Case 3

Lesson learnt

Approach to short stature

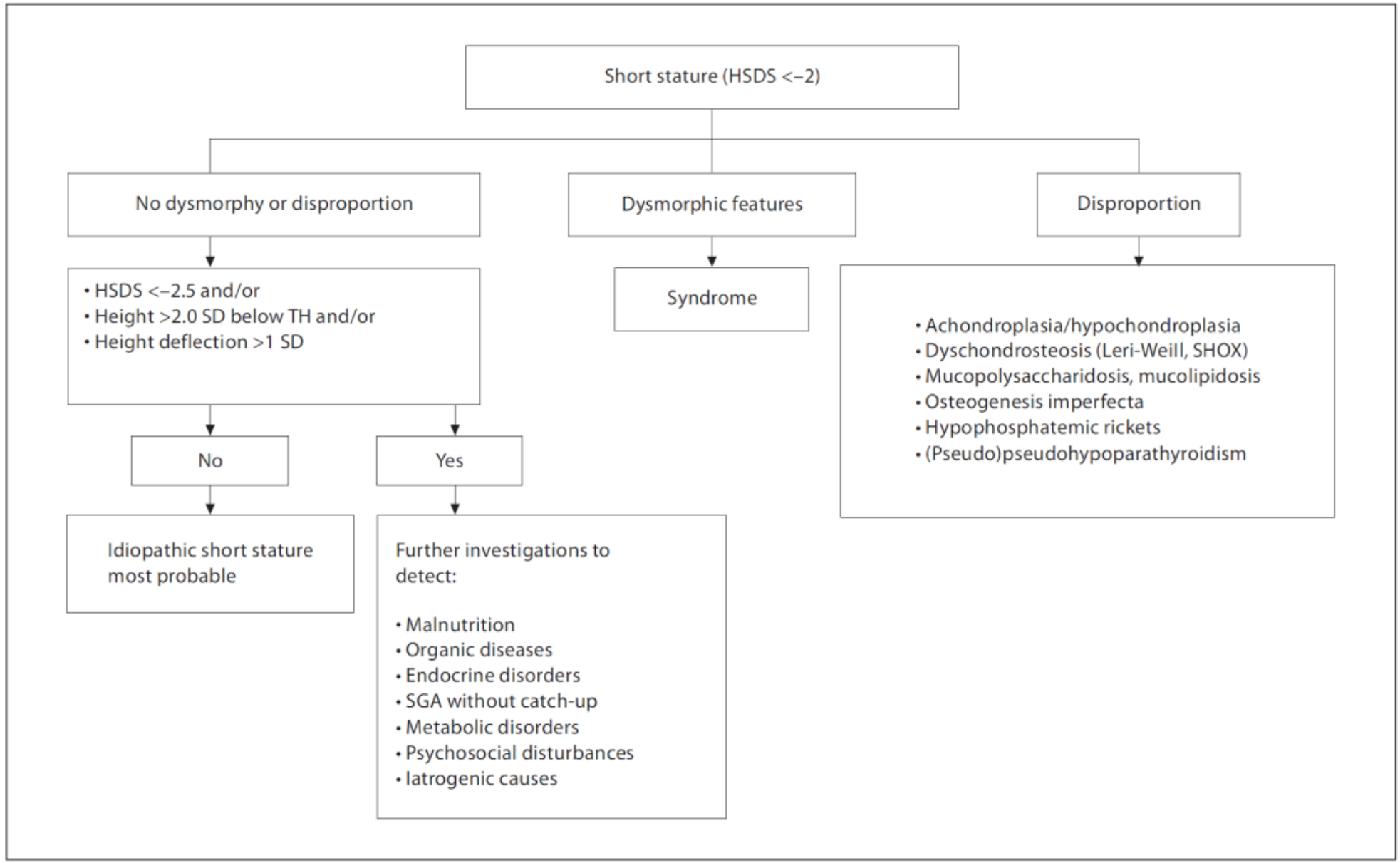


Fig. 2. Diagnostic approach in children with short stature. TH = Target height; SGA = small for gestational age.

