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Disorders of Sexual Development in Adult Women

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Abstract

Disorders (differences) of sexual development (DSD) encompass a variety of conditions with atypical development of chromosomal, gonadal, or anatomic sex. Three of the most common differences of sex development conditions include congenital adrenal hyperplasia, complete androgen insensitivity and Turner syndrome. Obstetrician–gynecologists who care for affected individuals in their practice must be familiar with the genetic, endocrine and anatomical considerations of the most common conditions in order to provide optimal care. As women with these conditions transition to adult care, the gynecologist needs to assess the patient's understanding and educate her regarding her diagnosis and ongoing medical care. All of these conditions may affect self-perception, mental health, fertility, sexual function, and bone and cardiovascular health. Women with congenital adrenal hyperplasia need lifelong endocrine management and require genetic counseling prior to pregnancy. Women with androgen insensitivity syndrome require counseling regarding gonadectomy and hormone replacement therapy, and may require vaginal elongation for intercourse. Most women with Turner syndrome experience premature ovarian insufficiency and require long-term estrogen replacement. Women with Turner syndrome often have congenital anomalies and autoimmune disorders which require regular monitoring and care during adulthood. The purpose of this review is to provide the obstetrician gynecologist who cares for adult women with the most common DSD conditions an outline of the current recommendations for screening and ongoing health care, with particular emphasis on the underlying genetics, management of subfertility, infertility and sexual concerns, approach to hypogonadism, and understanding of associated comorbidities.

Background

In 2006 a consensus statement introduced the term *disorders of sex development* or DSD to describe a spectrum of conditions that may be diagnosed in infancy due to atypical development of the external genitalia, in adolescence due to atypical pubertal development, or when a person is experiencing infertility.¹ More recently the term *differences in sex development* has been advocated as less pejorative and has gained acceptance. When these

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conditions are identified in infancy or around puberty, these patients are often cared for by pediatric providers, and decisions around genital alterations, management of gonadal tissue, and introduction of hormones may occur in childhood and early adolescence. Gynecologists often function as primary care providers for women and thus must be familiar with these conditions and know how to best care for their affected patients in late adolescence and in adulthood.² Here we review the care and management of three of the most common disorders of sexual development (DSD) conditions: 46 XX congenital adrenal hyperplasia (CAH), 46 XY complete androgen insensitivity syndrome (CAIS), and 45 X with or without mosaicism (Turner syndrome or TS).

General Considerations

Though these conditions are varied in their genetic, hormonal and medical implications, there are common themes in transition from pediatric to adult care, and gynecologists should not assume that the adolescent has been fully prepared.³ It is important that the gynecologist assess previous records to assure that the diagnosis is accurate and also make sure that the patient completely understands her condition and prior interventions (Table 1). The gynecologist should educate the patient about how genes, gonads, and hormones function in terms that are clear, and may also need to assist the patient in developing ways to potentially share such information with others.⁴ With advances in genetic and hormonal diagnostic testing, if the patient has not had complete evaluation, she may need to be referred for further evaluation by other specialists, including adult endocrinologists, geneticists, and urologists. Finally, as providers of care for women, the gynecologist will need to perform condition-specific and routine health care assessments.

As gynecologists, we are trained to discuss sexual health and intimacy, fertility, and reproductive options, and can address, in combination with our mental health colleagues, the complexities of gender identity, personal expression, and sexual orientation. It is important throughout these health care encounters to keep in mind that many of these women do not want to be defined by their condition but rather as an individual who happens to have such a condition. Many women with DSD conditions express anxiety, depression, and decreased quality of life which may be related to shame, stigma, infertility, and identity concerns.⁵ Physicians may need to connect the patient with psychological support, not only through mental health providers but also through support groups. (Table 1)

