Disorders of sex development (DSD), previously referred to as intersex disorders, comprise a variety of congenital diseases with anomalies of the sex chromosome, the gonads, the reproductive ducts and the genitalia. DSD is loosely classified into four groups on the basis of histological features of the gonadal tissue: XX-DSD with two ovaries (female pseudohermaphroditism), XY-DSD with two testicles (male pseudohermaphroditism), ovotesticular DSD with both ovarian and testicular tissue (true hermaphroditism) and gonadal dysgenesis.

In the present article, only gonadal dysgenesis is discussed. Gonadal dysgenesis includes pure gonadal dysgenesis (46,XX or 46,XY = Swyer syndrome; bilateral streak gonads), mixed gonadal dysgenesis (e.g. mosaicism 45,X0/46,XY; differentiated testicles or ovaries on one side and a streak gonad on the other side) and the Turner syndrome.

Testicular dysgenesis is a multifactorial and complex syndrome with a broad spectrum of phenotypes ranging from moderate impairment of spermatogenesis to severe disorders in sexual development and sex differentiation. DSD patients with XY-gonadal dysgenesis have an increased risk of developing seminomatous and nonseminomatous germ cell tumors.

Turner syndrome is a DSD associated with abnormalities of the X chromosome (45,X0 or mosaicism), occurring in approximately 1 in 2500 live-born female infants. Turner syndrome is usually associated with a short stature, gonadal dysgenesis and, as a consequence, insufficient circulating levels of female sex steroids leading to primary amenorrhea, premature ovarian failure and infertility. The average intellectual performance is within the normal range. Parents who receive an early diagnosis of Turner syndrome during prenatal testing should be advised of the broad phenotypic spectrum and the nowadays improved quality of life in patients with Turner syndrome. In patients with ovarian failure, hormone replacement therapy (HRT) is indicated to stimulate the development of the female secondary sex characteristics, to promote a healthy physical and psychological personal image and to prevent osteoporosis. In rare cases, pregnancy occurs spontaneously, however, oocyte donation can be successful. A careful cardiovascular follow-up during pregnancy and labor is necessary. In general, children with DSD should be cared for by an interdisciplinary team including a gynecologist, pediatric endocrinologist, geneticist, neonatologist, urologist, radiologist, psychiatrist and a social worker for the management of the clinical and diagnostic evaluation, therapy and psychosocial care and, if applicable, sex steroid replacement and growth hormone therapy.

Introduction

Sexual differentiation underlies complex, partly also gene-regulated developments. In the various phases of differentiation, the genetic, gonadal and somatic gender is determined. Mistakes in these developmental processes lead to disorders of sexual differentiation that can further be differentiated into chromosomal, gonosomal and phenotypical anomalies (Buselmaier and Tariverdian 1999; Hughes et al. 2006, 2008; Kolon 2008).

The result of the international consensus conference of the Lawson Wilkins Pediatric Endocrine Society (LWPES) and the European Society for Pediatric Endocrinology (ESPE) held in Chicago, USA, in 2005, in which also members of the support groups of affected patients participated, was a revised nomenclature of Disorders of Sexual Development (Hughes et al. 2006, 2008; Kolon 2008).

Especially the terms “intersexuality”, “hermaphrodite” and “pseudohermaphrodite” should be avoided and instead have been substituted by the term »disorders of sexual development« (DSD). Female and male pseudohermaphrodism are called XX-DSD and XY-DSD and the term “true hermaphroditism” has been replaced by “ovotesticular DSD”.

Furthermore, the discriminating character of terms such as “disorder” or “abnormality” is misleading and should thus be avoided. The new classification of DSDs is outlined in Table 1. The following article only discusses gonadal dysgenesis.
Table 1: Classification of disorders of sexual development (DSD), modified by Hughes et al. 2006. Gonadal dysgeneses are highlighted in blue.