Horm Res 2009;72:206–217

Causes of short stature according to the ESPE classification

A Primary growth disorders

A1 Clinically defined syndromes
- Turner syndrome
- Cornelia de Lange syndrome
- DiDeorge syndrome (velocardiofacial syndrome)
- Down syndrome
- Noonan syndrome
- Prader-Willi-Labhart syndrome
- Von Recklinghausen's disease (neurofibromatosis type 1)
- Silver-Russell syndrome

A2 Small for gestational age with failure of catch-up growth
- IGF-I deficiency, IGF resistance
- Due to known cause, e.g. prenatal infections, drugs, smoking, alcohol
- Idiopathic

A3 Skeletal dysplasias
- Achondroplasia
- Hypochondroplasia
- Dyschondrosteosis (Leri-Weill and other defects in the SHOX gene)
- Osteogenesis imperfecta I–VI
- Mucopolysaccharidosis (type IH, IS, II–VII)
- Mucolipidosis (type II and III)

A4 Dysplasias with defective mineralization

B Secondary growth disorders

B1 Insufficient nutrient intake (malnutrition)

B2 Disorders in organ systems
- Cardiac disorders
- Pulmonary disorders, e.g. cystic fibrosis
- Liver disorders
- Intestinal disorders, e.g. Crohn's disease, malabsorption syndromes
- Short bowel syndrome
- Renal disorders, e.g. Fanconi syndrome, renal acidosis
- Chronic anemia

B3 Growth hormone deficiency (secondary IGF-I deficiency)
- Idiopathic
- Genetic (HESX1, PROP1, POU1F1, LHX3, LHX4, GHRHR, GH)
- Associated with syndromes or cerebral or facial malformations, e.g. septo-optic dysplasia, empty sella syndrome
- Associated with prenatal infections, e.g. rubella
- Acquired (craniopharyngioma, other pituitary tumors, e.g. germinoma, hamartoma)
- Head trauma
- Central nervous system infections
- Granulomatous diseases, e.g. histiocytosis

B4 Other disorders of the growth hormone-IGF axis (primary IGF-I deficiency and resistance)
- Bioinactive growth hormone
- Abnormalities of the growth hormone receptor (growth hormone insensitivity syndrome, Laron syndrome)
- Abnormalities of GH signal transduction, e.g. STAT5B defect
- ALS (acid-labile subunit) deficiency
- IGF-I deficiency
- IGF resistance (IGF1R defects, postreceptor defects)

B5 Other endocrine disorders
- Cushing syndrome
- Hypothyroidism
- Leprechaunism
- Diabetes mellitus (poorly controlled)
- Short adult stature caused by accelerated bone maturation, e.g. precocious puberty, hyperthyroidism, congenital adrenal hyperplasia, exogenous estrogens or androgens

B6 Metabolic disorders
- Disorders of calcium and phosphorus metabolism
- Disorders of carbohydrate metabolism
- Disorders of lipid metabolism
- Disorders of protein metabolism

B7 Psychosocial
- Emotional deprivation
- Anorexia nervosa
- Depression

B8 Iatrogenic
- Systemic glucocorticoid therapy
- Local glucocorticoid therapy (inhalation, intestinal, other)
- Other medication
- Treatment of childhood malignancy
- Total body irradiation
- Chemotherapy
- Other specified iatrogenic causes

C Idiopathic short stature

C1 Familial (idiopathic) short stature

C2 Non-familial (idiopathic) short stature

Horm Res 2009;72:206–217

Special points of interest in medical history and physical examination of short children

Medical history
Birth length, weight, head circumference, gestational age
Special features regarding pregnancy (intrauterine growth retardation, drug intoxications, infections) and birth (breech delivery, asphyxia, jaundice)
Previous growth data
Age at start of pubertal signs (girls: breast development, boys pubic hair and testicular enlargement)
Previous diseases and operations, medication (e.g. inhalation therapy with corticosteroids)
Medical history of the various systems, e.g. symptoms suggestive of heart, pulmonary, intestinal (abdominal pain, distended abdomen, diarrhea, constipation), kidney, endocrine (fatigue) and CNS (headache, visual disturbance nausea, vomiting); fatigue
Hypotonia, snoring
Feeding history first year/nutrition (if nutrition is poor, weight is usually affected more than height)
Country of origin, ethnicity
Consanguinity
Parental height (preferably measured, rather than reported)
Global impression of the parents
Tempo of puberty of the mother (age at menarche)
Tempo of puberty of the father (age at start of pubic hair, age at growth spurt, prolonged growth)
Family history (autoimmune diseases, thyroid disorders, growth disorders, skeletal disorders, endocrine disorders)
Milestones delayed, intellectual retardation
Social environment and psychosocial functioning; school performance (grade, social behavior, physical activities); social contacts; personality development (self-reliance); vitality (mood, activities, sleeping, drinking); behavior (mascot, clown, aggressive); unexplained physical complaints; parental attitude