Congenital Adrenal Hyperplasia

Background

Congenital adrenal hyperplasia is typically an autosomal recessive congenital condition defined by a deficiency in enzymes in the cortisol steroidogenesis pathway, affecting the conversion of cholesterol into cortisol, testosterone, and estradiol. The most common form of congenital adrenal hyperplasia identified at birth is related to mutations in the *CYP21A2* gene, which results in decreased enzymatic activity of 21-hydroxylase. This causes decreased levels of cortisol and aldosterone which results in increased levels of adrenocorticotrophic hormone (ACTH). The increased ACTH induces adrenal hyperplasia and consequently elevated levels of 17-OH progesterone (17OHP) and testosterone. The

elevated levels of androgens in utero cause varying degrees of virilization of the external genitalia in female newborns and genital ambiguity at birth. Due to life-threatening hypoglycemia and hyponatremia associated with classic salt-wasting congenital adrenal hyperplasia (CAH), universal screening is performed in the United States and results in many neonates being diagnosed at birth. There are other enzymes that can be affected and also alter the production of sex steroid hormones in utero and postnatally thus leading to less common forms of congenital adrenal hyperplasia. For the purpose of this review, we will focus on 21 hydroxylase deficiency, which causes classic CAH and nonclassic CAH. Congenital adrenal hyperplasia typically presents at birth with or without salt wasting. Non-classic CAH presents in later childhood, adolescence or adulthood with symptoms overlapping those of polycystic ovary syndrome (PCOS).

Medical Management

In infancy and childhood, medical management of CAH involves repletion of cortisol and mineralocorticoid. Treatment goals include: 1) management of salt wasting and adrenal insufficiency; 2) prevention of precocious puberty and optimizing stature; and 3) decreasing progressive virilization in females. Most children are treated with hydrocortisone to replete cortisol and with fludrocortisone to replete mineralocorticoids. A plan for stress dose steroids is also recommended to prevent adrenal crisis in times of infections, trauma, and surgery. After growth is completed, longer-acting steroid repletion may include prednisone or dexamethasone. The endocrinologic challenge is to decrease hyperandrogenemia without hypercortisolism, which would result in signs of Cushing syndrome. Use of antiandrogens and oral, transdermal, or transvaginal contraceptives after puberty to minimize hyperandrogenic symptoms may decrease the need for steroid treatment. Furthermore, patients occasionally undergo adrenalectomy in order to decrease androgens and corticosteroid use.⁶ Gynecologists caring for women with CAH should make sure that their patients are followed closely by an adult endocrinologist and should also reinforce the importance of adherence to medical treatment.^{7,8}

Surgery and outcomes

On physical examination at birth, common findings of classic CAH include a urogenital sinus, clitoromegaly, and fusion and rugation of the labia majora. A urogenital sinus is a single distal perineal opening that separates more proximally into the urethra and vagina. Surgical intervention has traditionally been performed in infancy or early childhood with the goal of making a separate distal opening for the urethra and the vagina. Feminizing genitoplasty may also include clitoroplasty and labioplasty. Surgical approaches have evolved from clitorrectomy (removal of the corpora and the glans) to more currently clitoroplasty (removal of the corporal tissue with preservation of the glans and dorsal neurovascular bundle). There is limited long-term data on the outcomes of these procedures; however, known complications include vaginal stenosis, hair bearing skin in the lower vagina, altered clitoral sensation, and urinary incontinence.⁹ If patients have had an operation in childhood, many patients will require an additional operation to alleviate vaginal stenosis in adolescence or adulthood.¹⁰ Genital examination may reveal persistent enlargement of the clitoral tissue, a hypospadiac urethra (urethra inserts into the vagina), and introital stenosis. Although the appearance may be atypical, the gynecologic focus of the

evaluation should be on genital function rather than appearance. The gynecologist should ask specifically about difficulties with placing tampons, penetrative sexual activity, arousal, and orgasm. Vaginal dilation and estrogen cream can be very helpful for patients with mild vaginal stenosis. For patients with severe vaginal stenosis or for those who have never had prior surgical intervention for a urogenital sinus, surgical intervention may be indicated if vaginal dilation is not possible and should be performed by a surgeon experienced in reconstructive vaginoplasty techniques.¹¹

Gender identity and psychosocial considerations

Women with CAH may report higher rates of same-sex attraction (19% of women with CAH vs. 2% of control women in a Swedish cohort study) compared to the general population.¹¹ In addition, 5.2% of chromosomal females with CAH report dissatisfaction with their gender of rearing.¹² As with other women, the gynecologist should ask questions about sexual attraction, sexual orientation, and gender identity in a non-biased and open manner. For example, “Are you attracted to men, women, both, not sure, or no one?” If the patient does not identify as strictly female, the gynecologist should ask how the patient would prefer to be addressed.

