460]
3. Sircili MH, Denes FT, Costa EM, Machado MG, Inacio M, Silva RB, Srougi M, Mendonca BB, Domenice S. Long-term followup of a large cohort of patients with ovotesticular disorder of sex development. J Urol 2014;191:1532–1536 [PubMed: 24679863]
4. Verkauskas G, Jaubert F, Lortat-Jacob S, Malan V, Thibaud E, Nihoul-Fekete C. The long-term followup of 33 cases of true hermaphroditism: a 40-year experience with conservative gonadal surgery. J Urol 2007;177:726–731 discussion 731 [PubMed: 17222668]

5. Matsui F, Shimada K, Matsumoto F, Itesako T, Nara K, Ida S, Nakayama M. Long-term outcome of ovotesticular disorder of sex development: a single center experience. Int J Urol 2011;18:231–236 [PubMed: 21255100]
6. Scarpa MG, Lesma A, Di Grazia M, Rigamonti W. Ovotesticular differences of sex development: male or female? Case series. Ital J Pediatr 2019;45:66 [PubMed: 31146767]
7. Mao Y, Chen S, Wang R, Wang X, Qin D, Tang Y. Evaluation and treatment for ovotesticular disorder of sex development (OT-DSD) - experience based on a Chinese series. BMC Urol 2017; 17:21 [PubMed: 28351396]
8. Starceski PJ, S.W., Lee PA. Fertility in True Hermaphroditism. Adolescent and Pediatric Gynecology 1988;1:55–56
9. Pleskacova J, Hersmus R, Oosterhuis JW, Setyawati BA, Faradz SM, Cools M, Wolffenbuttel KP, Lebl J, Drop SL, Looijenga LH. Tumor risk in disorders of sex development. Sex Dev 2010;4:259–269 [PubMed: 20558977]
10. Wiersma R, Ramdial PK. The gonads of 111 South African patients with ovotesticular disorder of sex differentiation. J Pediatr Surg 2009;44:556–560 [PubMed: 19302858]
11. Roth JD, Haddad NG, Albright EA, Cheng L, Rink RC, Kaefer M. An ovulating follicle presenting as a testicular mass in a teenage patient with ovotesticular DSD. Urol Case Rep 2018;18:26–28 [PubMed: 29686967]
12. Mirshahvalad SA, Alinia P, Hekmati P, Nafisi N, Kajbafzadeh AM. Ovotesticular Disorder of Sex Development Presenting as an Acute Scrotum. Urology 2018;116:176–179 [PubMed: 29548867]
13. Shankara Narayana N, Kean AM, Ewans L, Ohnesorg T, Ayers KL, Watson G, Vasilaras A, Sinclair AH, Twigg SM, Handelsman DJ. Painful ovulation in a 46,XX SRY -ve adult male with SOX9 duplication. Endocrinol Diabetes Metab Case Rep 2017
14. Barseghyan H, Villain E. The Genetics of Ovotesticular Disorders of Sex Development, in Genetic Steroid Disorders (ed. New MI) Academic Press 261–263
15. van Niekerk WA, Retief AE. The gonads of human true hermaphrodites. Hum Genet 1981;58:117–122 [PubMed: 6895206]
16. McElreavey K, Achermann JC. Steroidogenic Factor-1 (SF-1, NR5A1) and 46,XX Ovotesticular Disorders of Sex Development:One Factor, Many Phenotypes. Horm Res Paediatr 2017;87:189–190 [PubMed: 27978531]
17. Houk CP, Hughes IA, Ahmed SF, Lee PA, Writing Committee for the International Intersex Consensus Conference P. Summary of consensus statement on intersex disorders and their management. International Intersex Consensus Conference. Pediatrics 2006;118:753–757 [PubMed: 16882833]
18. Arboleda VA, Sandberg DE, Vilain E. DSDs: genetics, underlying pathologies and psychosexual differentiation. Nat Rev Endocrinol 2014;10:603–615 [PubMed: 25091731]
19. Lee PA, Nordenstrom A, Houk CP, Ahmed SF, Auchus R, Baratz A, Baratz Dalke K, Liao LM, Lin-Su K, Looijenga LH 3rd, Mazur T, Meyer-Bahlburg HF, Mouriquand P, Quigley CA, Sandberg DE, Vilain E, Witchel S, Global DSDUC. Global Disorders of Sex Development Update since 2006: Perceptions, Approach and Care. Horm Res Paediatr 2016;85:158–180 [PubMed: 26820577]
20. Grinspon RP, Rey RA. Disorders of Sex Development with Testicular Differentiation in SRY-Negative 46,XX Individuals: Clinical and Genetic Aspects. Sex Dev 2016;10:1–11 [PubMed: 27055195]