<table>
<thead>
<tr>
<th>Definition</th>
<th>45,X0 = Turner syndrome (and variant)</th>
</tr>
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<tbody>
<tr>
<td>Indifferent gonads only consisting of fibrous tissue and with no histological evidence of germ cells are known as streak gonads (Hughes et al. 2006, 2008; Kolon 2008). Dysgenetic testes have a high risk for malignancy and can develop into malignant germ cell tumors such as dysgerminomas or gonadoblastomas (Looijenga et al. 2007; Raper-de Meyts and Hoelt-Hansen 2007; Olsen et al. 2007; Heffner et al. 2008). In all primary gonadal disorders, there is a hypergonadotropic hypogonadism.</td>
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<table>
<thead>
<tr>
<th>45,X0/46,XY-mosaicism (mixed gonadal dysgenesis)</th>
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<tr>
<th>Disorders in androgen synthesis or action:</th>
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<tbody>
<tr>
<td>Androgen biosynthesis defect (e.g. luteinizing hormone receptor defects, mutations in 5α-reductase 2, 17β-hydroxysteroid dehydrogenase, 3β-hydroxysteroid dehydrogenase, 17α-hydroxylase/17,20 lyase, etc.)</td>
</tr>
<tr>
<td>Androgen action defects (complete or partial androgen resistance, endocrine disruption)</td>
</tr>
</tbody>
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<tr>
<th>Disorders of ovarian development:</th>
</tr>
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<tbody>
<tr>
<td>1. Ovotesticular DSD</td>
</tr>
<tr>
<td>2. Gonadal dysgenesis (e.g. FSH receptor mutation)</td>
</tr>
<tr>
<td>3. Testicular DSD (e.g. SRY+, duplicate)</td>
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</tbody>
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</tr>
</tbody>
</table>
In contrast, dysgenetic ovaries do not seem to comprise an increased risk for malignancy, as the existence of the GBY region on the Y chromosome as well as the testes specific protein gene (TSPY) on the Y chromosome predispose for a malignant transformation (Looijenga et al. 2007). The mother’s lifestyle, prenatal exposition to chemicals or endocrine dysfunction play an additional role in tumor development (Olesen et al. 2007; Rajpert-de Meyets and Hoei-Hansen 2007).

As a preventive measure, bilateral surgical gonadectomy is recommended (Buselmaier and Tariverdian 1999; Ulrich et al. 1996). Due to the malignancy risk, this should take place as early as possible, i.e. at the time of diagnosis. However, as gonadal dysgenesis usually only becomes apparent when pubarche, thelarche and menarche are absent, the disease is usually diagnosed in children around puberty. A publication by Looijenga et al. recommends biopsy in combination with the serum TSPY and serum OCT3/4 as tumor-markers as an alternative for preventive gonadectomy (Looijenga et al. 2007).

Pathophysiology
The genetic sex is determined by the karyotype, which is either XX or XY. The Y chromosome contains the SRY (sex-determining region of the Y chromosome), which induces male sex development during embryogenesis, especially the development of the testes. In the absence of the SRY or in the presence of a second X chromosome, ovaries develop. This then determines the gonadal sex (Kolon 2008; MacLaughlin and Donahoe 2004; Hughes 2001). The XY type is named after G. J. Swyer, the first person who described the syndrome (Fig. 2) (Müller et al. 1992; Swyer 1955). A major part of the patients carries a mutation of the SRY gene (Hughes 2001; Hughes et al. 2008; MacLaughlin and Donahoe 2004; Shahid et al. 2008), which inhibits the differentiation of the testes. Due to the lack of testosterone and AMH, the vagina and the uterus develop. The affected people have external female genitals and streak gonads. The phenotype is female, however, the secondary sex characteristics are missing (Aittomäki et al. 1996; Michala et al. 2008).

However, dysgenetic testes do not produce a sufficient amount of testosterone in order to achieve a complete masculinization of the genitals. Furthermore, AMH is not produced, which suppresses the development of the müllerian ducts, precursors of the fallopian tubes, the uterus and the upper vagina. The ovaries produce estrogens. As a response to this hormone production of the testes or ovaries, the phenotypic sex develops (Hughes 2001; MacLaughlin and Donahoe 2004).

DSD is defined as the non-correspondence of the phenotype to the genotype or the impossibility of clearly attributing the phenotype to the gender. A number of genes have been identified that play a crucial role in sexual differentiation and that can lead to DSD (Table 1) or gonadal dysgenesis (Table 2, Fig. 1) if mutated.