Sexuality and sexual function

Women with DSD conditions, particularly women with CAH, report difficulties with sexual function, including decreased sexual frequency, sexual satisfaction, and sensuality.¹³ They report high rates of sexual avoidance and difficulty with vaginal penetration and orgasm regardless of whether they have undergone prior surgery.¹⁰ A case series of 28 women born with ambiguous genitalia (56% with CAH) reported that those with a prior history of clitoral surgery are more likely to report anorgasmia (39%) compared to women with CAH who have not undergone clitoral surgery (0%).¹⁴ Another series of 28 women with CAH and 10 controls revealed decreased sensitivity to temperature and vibration in those who had undergone clitoral surgery when compared to affected women who had not had surgery and nonaffected controls.¹³ Due to concerns about long-term effects on sexual function from surgery performed in infancy, arguments have been made for delaying surgical intervention until the patient can consent for the procedure. With or without surgical intervention, physicians should be aware that patients may be self-conscious about their genital appearance and ask if she has any concerns regarding her diagnosis and previous treatment.

Genetics

Congenital adrenal hyperplasia is an autosomal recessive condition caused by mutations in the *CYP21A2* gene, and any patients at increased risk of having a child affected by CAH should be offered genetic counseling. The incidence of homozygous CAH is 1:14199 and for heterozygous CAH is 1:60 for the general worldwide population. The highest incidence of classic CAH, 1:131, is in the Alaskan Yupik Eskimo population. Based on universal newborn screening, the carrier rate for mutations in this *CYP21A2* gene may be as high as 1:10 to 1:25.^{15,16}

Unaffected parents with a prior infant with CAH—Slightly more males are born each year than females; however males with CAH do not have genital ambiguity. When neither

parent is affected by CAH or nonclassic CAH the rate of a future affected fetus is 1:4, and the rate of an affected female is slightly more than 1:8.

Parent affected by CAH—Based on genetic carrier estimates, a woman with classic CAH and a woman with nonclassic CAH have a 1:120 and a 1:480 risk of having an affected CAH offspring respectively. Studies, however, have shown the actual rate of a newborn born with CAH may be much higher: 2.5% (CAH) and 14.8% (nonclassic CAH). This is likely due to intermarrying within ethnic subpopulations with higher carrier rates.¹⁷

Fertility and pregnancy

CAH—Some patients who are oligoovulatory may falsely assume that they do not need contraception and therefore should be counseled if they are at risk of unintended pregnancy. Rates of spontaneous pregnancy for women with classic CAH who are attempting pregnancy without fertility treatment beyond appropriate steroid repletion have been reported between 33% and 60%. Consultation with a reproductive endocrinologist is highly recommended for those desiring pregnancy to assist with optimizing the dosing of steroids. Success has been described with increasing the frequency of steroid repletion to three times per day. Medical ovulation induction may be needed for those who don't conceive with steroid treatment alone.¹⁸

Preconception counseling with an obstetrician experienced in the management of this population, eg, a maternal–fetal medicine specialist, is recommended to outline recommended monitoring and to develop close communication with her endocrinologist. While pregnant, hydrocortisone is typically used to treat maternal CAH as it is inactivated by the placenta, or alternatively prednisone may be used. In addition, mineralocorticoid repletion is used when salt wasting features are present. The patient should be carefully monitored in pregnancy for signs of adrenal insufficiency. Rates of cesarean delivery are high (67–72%) with classic CAH, likely due to vaginal stenosis.¹⁹

Nonclassic CAH—Though infertility may be the presenting symptom in women with nonclassic CAH, a case series of 95 women desiring pregnancy demonstrated that 107 of 187 pregnancies were spontaneous and 85 of 95 women (89.5%) achieved pregnancy when those receiving fertility interventions were included. The overall rate of spontaneous abortion was similar to the general population (19.4%), and was higher for those who did not receive glucocorticoid treatment. For patients with nonclassic CAH who conceive without steroids however, steroid treatment is not usually required while pregnant.²⁰