21. Kremen J, Chan YM. Genetic evaluation of disorders of sex development: current practice and novel gene discovery. Curr Opin Endocrinol Diabetes Obes 2019;26:54–59 [PubMed: 30507699]
22. Vogt PH, Besikoglu B, Bettendorf M, Frank-Herrmann P, Zimmer J, Bender U, Knauer-Fischer S, Choukair D, Sinn P, Lau YC, Heidemann PH, Strowitzki T. Gonadoblastoma Y locus genes expressed in germ cells of individuals with dysgenetic gonads and a Y chromosome in their karyotypes include DDX3Y and TSPY. Hum Reprod 2019;34:770–779 [PubMed: 30753444]
23. van der Zwan YG, Biermann K, Wolffenbuttel KP, Cools M, Looijenga LH. Gonadal maldevelopment as risk factor for germ cell cancer: towards a clinical decision model. Eur Urol 2015;67:692–701 [PubMed: 25240975]

24. Spoor JA, Oosterhuis JW, Hersmus R, Biermann K, Wolffenbuttel KP, Cools M, Kazmi Z, Ahmed SF, Looijenga LHJ. Histological Assessment of Gonads in DSD: Relevance for Clinical Management. Sex Dev 2018;12:106–122 [PubMed: 29131109]
25. Ulbright TM, Young RH. Gonadoblastoma and selected other aspects of gonadal pathology in young patients with disorders of sex development. Semin Diagn Pathol 2014;31:427–440 [PubMed: 25129544]
26. Huang H, Wang C, Tian Q. Gonadal tumour risk in 292 phenotypic female patients with disorders of sex development containing Y chromosome or Y-derived sequence. Clin Endocrinol (Oxf) 2017;86:621–627 [PubMed: 27862157]
27. Esin S, Baser E, Kucukozkan T, Magden HA. Ovarian gonadoblastoma with dysgerminoma in a 15-year-old girl with 46, XX karyotype: case report and review of the literature. Arch Gynecol Obstet 2012;285:447–451 [PubMed: 21879333]
28. Jaruratanasirikul S, Engchaun V. Management of children with disorders of sex development: 20-year experience in southern Thailand. World J Pediatr 2014;10:168–174 [PubMed: 23775676]
29. Damiani D, Guedes DR, Damiani D, Setian N, Maciel-Guerra AT, Mello MP, Guerra-Junior G. [True hermaphroditism: experience with 36 patients]. Arq Bras Endocrinol Metabol 2005;49:71–78 [PubMed: 16544036]
30. Zucker KJ, Bradley SJ, Hughes HE. Gender dysphoria in a child with true hermaphroditism. Can J Psychiatry 1987;32:602–609 [PubMed: 3676994]
31. Ganie Y, Aldous C, Balakrishna Y, Wiersma R. The Spectrum of Ovotesticular Disorders of Sex Development in South Africa: A Single-Centre Experience. Horm Res Paediatr 2017;87:307–314 [PubMed: 28376506]
32. Bangalore Krishna K, Houk CP, Lee PA. Pragmatic approach to intersex, including genital ambiguity, in the newborn. Semin Perinatal 2017;41:244–251
33. Cools M, Hoebeke P, Wolffenbuttel KP, Stoop H, Hersmus R, Barbara M, Wedell A, Brüggenwirth H, Looijenga LHJ, Drop SLS. Pubertal androgenization and gonadal histology in two 46,XY adolescents with NR5A1 mutations and predominantly female phenotype at birth. Eur J Endocrinol 2012;166:341–349 [PubMed: 22080441]
34. Bayraktar Z. Potential autofertility in true hermaphrodites. J Matern Fetal Neonatal Med 2018;31:542–547 [PubMed: 28282768]
35. Sugawara N, Kimura Y, Araki Y. Successful second delivery outcome using refrozen thawed testicular sperm from an infertile male true hermaphrodite with a 46, XX/46, XY karyotype: case report. Hum Cell 2012;25:96–99 [PubMed: 23203848]
36. Sha YW, Sha YK, Ding L, Lin SB, Ji ZY, Wang X, Song YQ, Li P. A successful pregnancy by intracytoplasmic sperm injection using ejaculate sperm from an infertile man with 46, XX/46, XY true hermaphrodite. Asian J Androl 2017;19:721–722 [PubMed: 27905326]
37. Taneja J, Ogutu D, Ah-Moye M. Rare successful pregnancy in a patient with Swyer Syndrome. Case Rep Womens Health 2016;12:1–2 [PubMed: 29629300]
38. Finlayson C, Fritsch MK, Johnson EK, Rosoklija I, Gosiengfiao Y, Yerkes E, Madonna MB, Woodruff TK, Cheng E. Presence of Germ Cells in Disorders of Sex Development: Implications for Fertility Potential and Preservation. J Urol 2017;197:937–943 [PubMed: 27840018]