Physical examination
Length or height, weight, head circumference, sitting height (or lower body segment), span, forearm length, weight, weight-for-height, BMI, head circumference are compared with reference charts
Underweight
Overweight, obese (note: children with nutritional obesity are often relatively tall for chronological age)
Dysmorphic features
Frontal bossing, mid-facial hypoplasia
Moon face, facial plethora
Inspection of tonsils
Thyroid size
Slow pulse rate, slow relaxation of the Achilles tendon reflex
Hypertension
Lobulated abdominal fat
Abdominal distension
Hepatomegaly, splenomegaly
Pubertal stage
Micropenis
Cryptorchidism
Virilization
Muscular hypotonia
Fundoscopy, vision, visual field defect
Signs of neglect or abuse

Horm Res 2009;72:206–217

46, XX DSD

Table 1. 46,XX DSD

Abnormal gonadal (ovarian) differentiation
Testicular DSD
With no overt gonadal dysgenesis (previously known as XX male)
With overt gonadal dysgenesis: DSD with ambiguous genitalia
Ovotesticular DSD
Normal gonadal (ovarian) differentiation
Androgen excess
Foetal
Congenital adrenal hyperplasia: deficiencies of 21-hydroxylase, 11-hydroxylase deficiency, or 3β-hydroxysteroid dehydrogenase
Glucocorticoid receptor mutations
Foeto-placental: aromatase deficiency, POR (P450 oxidoreductase)
Maternal (luteoma, exogenous, etc.)
Malformative DSD
Defective Müllerian duct formation
Defects of the urogenital sinus and external genitalia: cloacal exstrophy, vaginal atresia, etc.

Sex Dev 2016;10:1–11

46, XX testicular DSD

46,XX testicular DSD

- 46,XX sex reversal, XX male syndrome, and XX sex reversal
- First described by la Chapelle et al. in 1964
- Frequency : approximately 1 in 20,000 males.
- Sporadic

46,XX testicular DSD

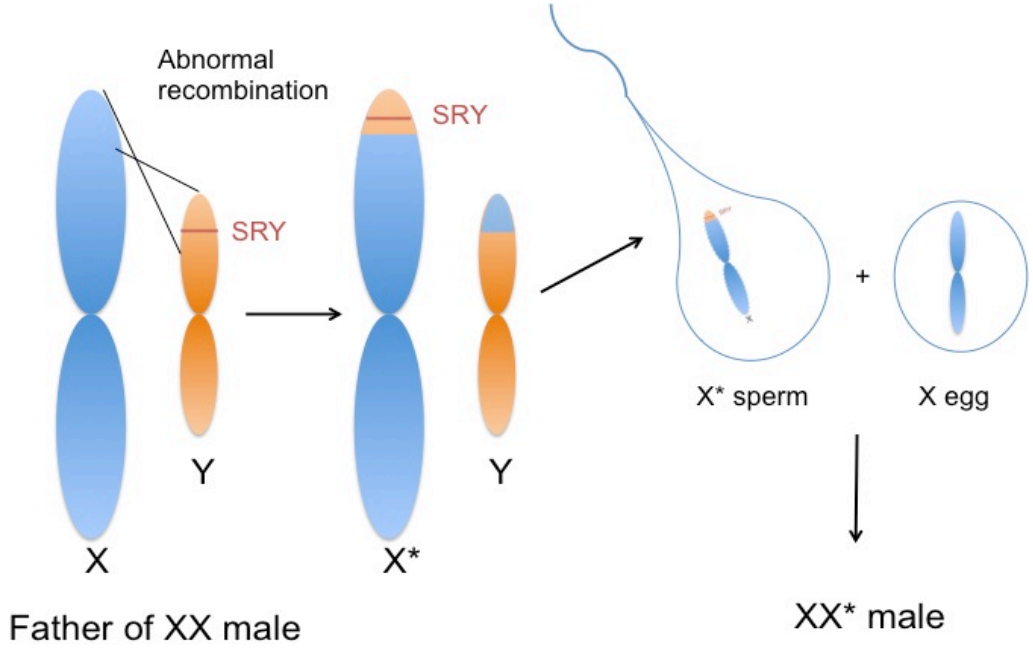
- At least 3 mechanisms have been suggested for the etiology of 46,XX male DSD

  1) **Translocation of Y chromosome including the SRY gene on the X chromosome** or on autosomal chromosomes (90% of the cases)