Nonaffected parents with a prior affected infant: Antenatal dexamethasone treatment as soon as pregnancy is diagnosed has been used for women with a prior infant affected with CAH.²¹ The purported benefit of this treatment has been to decrease virilization of a female infant. Treatment may be ceased after genetic testing by chorionic villus sampling or amniocentesis if the karyotype is 46 XY, or if the genetic change is not identified in the female fetus. Genital differentiation is initiated in the first trimester of pregnancy; therefore approximately eight fetuses need to be treated to prevent virilization of one female infant. The long-term outcomes of supraphysiologic dexamethasone treatment have been limited to

small studies, but there is a suggestion of decreased working verbal memory in the exposed offspring and increased weight gain and striae in the mother. Given the possible risks without benefit to unaffected fetuses, the Endocrine Society currently recommends that any antenatal dexamethasone treatment be considered experimental and used with an investigational review board–approved protocol.⁸

Other Considerations

Patients with CAH are at higher risk for cardiovascular and metabolic morbidity. In a large population-based study in Sweden, compared with age matched controls, adult females with CAH had a significantly higher rate of cardiovascular disease (odds ratio (OR) 3.9, confidence interval (CI) 2.5-6.1), obesity (OR 11.3, CI 6.8-18.7), diabetes (OR 4.0, CI 1.8-9.1), hypertension (OR 4.1, CI 2.4-7.3), venous thromboembolism (OR 5.0, CI 2.0-12.7), thyrotoxicosis (OR 3.5, CI 1.6-7.6) and hypothyroidism (OR 2.3, CI 1.1-4.6).²² For this reason, patients should be screened regularly for co-morbid conditions by their health care team.

Androgen Insensitivity

Background

Androgen insensitivity syndrome (AIS) is a condition caused by androgen receptor dysfunction due to mutations in the androgen receptor gene, which then leads to hormone resistance. This condition can present with three general phenotypes: female phenotype in CAIS, ambiguous genitalia in partial androgen insensitivity syndrome (PAIS), and hypospadias or mild undervirilization in males. The incidence of CAIS is 1/20,000 to 1/64,000 births, and these women have female external genitalia with absence of müllerian structures (due to high levels of antimüllerian hormone in utero). Although women with CAIS have testes and levels of testosterone that are higher than the typical male range, they have systemic estrogen through peripheral aromatization of testosterone. Thus they develop female secondary sexual characteristics with normal breasts, vulvar appearance, and fat distribution. Due to the androgen insensitivity, women with CAIS will have little to no pubic hair or other signs of adrenarche.²³

Situations in which an obstetrician–gynecologist may be called upon to assist in the diagnosis of CAIS include when a pregnant woman presents with genetic testing (cell-free DNA, chorionic villus sampling, or amniocentesis) discordant from genital appearance of the fetus on ultrasonography or at birth, and when an adolescent presents with amenorrhea and absent uterus. Some patients will be diagnosed when a testis is discovered in childhood at the time of a herniorrhaphy. Partial androgen insensitivity syndrome represents a much less common female phenotype and most commonly diagnosed with genital ambiguity at birth, but may present for gynecologic care with either amenorrhea or external genital virilization.

Laboratory testing and Genetics

Women with CAIS should have chromosomal analysis to confirm XY karyotype, testosterone to dihydrotestosterone ratio to rule out 5 α -reductase deficiency in cases of

PAIS, as well as androgen receptor gene mutation testing (sequencing and deletion–duplication evaluation). The androgen receptor gene is found on the X chromosomes (Xq11–12). Over 400 mutations have been described but the mechanism of action is not fully understood, and phenotypic expression varies considerably within affected families. A thorough family history, genetic testing of the mother, and then testing other affected family members and siblings is essential in order to properly counsel the family about appropriate care for affected individuals and future pregnancies.

Androgen receptor mutations account for approximately 90–95% of clinical CAIS, while less than a third of clinical cases of PAIS are associated with an androgen receptor gene mutation.²⁴ Many adults have received the diagnosis of CAIS or PAIS without confirmatory genetic testing; it is essential that all cases thought to represent androgen insensitivity be evaluated through androgen receptor gene-mutation testing. In cases of PAIS without confirmed androgen receptor mutations, the physician must consider other causes of 46 XY DSD, and provide a referral for genetic testing and evaluation by a geneticist with expertise in DSD, which is essential for accurate diagnosis and health care management.