Table 2: Mutations that can lead to gonadal dysgenesis (modified by Correa et al. 2004; Cotinot et al. 2002; MacLaughlin and Donahoe 2004)

<table>
<thead>
<tr>
<th>Gene</th>
<th>Protein and function</th>
<th>Phenotype of the mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>WT-1</td>
<td>Transcription factor</td>
<td>Frasier and Denys-Drash syndrome</td>
</tr>
<tr>
<td>SF-1</td>
<td>Transcription factor</td>
<td>Gonadal dysgenesis and adrenal insufficiency</td>
</tr>
<tr>
<td>SOX9</td>
<td>Transcription factor</td>
<td>XY gonadal dysgenesis with sex reversal</td>
</tr>
<tr>
<td>DAX-1</td>
<td>Nuclear receptor protein, regulator of transcription</td>
<td>Gonadal dysgenesis and congenital adrenal hypoplasia</td>
</tr>
<tr>
<td>SRY</td>
<td>Transcription factor</td>
<td>XY gonadal dysgenesis</td>
</tr>
<tr>
<td>AMH- or AMH-receptor</td>
<td>Secretion protein with receptor</td>
<td>Persistent Müllerian duct syndrome</td>
</tr>
<tr>
<td>DHH</td>
<td>Signal protein</td>
<td>Mixed gonadal dysgenesis</td>
</tr>
</tbody>
</table>

Pure gonadal dysgenesis
Pure gonadal dysgenesis is defined as the absence of differentiated gonads, but with normally developed internal and external genitalia. The exact cause has not yet been completely elucidated. The karyotype is either 46,XX or 46,XY. The XX type is usually transmitted by autosomal recessive inheritance, while the XY type is transmitted by X-linked inheritance (Buselmaier and Tariverdian 1999). The XY type is named after G. J. Swyer, the first person who described the syndrome (Fig. 2) (Müller et al. 1992; Swyer 1955). A major part of the patients carries a mutation of the SRY gene (Hughes 2001; Hughes et al. 2008; MacLaughlin and Donahoe 2004; Shahid et al. 2008), which inhibits the differentiation of the testes. Due to the lack of testosterone and AMH, the vagina and the uterus develop. The affected people have external female genitals and streak gonads. The phenotype is female, however, the secondary sex characteristics are missing (Aittomäki et al. 1996; Michala et al. 2008).
Figure 1: Influence of important genes on sex determination

As these patients usually do not have any visible abnormalities, the disease is often only detected at puberty, when the secondary sex characteristics fail to develop, or when the menarche is absent (primary amenorrhea) (Michala et al. 2008).

Hypogonadism with elevated gonadotropin levels is a characteristic finding in the affected patients.

Histologically, we find streak gonads composed of fibrous tissue or dysgenetic testes with Leydig and Sertoli cells but no or only few germ cells, which have a malignancy potential of 25% (Aittomäki et al. 1996; Pauls et al. 2005). Thus, therapy is usually the surgical excision (Ulrich et al. 1996, 1998).

Hormone replacement therapy (HRT) with sexual steroids is important for the maintenance of bone density and for the induction of female genital development (Michala et al. 2008). Pregnancy would be only possible with oocyte donation (Pienkowsky et al. 2008), however, this is not permitted in Germany.

In 46,XX gonadal dysgenesis, the patient usually has a homozygote or heterozygote mutation of the FSH receptor gene. A homozygote mutation on exon 8 of the FSH receptor was first described in 1995 by Aittomäki et al. Since then, approximately six other FSH receptor mutations on various positions have been detected, which can also cause primary ovarian insufficiency (Aittomäki et al. 1998; Huhtaniemi and Aittomäki 1998; Levallet 1999; Nakamura et al. 2008; Simoni et al. 1998).

An FSH receptor mutation causes a female phenotype in the absence of secondary sex characteristics. The leading symptom is usually primary amenorrhea that results from a primary or premature ovarian insufficiency (Aittomäki et al. 1996; Heiman 2009).

A homozygote FSH receptor mutation in patients with a female karyotype always causes ovarian insufficiency and infertility, while the heterozygote or the homozygote form in patients with a male karyotype not always causes gonadal dysfunction or infertility (Levallet et al. 1999; Simoni et al. 1998). Asymptomatic genetic polymorphisms of the FSH receptor can also be found in the general population (Levallet et al. 1999; Simoni et al. 1998).