  2) **X-linked mutation/ overexpression in the genes that cause testes differentiation** or mutation/overexpression in autosomal genes [e.g. SRY box-related gene 9 (SOX9), SOX3, FGF9] in SRY negative XX males

  3) **secret Y mosaicism** found only in the gonads

XX with SRY



During meiosis gives rise to sperm

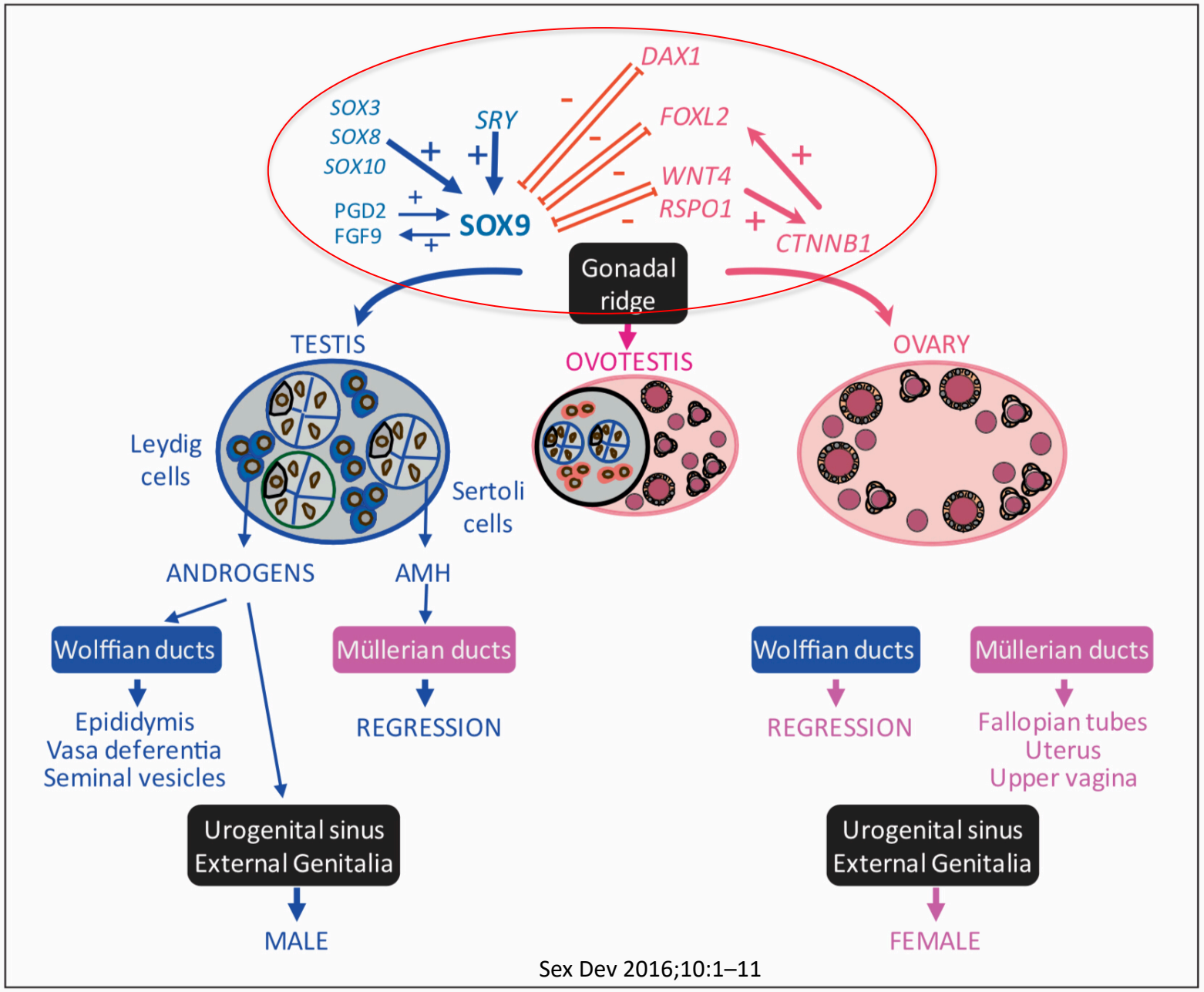
Biomed J Sci & Tech Res 14(2)-2019. BJSTR. MS.ID.002531.

46,XX testicular DSD

Subclassified into

- *SRY*-positive (80%)
- *SRY*-negative (20%)

  SOX9, SOX3, DAX1, WT1, FGF9, and SF1.