Gender identity and psychosocial considerations

Although female individuals with higher levels of presumed prenatal androgen exposure with 46,XY DSD conditions may demonstrate gender nonconforming behavior, most individuals do not report gender dysphoria in childhood. Women with complete androgen insensitivity usually present with female gender identity and should be considered women.²⁵ On the other hand, as high as 33% of patients with PAIS may be dissatisfied with their gender of rearing.²⁶ All women with androgen insensitivity should be screened for depression and if screen they positive referred for psychosocial support as they report higher rates of anxiety and depression compared to controls.⁵

Vaginal elongation

Women with CAIS will often have a short vagina. The term *blind vaginal pouch* or *absent vagina* has been used in the past but causes confusion for women with CAIS. Vaginal dilation is considered the least invasive and safest method for vaginal elongation in patients with CAIS as well as some PAIS patients; this is accomplished by patients through vaginal dilators and sexual activity.²⁷ Vaginal dilation is often required after vaginoplasty procedures to maintain patency and length, and thus these procedures are not a way to avoid dilation. It is important to note that women do not necessarily require vaginal elongation for their well-being. The patient should be the one to decide when to proceed with vaginal dilation, whether or not she desires to have penetrative intercourse. When she is ready to proceed with vaginal elongation treatments, the gynecologist can provide guidance, refer to a specialist with expertise or a local physical therapist who provides care for women with pelvic floor dysfunction or pain. It is important to note that the vagina created through dilation may function well during intercourse, but may not be as deep as a gynecologist may expect. If the patient is able to have comfortable intercourse, the vagina is likely adequate and requires no further intervention regardless of the appearance and length.

Gonadal Management

As in other DSD conditions in which a Y chromosome is present, women with CAIS are at risk for testicular cancer with an estimated prevalence of 2%; studies are limited due to high rates of prophylactic gonadectomy in women with this condition.²⁸ Some patients will have undergone gonadectomy prepubertally and will require induction of puberty with estrogen therapy. However, because conversion of testosterone to estrogen allows for excellent breast development, the current standard of care has been to offer gonadectomy and estrogen therapy after pubertal development is completed. Patients have recently questioned this practice due to reports of symptomatic effect despite estrogen therapy in the setting of a relatively low-risk tumor. The invasive germ cell tumor that is seen in adults with CAIS is generally seminoma or gonadoblastoma, an in situ lesion, and both can be treated with gonadectomy with excellent outcomes (greater than 90% overall survival rates if stage 3 or less).²⁹ Although gonadoblastoma and early seminoma have been frequently reported in patients with CAIS, advanced disease is rare and thus these rarely require chemotherapy.²⁸ Furthermore, data regarding prophylactic oophorectomy in adult women suggest a possible negative effect of early surgical gonadectomy and practice on cardiovascular health and all-cause mortality.³⁰ Although these data cannot be extrapolated to women with complete androgen insensitivity, further investigation is warranted to understand the absolute benefit of prophylactic gonadectomy compared to the risk of early surgical hypogonadism. Women with PAIS may have further virilization due to partial sensitivity to androgens and also have a higher risk of gonadal tumors if testes are intra-abdominal. Thus the benefits of gonadectomy in women with PAIS may significantly outweigh risks.³¹

Women who have undergone gonadectomy need estrogen replacement for cardiovascular protection, bone health maintenance, and to prevent vulvovaginal atrophy. Optimal replacement, however, has not been established and anecdotally some patients report not feeling well after gonadectomy. Some adult patients have requested testosterone replacement, but data regarding the effects of testosterone replacement in women with CAIS are lacking.²⁴ There are not adequate data to suggest an ideal time to stop estrogen therapy. We recommend that the gynecologist offer bone density and mammography testing at age 50, and have a frank discussion of the risks and benefits of prolonged treatment while acknowledging the lack of data for women with androgen insensitivity.

For women who decide to forgo gonadectomy, there is little information regarding the imaging appearance of early malignancy in these gonads, and proposed paradigms for cancer screening have not been evaluated. Most screening paradigms proposed involve evaluation with pelvic ultrasound (if the testes can be visualized) or magnetic resonance imaging at regular intervals.²⁸ Patients with in situ gonads should be offered referral to a DSD center of excellence for comprehensive counseling and screening for malignancy. Given recommendations for multidisciplinary care of children born with DSD, most large academic children's hospitals currently host such teams and can serve as resources to the gynecologist.