Figure 2: Streak gonads in gonadal dysgenesis (DSD, 46,XY, Swyer syndrome)
Rare syndromes/other mutations
Apart from the mentioned FSH receptor mutations and the SRY gene mutations, a number of other mutated genes have been identified that can cause gonadal dysgenesis. After the SRY gene, other subordinate genes play an important role in testes development. Mutations of these genes cause XY gonadal dysgenesis (Table 2 and Fig. 1).

Due to the characteristic tissue expression pattern, malformations of other organs are frequently associated, for example mutations in the WT-1 gene, which lead to kidney malformations or a Wilms’ tumor. In general, WT-1 associated gonadal dysgenesis can cause different clinical entities. The combination of gonadal dysgenesis, nephropathy, mesangial sclerosis and Wilms’ tumor is called Denys-Drash syndrome. Gonadal dysgenesis combined with Wilms’ tumor, aniridia and mental retardation can be found in the WAGR syndrome (Wilms’ tumor, aniridia, genitourinary anomalies, mental retardation). The Frasier syndrome comprises gonadal dysgenesis with late onset of progressive glomerulopathy (focal glomerulosclerosis) and an increased risk for gonadoblastoma. However, Wilms’ tumor is not a usual feature here.

Mutations of the SF-1 gene can lead to isolated gonadal dysgenesis or gonadal dysgenesis in combination with adrenal insufficiency (Sadovsky and Dorn 2000). Mutations in the SOX9 gene can lead to campomelic dysplasia, a skeletal dysplasia in the newborn. The involvement of the skeleton can be explained by the expression of the transcription factor SOX9 in the embryological skeletal system (Correa et al. 2004; Cotinot et al. 2002; Holterhus 2008; MacLaughlin and Donahoe 2004).

Mixed gonadal dysgenesis
In contrast to pure gonadal dysgenesis, chromosomal mosaicism (45,X0/46,XY) causes mixed gonadal dysgenesis. The clinical picture of mixed gonadal dysgenesis is heterogeneous, as the endocrine function of the testes can be affected to various degrees. The external genitals can have a phenotype ranging from female to male (Layman et al. 2009). Although in most cases, the genitals are intersexually with a hypertrophy of the clitoris or hypospadias. As the AMH secretion is also affected to different degrees, variable constellations of the müllerian duct derivatives are possible.

Cases with a 45,X0/46,XY or 46,XX/46,XY mosaicism occur (Buselmaier and Tariverdian 1999). In most cases, the gonads have developed asymptomatically, i.e. streak gonads on one side and normal or dysgenetic testes on the other side (Hughes et al. 2008), usually intra-abdominal or inguinal. However, in some cases, the streak gonads are bilateral. It is assumed that the 45,X0 cell line causes the development of the streak gonads and that the 46,XY cell line is associated with the differentiated testis. The testes have a normal histological appearance before puberty. Sertoli and Leydig cells are present but germ cells are missing. Due to cumulating cases among siblings, we assume autosomal recessive inheritance (Buselmaier and Tariverdian 1999).

As in all gonadal dysgeneses with Y-chromosomes, there is a certain risk for malignancy, which is why gonadectomy is indicated as early as possible (Ulrich et al. 1996, 1998).

From a genetic point of view, the most frequent form of mixed gonadal dysgenesis with chromosomal mosaicism (45,X0/46,XY) can be classified as Turner syndrome (Aittomäki et al. 1996; Sybert and McCauley 2004). Therefore the typical symptoms of the Turner syndrome such as the small stature and the missing secondary sex characteristics can be found in these cases with mosaicism. Therapeutic options also correspond to those of the Turner syndrome (see below) (Baxter et al. 2007; Sybert and McCauley 2004).

When counseling affected parents who have received a prenatal diagnosis of a 45,X0/46,XY karyotype, it is especially important to mention the variations in somatic abnormalities (Layman et al. 2009).

Turner syndrome
The classical Turner syndrome is characterized by a short stature, missing secondary sex characteristics and lymphedema of the head and neck (lymphangiosis colli). It was first described by Otto Ullrich in 1930, a pediatrician from Munich, and in 1938 by the American physician Henry Turner (Turner 1938; Ullrich 1930).

With a prevalence of 40%, Turner syndrome is the most frequent form of gonadal dysgenesis. The incidence is estimated to be between 1 in 3000 and 1 in 2500 live-born female infants (Bondy 2007; Hjerrild et al. 2008; Sybert and McCauley 2004).