Sex Dev 2016;10:1–11

Classical 46, XX male have normal testosterone level and free testosterone level during adolescence, but may decrease in adulthood, leading to hypergonadotropic hypogonadism

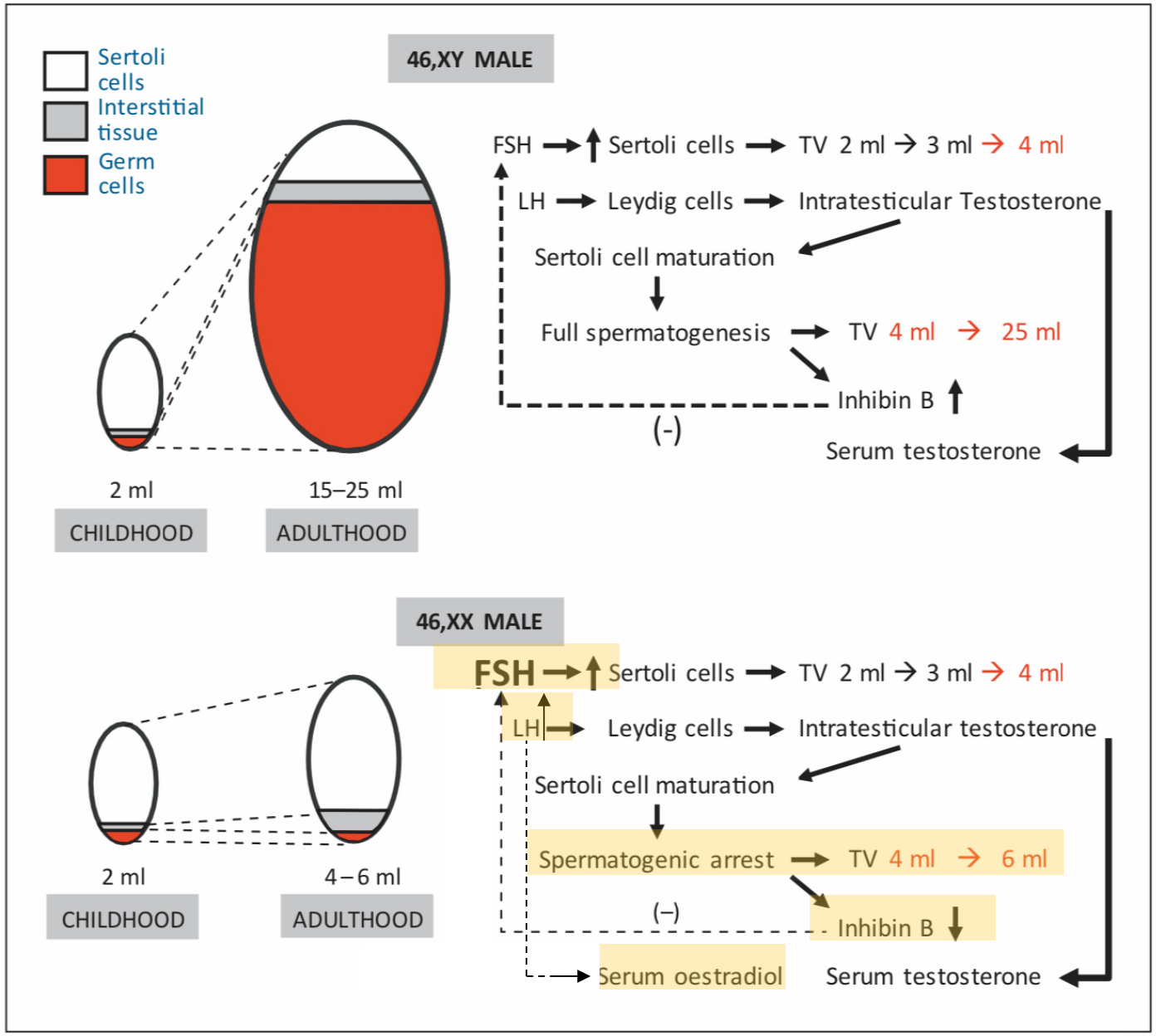


Fig. 2. Functional evolution of the gonads in 46,XX testicular DSD. In normal XY testes, at pubertal onset FSH promotes Sertoli cell proliferation, which results in a mild increase in testicular volume. LH induces Leydig cell testosterone production, which provokes Sertoli cell maturation. Consequently, meiosis is triggered; complete spermatogenesis results in the enlargement of the testes to adult size and the increase of inhibin B, which exerts a negative feedback on FSH. In the XX male, there is a meiotic arrest and germ cell degeneration. Consequently, testis size persists small and inhibin B production decreases, resulting in an increase of FSH levels.