Fertility

Currently women with CAIS are counseled that they cannot have their own biologic children given the absence of a uterus and the standard of care of removal of testes shortly after puberty. Evaluation of testes removed from women with CAIS reveals a decrease in germ cells within the testes as they age.³² The possibility of fertility, however, has been piqued by recent reports of pregnancies after uterus transplant.³³

Other Considerations

Women with CAIS have a 46,XY karyotype, testes, and high testosterone levels. The effects of other genes on the Y chromosome, hormonal profile, and androgen receptor mutations in nongonadal tissues are poorly understood. The androgen receptor gene is expressed ubiquitously and plays a role in bone mineralization.³⁴ Thus, there is concern that AIS is associated with effects on bone health separate from gonadectomy. Current practice is to assess bone density through dual-energy X-ray absorptiometry (DEXA) scan in all women with CAIS, regardless of gonadectomy status.^{35,36} It is unclear whether the scans should be compared to female or male normative values and how often the scans should be repeated. Those with evidence of osteopenia should be counseled about increasing weight bearing exercise and calcium and vitamin D intake, and hormone therapy should be optimized.

Although women with CAIS have testes, they have estrogen through peripheral aromatization of testosterone, and gonadectomy may have a similar effect on their cardiovascular health as seen in the general population. Estrogen therapy has been noted to have beneficial effects on biochemical metabolic markers in women with and without CAIS.³⁷ Hormone levels in women with CAIS, however, differ from those of both typical men and women, and the effects of hormones and the androgen receptor gene mutation on cardiovascular markers are poorly understood.^{34,37-39} Data suggest that women with CAIS may have increased risks of metabolic syndrome and cardiovascular disease regardless of gonadectomy status, and thus healthy diet, exercise, and smoking cessation should be stressed.³⁸

Turner Syndrome

Background

Turner syndrome affects 1:2500 live born female infants, and diagnosis includes the combination of physical findings with complete or partial absence of a sex chromosome. Sex chromosome abnormalities may be detected prenatally by fetal karyotype performed for advanced maternal age, after elevated concern due to abnormal cell-free DNA results, or by ultrasound findings of increased nuchal translucency or cystic hygroma. Postnatally, it may be diagnosed due to physical findings including nuchal folds, edema, low set ears, cardiac anomalies, and renal anomalies. In childhood, it is the most common etiology of short stature, and is the most common diagnosis for primary amenorrhea for adolescents aged 16 years and older.⁴⁰ Finally, for those who are able to enter puberty and menstruate, the condition is associated with early ovarian insufficiency and recurrent pregnancy loss.

Genetics

It is important to remember that Turner syndrome is clinically suspected and encompasses a broad phenotype spectrum with variable genotype–phenotype correlation. All patients with clinical suspicion of Turner syndrome should have a karyotype. Most patients with Turner syndrome identified will have monosomy X (45,X). Approximately 15% of girls will have a 46 XX mosaic cell lineage and 7-10% of patients may have Y chromatin present. Deletions of the short arm (Xp) or the long arm (Xq) of the X chromosome as well as 45X,47XXX can also be found. Additional testing for mosaicism with a Y chromosome should be considered when there a marker is present (a fragment of a sex chromosome of uncertain X or Y origin) or if there is virilization noted on physical examination. *SRY* gene marker evaluation can be performed by serum DNA testing, fluorescence in situ hybridization (FISH), assessing additional metaphases, or by skin biopsy. The results should be interpreted by a cytogeneticist.^{41,42} As antenatal genetic testing may identify 45,X/46 XY mosaicism, obstetricians should be aware that affected individuals may present with a variety of phenotypes including girls with Turner syndrome features, children with ambiguous internal and external genital anatomy, as well as phenotypic males with infertility. Infants with incidental antenatal genetic testing revealing Turner syndrome sex chromosome abnormalities typically have a milder phenotype than those diagnosed based on postnatal clinical suspicion.⁴³