50% of the patients have pure 45,X0 monosity, 5% to 10% have a duplication of the long arm of one of the X chromosomes (46Xi(Xq)) and the rest are mosaicisms of 45,X0 with one or more cell lines (see mixed gonadal dysgenesis) (Araujo 2008; Heiman 2009; Sybert and McCauley 2004).

The Turner syndrome lets us suggest that for the development of a normal female phenotype, two functioning X chromosomes are required. The loss of the second sex chromosome (X or Y) takes place postzygotically. Depending on what cell stage the sex chromosome is lost during the early embryonic phase, different chromosomal cell lines can be found concurrently. This leads to the development of mosaicisms. (Fernandez et al. 1996; Ulrich et al. 1998).
Due to the numerous chromosomal aberrations that can cause the Turner syndrome, the clinical picture varies widely (Bondy 2007). Apart from streak gonads or malformations of the inner organs, there can be a hypertrophy of the clitoris or hypospadias and the phenotype can be pure female or male. In some patients, the function of the gonads is partly or completely maintained. In these patients, we can sometimes find the spontaneous onset of puberty, menstruation or even pregnancy (Borgström et al. 2009; Fénichel and Letur 2008; Sybert and McCauley 2004).

Patients with a normal phenotype or a spontaneous onset of puberty are often carriers of mosaicisms (Borgström et al. 2009; Simpson and Rajkovic 1999). However, also the Y chromosome and its fragments can appear in the carriers of mosaicisms (Araujo et al. 2008).

As patients with mosaics usually do not have any stigmata, the diagnosis can be an accidental finding in infertility diagnostics or recurrent abortions.

Patients with the karyotype 45,X0 with no clinical abnormalities or with a purely male phenotype are not considered to have Turner syndrome, independent of their genotype (Bondy 2007). The symptoms and organ malformations in the Turner syndrome are thoroughly outlined in various review articles (Bondy 2009; Sybert and McCauley 2004).

Today, diagnosis can often be made during prenatal check-ups, for example abnormal neck transparency or neck edema in ultrasonography or in the amniotic fluid in mothers who perform an amniocentesis due to their advanced age (Bondy 2007; Sybert and McCauley 2004). In the course of the first trimester screening, the neck transparency is related to the mother’s age and a serum screening of the mother. In the mother’s serum, the IGF binding protein PAPP-A (Pregnancy associated Plasma Protein A) and free β-HCG are measured. As in most numerical chromosomal aberrations, PAPP-A is reduced in the Turner syndrome. The free β-HCG, however, is not significantly altered (Spencer et al. 2000).

Normal PAPP-A values do not exclude a Turner syndrome. Correspondingly, low PAPP-A values are not specific for the Turner syndrome.

In newborns, the clinical sign is lymphedema, while in the infant, the small stature is the most apparent clinical finding. The few girls who remain unidentified until puberty are then presented to the gynecologist or pediatrician due to primary amenorrhea or the missing development of secondary sex characteristics (Sybert and McCauley 2004). In these cases, hormone levels should be determined (FSH, LH, estradiol) in order to show hypergonadotropie hypogonadism. Chromosomal analysis from peripheral blood secures the diagnosis (Bondy 2007; Heiman 2009; Sybert and McCauley 2004).

If the clinical picture corresponds to that of a patient with Turner syndrome, but the karyotype in the peripheral blood is female, genetic mosaicism has to be considered. Here, a second tissue should be analyzed, for example a skin biopsy (Bondy 2007).

If there are hyperandrogenemic signs, a targeted search for Y-specific chromosomal material by polymerase chain reaction (PCR) or fluorescence in situ hybridization (FISH) should be carried out (Bondy 2007), due to the increased risk for malignancy in Y chromosome associated gonadal dysgenesis (Bondy 2007; Gravholt et al. 2000; Larsen et al. 1995; Ulrich et al. 1996, 1998). Bone density measurement completes the diagnosis in adolescents.

The small stature of Turner syndrome patients is usually not characterized by an initially restricted growth but rather by a continuous flattening of the growth charts during childhood or adolescence.

The combination of restricted growth and the missing onset of puberty can easily be misinterpreted as a constitutional growth delay (Sybert and McCauley 2004).