Puberty and hormonal management

Most patients with Turner syndrome who are not identified in utero, at birth, or with short stature in childhood will present with pubertal delay and primary amenorrhea. Although approximately as many as 30% of girls will have some pubertal development, most will experience gonadal failure and not be able to enter puberty spontaneously.^{44,45} Thus, a slow induction of puberty is started with low-dose estradiol treatment with gradual increasing doses, typically transdermal, until she is able to start menses, at which time progestins can be added. Progestins are avoided initially in order to avoid the development of tubular breasts.⁴⁶ In adult women, the risk of endometrial cancer is higher than the general population, and therefore evaluation should include pelvic ultrasound, endometrial biopsy, or both to evaluate irregular bleeding.⁴⁷

It is important for gynecologists to be aware that early identification of Turner syndrome is paramount to addressing the short stature. A decrease in height velocity is often identified when the typical growth spurt does not happen in early puberty; however, most girls with Turner syndrome demonstrate a decreased height velocity by age 3. Treatment with growth hormone and pubertal estradiol induction may increase adult height by 0-11 cm (on average 7 cm) over untreated controls.⁴⁸

Gonadal considerations

When genetic testing reveals *SRY* gene or Y chromosome, the incidence of gonadoblastoma is 7-12% (although evidence is limited given nonprospective case series and high rates of prophylactic gonadectomy in this population). Currently, given a nonfunctioning gonadal status, surgical removal of dysgenetic gonads is typically recommended.^{47,49,50}

Medical Management (bone health, cardiac considerations)

Close annual monitoring of patients with Turner syndrome is warranted due to the elevated risk of multiple systemic conditions.

Anomalies

Heart: The most common cardiac anomaly associated with Turner syndrome is bicuspid aortic valve followed by coarctation of the aorta. Patients are at very high risk for cardiovascular complications related to aortic stenosis and regurgitation as well as aortic dissection, with mortality rates as high as 1-2% for Turner syndrome patients who are pregnant or in the postpartum period. Cardiac imaging should be repeated if normal in early childhood, as some anomalies are not always evident until age 8-10 years, and thereafter periodically, as well as prior to pregnancy.⁵¹⁻⁵³ Close monitoring for cardiovascular health is necessary, including blood pressure monitoring. Twenty percent of patients will have hypertension and early aggressive treatment can decrease long-term cardiovascular complications.⁵⁴

Renal: Women with Turner syndrome have 30-40% incidence of renal anomalies including abnormalities of the collecting systems and horseshoe kidneys. Thus, imaging should have been performed at the time of diagnosis to evaluate the renal system. Those with renal anomalies are at higher risk for hypertension and urinary tract infections.

Hearing: Conductive hearing loss is common due to recurrent otitis media in childhood and up to 60% of adults will experience sensorineural hearing loss. For women without hearing loss, audiology screening should be recommended every 2-3 years.⁵⁵

Autoimmune conditions—Children and adults with Turner syndrome are at high risk of developing autoimmune conditions. Prior to adulthood, 24% of patients with Turner syndrome will have hypothyroidism diagnosed and 2.5% will have hyperthyroidism diagnosed. Annual thyroid-stimulating hormone and T4 serum testing is recommended for all patients.⁵⁶ The risk of celiac disease is 4-6%. Current recommendation is to screen transglutaminase immunoglobulin (Ig)A antibodies and refer to a gastroenterologist for endoscopy if positive.⁵⁷ Type 2 diabetes, elevated low-density lipoprotein cholesterol, and triglycerides are more common in women with Turner syndrome. Regular screening is warranted and counseling about exercise and diet are critical. Elevated liver enzymes are common but it is unclear what the risk of overt liver disease is. Elevated liver enzymes are not a contraindication to oral hormone therapy, but transdermal hormone therapy should be considered. If the liver enzymes are persistently elevated, right upper quadrant ultrasound may be indicated.⁵⁸

Bone health—Women with Turner syndrome are at higher risk of osteoporosis, due to hypogonadism, potentially bone development issues related to the *SHOX* gene and often noncompliance with hormone therapy. Women should have a bone density scan when transitioning to adult care. If bone mineral density is found to be normal, it should be reassessed when considering decreasing hormone therapy. Weight-bearing exercise and

adequate vitamin D and calcium intake should be encouraged. If osteopenia is present in young women, optimizing estrogen levels is typically the best initial treatment.

Psychosocial—Most women with Turner syndrome have a normal-range IQ, but may have difficulties with specific learning disabilities including spatial–perceptual processing, visual-motor integration, and executive function skills.⁵⁹ Women with Turner syndrome report that their primary concern associated with Turner syndrome is infertility and that it affects their interactions with potential romantic partners. This indicates that perhaps the effect of premature ovarian failure and infertility may be the hardest social aspects of Turner syndrome.⁶⁰

Fertility and Pregnancy

Spontaneous pregnancies in women with known Turner syndrome are rare, and may be associated with higher rates of spontaneous abortions, fetal malformation, and chromosomal abnormalities. As most patients are infertile, donor oocyte with in vitro fertilization has been used for fertility treatment. Patients must be counseled, however, that due to the risk of aortic dissection, death rates with pregnancies have been estimated at 2%.^{61,62} Preconceptual cardiac evaluation and close gestational monitoring is essential. In addition, it appears that there is a higher rate of cesarean delivery related to cephalopelvic disproportion.⁶³

If the woman has entered puberty spontaneously, it is important that the gynecologist counsel her about the possibility and risks of pregnancy and offer appropriate contraception. Evaluation of ovarian reserve may reveal evidence of ovarian function, but these women are likely to experience an accelerated decline in ovarian reserve. Thus, in such cases, early referral to a reproductive endocrinologist for fertility preservation counseling is warranted.⁶⁴

Discussion

Gynecologists who care for women with differences in sex development should understand the genetics, pathophysiology, and anticipate the fertility and sexual health care needs of their patients. Close collaboration with endocrinologists, reproductive endocrinologists, perinatologists, geneticists, psychologists, and other specialists will facilitate improving general health and obstetric outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Initial Evaluation: Obtain prior medical records including prior genetic, radiologic, hormonal evaluation and treatments, as well as operative and pathology reports.

Condition	Prior surgical interventions	Genetic Testing	Current medications	Studies to assess at transition to adult practice	Patient Resources
CAH	Clitoroplasty Vaginoplasty Urogenital sinus mobilization Adrenalectomy	CYP21A2 gene mutation testing	Corticosteroids Mineralocorticoids Oral contraceptive pills	17-hydroxyprogesterone Total and free testosterone Bone density	CAH: caresfoundation.org
CAIS	Gonadectomy Vaginoplasty	Androgen receptor gene mutation testing for confirmation of diagnosis	Estrogen replacement Occasionally testosterone replacement	Bone density If no gonadectomy: imaging of gonads	Accord Alliance: accordalliance.org DSD: dsdfamilies.org Androgen Insensitivity: aisdsd.org
Turner	Gonadectomy if Y chromosome or SRY noted	Should be performed to rule out Y mosaicism	Hormone replacement estrogen and progesterone	Bone density Screening blood pressure (4 extremities) Cardiac imaging with echocardiography or MRI	Turner Syndrome: turnersyndrome.org

Table 2

Special Considerations for Health Screening

Preventive Screening Focus	CAH	CAIS	Turner
Cervix/Uterus	Vaginal stenosis common. Routine Pap screening recommended.	Pap screening not recommended. Inspect vagina if bleeding, discharge. Biopsy suspicious lesions	Higher rate of endometrial cancer. Endometrial biopsy or ultrasound evaluation if irregular bleeding. Routine Pap screening recommended if cervix present.
Breast	Standard	Standard	Standard
Colon/Gastrointestinal	Standard	Standard	Screen for celiac disease, referral to gastroenterologist if screen positive
Bone Health	Assess at transition to adult practice; followup based on initial results.	Assess at transition to adult practice; followup based on initial results.	Assess at transition to adult practice; followup based on initial results.
Cardiovascular	Routine blood pressure evaluation	Standard	MRI or echocardiogram of heart and aorta every 5-10 years, and prior to pregnancy. Referral to cardiology for HTN or anomaly.
Serum	Every 1-2 years: Lipid profile, diabetes screen, thyroid screen Endocrinology consult for management of steroid and mineralocorticoid repletion and co-morbid conditions.	Standard	Every 1-2 years: hemoglobin, creatinine, blood urea nitrogen, lipid profile, liver enzymes, TSH, T4, blood glucose
Gonadal evaluation	Routine	Testicular cancer risk, evaluation with MRI or ultrasound if gonads in situ every 6-12 months	If Y chromatin present, gonadectomy recommended