The small stature of girls with Turner syndrome is usually not due to growth hormone deficiency, but several studies have proven that the median final height can be increased by an average of 11.9 cm by growth hormone therapy (Baxter et al. 2007; Sybert and McCauley 2004). However, as the parent’s height can usually not be achieved, growth hormone therapy is questionable (Baxter et al. 2007; Havercamp 1997).
In addition, not every patient suffers from the small stature and therapy has to be adapted individually (Haverkamp 1997). Sybert and McCauley postulate that every patient with Turner syndrome should be informed about the possibility but also the limitations of growth hormone therapy. Growth hormone therapy should be considered early on, i.e. at the time of diagnosis, which is usually at preschool age. An ideal therapy concept concerning the dose and duration of therapy does not exist until today (Haverkamp 1997; Sybert and McCauley 2004).

In the USA, growth hormone therapy is performed with a dose of 0.375 mg per kg body weight and week. However, administration should be daily and preferably in the evening (Bondy 2007).

Girls under the age of nine years receive growth hormones only. In older or extremely small girls, an anabolic steroid such as oxandrolon 0.05 mg per kg and day can be added. Higher doses can lead to virilization and premature skeletal maturation. It is recommended to continue growth hormone therapy until bone age of 14 years or until deceleration of growth speed to less than 2 cm per year (Bondy 2007).

In 90% of the patients with Turner syndrome, hormone replacement therapy with natural estrogens and gestagens for the induction of secondary female sex characteristics and for the prophylaxis of chronic estrogen deficiency is necessary (Bondy 2007; Fénichel and Letur 2008; Pienkowski et al. 2008; Sybert and McCauley 2004).

Already in utero, the fetal ovaries of these patients have a reduced number of primordial follicles, which then undergo premature apoptosis (Modi et al. 2003).

In former times, substitution was thought to begin only at the age of 14 in order to prevent iatrogenic premature closure of the epiphyseal gap and thus a reduced body length (Sybert u. McCauley 2004; Sybert 1984). This is no longer justifiable today, as the psychosocial aspects of the development of secondary sex characteristics is considered to be more important (Bondy 2007). The recommendation is thus to begin substitution at the age of 12 (Bondy 2007).

However, the individual bone age of the patients between 12 and 14 can influence the onset of therapy (Lauritzen et al. 1998; Stahnke 1998; Sybert and McCauley 2004), as a too late initiation of replacement therapy can lead to irreversible consequences of primary chronic estrogen deficiency, especially osteoporosis (Göretzlehner et al. 1995; Lauritzen et al. 1998; Stahnke 1998; Ulrich et al. 1995).

A possible therapeutic strategy for hormone replacement therapy in patients with Turner syndrome is outlined in Table 3 (Bondy 2007). Estradiol valerate should be the first-line therapy, followed by ethinylestradiol (Stahnke 1998; Sybert and McCauley 2004; Ulrich et al. 1995).

<table>
<thead>
<tr>
<th>Age</th>
<th>Age-specific hormone replacement</th>
</tr>
</thead>
<tbody>
<tr>
<td>10-11 years</td>
<td>Monitoring of the spontaneous onset of puberty according to the Tanner stages and the serum FSH levels; if applicable, therapy initiation with low-dose estrogens and growth hormone therapy</td>
</tr>
<tr>
<td>12-13 years</td>
<td>If there is no spontaneous onset of puberty and FSH levels are increased: Low-dose estrogen therapy; equivalent doses: 0.2 to 0.4 mg/month i.m.; 6.25 μg/day transdermal; 0.25 mg/day oral; induction of puberty is also possible with estradiol valerate drops: 2 mg are equivalent to 20 drops in 96% ethanol; 1st month 1 drop, 2nd month 2 drops until the 20th month are equivalent to 2 mg, continuation with, for example, 2 mg oral application</td>
</tr>
<tr>
<td>12.5-15 years</td>
<td>Gradual and continuous increase in estrogen dose over a two-year period, for example: 14, 25, 37,50, 75, 100 μg/day transdermal application; 2 to 4 mg/day oral or 20 μg ethinylestradiol or 1.25 to 2.5 mg/day estradiol valerate, if applicable combined with a progestogen</td>
</tr>
<tr>
<td>14-16 years</td>
<td>After the completion of a two-year estrogen monotherapy, initiation of cyclic progesterone administration. Target dose for adults: 200 mg/day from the 20th to the 30th cycle day of the monthly cycle or from the 100th to the 120th cycle day in a three-month cycle</td>
</tr>
<tr>
<td>14-30 years</td>
<td>Continuation of adult sustaining dose at least until the age of 30 years, as until then, the natural estrogen levels are highest</td>
</tr>
<tr>
<td>30-50 years</td>
<td>Reduction of estrogen dose until a minimum of 0.625 mg/day conjugated estrogens or estradiol valerate as an equivalent</td>
</tr>
<tr>
<td>&gt;50 years</td>
<td>The indication for HRT is no different from that of postmenopausal women</td>
</tr>
</tbody>
</table>
The dose for a child should correspond to an eighth to a tenth of the adult dose and is continuously increased over a two- to four-year period (Bondy 2007); equivalent estrogen doses are 2 mg p.o. per day, 0.1 mg per day transdermal and 2.5 mg per month i.m. (Bondy 2007).

For the prevention of endometrial carcinoma, a progestogen should be added (Sybert and McCauley 2004). For an optimal development of breast and uterus, the recommendation today is to initiate therapy only two years after the onset of estrogen monotherapy (Bondy 2007). Administration of progestogens should occur earlier if the endometrial thickness is 6 mm to 8 mm or the patient has reached Tanner stadium B3 (Sybert and McCauley 2004).

In general, hormone replacement therapy should be continued until the natural onset of menopause as it promotes the feminization and prevents osteoporosis (Bondy 2007).

The effects of hormone substitution therapy on liver function, bone density, blood pressure and malignancy risk have not been completely elucidated. Until now, there are no well-defined data on whether the continuation of substitution for more than menopause age is beneficial or not concerning the eventual risks or whether substitution remains effective at that age (Sybert and McCauley 2004).

Primary ovary insufficiency does not only cause primary amenorrhea and lead to the absence of the development of secondary sex characteristics, but also causes primary sterility (Bondy 2007; Heiman 2009; Sybert and McCauley 2004).

Several clinical and laboratory parameters are positive prognosis factors for a normal ovarian function, such as a normal hormone concentration of FSH and AMH in the blood, mosaicism, and the spontaneous onset of puberty (Borgström et al. 2009). Spontaneous pregnancies occur in less than 10% of the patients with Turner syndrome and bear a high risk for abortions and cardiovascular diseases of the mother (Fénichel and Letur 2008).

In conclusion, all girls with growth impairment and all women with unclear sterility and/or abortions should be tested for Turner syndrome, including the mosaisms. The care for patients suffering from DSD should be carried out in a multidisciplinary team of pediatricians, gynecologists, specialists in internal medicine, endocrinologists, urologists, as well as geneticists and psychotherapists (Bondy 2007; Hjerrild et al. 2008).

**Summary**

**Gonadal dysgenesis**

Disorders of sex development (DSD), previously referred to as intersex disorders, comprise a variety of congenital diseases in which the development of chromosomal, gonadal, or anatomic gender is atypical. DSD can be classified broadly into four categories on the basis of gonadal histologic features: female pseudohermaphroditism (46,XX with two ovaries), male pseudohermaphroditism (46,XY with two testes), true hermaphroditism (ovotesticular DSD with both ovarian and testicular tissues) and gonadal dysgenesis.

In the present article, only gonadal dysgenesis is discussed. Gonadal dysgenesis summarizes the syndromes of either pure gonadal dysgenesis (46,XX or 46,XY = Swyer syndrome; with bilateral streak gonads) or mixed gonadal dysgenesis (i.e. with mosaic 45,XO /46,XY; a testis or ovary and a streak gonad) and the Ullrich-Turner syndrome.
Testicular dysgenesis is a multifactorial and complex syndrome that has a broad spectrum of phenotypes ranging from moderate impairment of spermatogenesis to severe disorders of sexual development and differentiation. DSD patients with XY-gonadal dysgenesis have an elevated risk of developing germ cell tumors, i.e. the seminomatous and nonseminomatous tumors.

Ullrich-Turner syndrome is a DSD associated with abnormalities of the X chromosome (45,Xo or mosaic), occurring in about 1 per 2 500 liveborn girls. Ullrich-Turner syndrome is usually associated with reduced adult height, gonadal dysgenesis and thus insufficient circulating levels of female sex steroids leading to a primary amenorrhea, premature ovarian failure and infertility. The average intellectual performance is within the normal range. Parents receiving a prenatal diagnosis of Ullrich-Turner syndrome should be advised of the broad phenotypic spectrum and the good quality of life observed in Ullrich-Turner syndrome in recent years. In Ullrich-Turner syndrome patients with ovarian failure, the hormone replacement therapy (HRT) is necessary to achieve the development of normal female sexual characteristics, a healthy physical and psychological personal image and to prevent osteoporosis. In rare cases, pregnancy occurs spontaneously, but, if desired, can be achieved by oocyte donation. A careful cardiovascular follow-up during pregnancy and labor is necessary. In children with DSD clinical and diagnostic evaluation, therapy and psychosocial management, the necessity of sex steroid replacement and growth hormone therapy should be solved in a team approach that involves a gynecologist, pediatric endocrinologist, geneticist, neonatologist, urologist, radiologist, psychiatrist and social worker allowing timely diagnosis and proper management.


Keywords
Disorders of sexual development (DSD), gonadal dysgenesis, Swyer syndrome, Turner syndrome, streak gonads

References


Hughes IA, Houn K, Ahmed SF, Lee PA; Lawson Wilkins Pediatric Endocrine Society (LWPES)/European Society


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Conflict of interest
The authors declare that there is no conflict of interest as defined by the guidelines of the International Committee of Medical Journal Editors (ICMJE; www.icmje.org).

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CME

Gonadal dysgenesis

Question 1
Which statement concerning Swyer syndrome is incorrect?
a. The karyotype is 46,XY.
b. Uterus is not present.
c. The patients have a short stature.
d. A common cause is an SRY mutation.
e. The patient suffers from hypergonadotrope hypogonadism.

Question 2
Which statement is correct? The most important key symptom in a patient with Swyer syndrome is:
a. Hirsutism
b. Vaginosis
c. Dysmenorrhea
d. Primary amenorrhea
e. Weight loss

Question 3
An 18 year-old patient with primary amenorrhea seeks your advice. After further diagnostic investigations, you suspect a Swyer syndrome. What do you expect?
a. Karyotype 46,XX
b. Secondary sex characteristics are developed
c. Uterus not present
d. PCO-like ovaries
e. Hypergonadotrope hypogonadism

Question 4
Which transcription factor in sexual differentiation often leads to kidney malformations?
a. SF-1
b. SOX 9
c. DAX 1
d. SRY
e. WT-1

Question 5
Which statement on endocrine therapy of the Turner syndrome is wrong?
a. Transdermal application is possible.
b. Oral administration is possible.
c. The estrogen dose is gradually and continuously increased over a period of two years.
d. Progestin administration is contraindicated.
e. Always start with a low estrogen dosage.

Question 6
In disorders of sex development, which of the following karyotypes does not occur in gonadal dysgenesis?
a. 46,XY-DSD
b. 47,XXY
c. 46,XX-DSD
d. 45,X0
e. 45,X0/46,XY mosaicism

Question 7
Which hormone plays the most important role in sexual differentiation concerning the formation and development of the uterus?
a. Testosterone
b. Prolactin
c. AMH
d. Oxytocin
e. TSH

Question 8
Which statement concerning the Turner syndrome is wrong?
a. A short stature is common.
b. The karyotype is 45,X0.
c. Turner syndrome is the least common type of gonadal dysgenesis.
d. Hormone replacement therapy is usually indicated.
e. Mosaicism can be found.

Question 9
Which statement concerning streak gonads is correct?
a. Malignant transformation is possible.
b. The karyotype is always 46,XX.
c. Excision is not necessary.
d. Patients with Swyer syndrome do not have streak gonads.
e. Streak gonads are usually functional.

Question 10
Which of the following statements concerning gonadal dysgenesis is wrong?
a. Turner syndrome is a gonadal dysgenesis.
b. Most patients suffer from secondary amenorrhea.
c. Dysgenetic testes often progress to dysgerminomas.
d. In pure gonadal dysgenesis, 46,XX, there is usually a defect in the FSH receptor.
e. Gonadal dysgenesis can be associated with renal insufficiency.