Adapted from Sex Dev 2016;10:1–11

Table 4. Comparison of *SRY*-positive and *SRY*-negative patients.

Patients	HD% Normal	GM% No	Penis size% Normal	ED% No	FSH mIU/mL Mean (SD)	LH mIU/mL Mean (SD)	TT ng/mL Mean (SD)	PRL ng/mL Mean (SD)
SRY+	73.3	55.2	90.9	90.0	38.63 (20.85)	29.40 (19.09)	2.64 (1.49)	12.93 (9.32)
SRY−	66.7	57.1	60.0	85.7	51.74 (28.14)	21.63 (9.56)	2.49 (1.79)	14.27 (4.07)
	$p = 0.422$	$p = 0.596$	$p = 0.144$	$p = 0.823$	$p = 0.195$	$p = 0.326$	$p = 0.819$	$p = 0.781$

HD: hair distribution; GM: gynecomastia; ED: erectile disfunction; FSH: follicle-stimulating hormone; LH: luteinizing hormone; TT: total testosterone; PRL: prolactin.

- **46,XX males DSD typically present after puberty:** small testes and may also have cryptorchidism or hypospadias, azoospermia, hypergonadotropic hypogonadism, varying degrees of gynecomastia, poor facial hair growth, diminished libido, and normal cognitive development
- No extra-genital abnormalities were found in all reported cases

Medicina **2019**, 55, 371; doi:10.3390/medicina55070371

Presentation

	SRY-positive patients	SRY-negative patients
Development of genitalia	Usually normal Cryptorchidism (15%) anterior hypospadias (10%)	Ambiguous
Sexual characteristic	Male but infertility or poor testicle development.	Female secondary sex
Masculinity	Normal	Not clear

Medicina 2019, 55, 371; doi:10.3390/medicina55070371

Possible mechanisms for short stature in 46,XX testicular DSD

1. Absence of specific growth genes mapped in Y chromosome (Y chromosome growth-control gene (GCY))[1]

2. genetic defects that affect growth hormone (GH) activity[2]

3. Overexpression of SOX9 interfering endochrondal growth[3]

1. Ann Hum Genet. 1984;48(3):261-267.

2. Endocrinol Diabetes Metab Case Rep. 2018; 2018: 18-0054.

3. Endocrinol Diabetes Metab Case Rep. 2018; 2018: 18-0054

Investigation

- Diagnosis is based on clinical signs and endocrine testing showing **hypergonadotrophic hypogonadism and karyotype confirming an XX genome**

- **Fluorescence in situ hybridization (FISH) of the SRY gene**

  or

- **Polymerase chain reaction (PCR) amplification of the SRY gene**

- There is no literature regarding the comparison between FISH and PCR for SRY detection and location.
- **FISH and RT-PCR should be used together in order to improve the sensitivity of SRY detection and location**

- In SRY-negative patients, suggest searching for mutations of other genes involved in the sex determination cascade such as SOX9, SOX3, DAX1, WT1, FGF9, and SF1.

Medicina **2019**, 55, 371; doi:10.3390/medicina55070371

Investigation

- An abdominal ultrasound is useful in order to exclude residual Müllerian structures

Medicina 2019, 55, 371; doi:10.3390/medicina55070371

Management

- Sex preference : male
- The mainstay of treatment is testosterone replacement therapy at puberty to correct hormonal imbalance, prevent gynecomastia and to induce development of male secondary sex characteristics.

Testosterone

- After age 14 years, low-dose testosterone therapy can be initiated.
- Testosterone enanthate is given IM every 3-4 weeks, starting at 100 mg and increasing by 50 mg every 6 months to 200-400 mg.
- Initial high doses of testosterone should be avoided to prevent priapism.
- The treatment should plateau, in adulthood, at the best possible dosage, typically between 50 and 400 mg every 2-4 weeks.
- If an individual has short stature and is eligible for growth hormone therapy, testosterone therapy should be either delayed or given at lower doses initially in order to maximize growth potential.

Délot EC, Vilain EJ. Nonsyndromic. 2003 Oct 30 [Updated 2015 May 7]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews

Management

- **Gynecomastia :** Regression of gynecomastia may occur with testosterone replacement therapy. If it does not, and if it causes psychological distress to the individual, reduction mammoplasty can be offered.
- **Osteopenia :** Depending on the degree of osteopenia, treatment may include: calcium, exercise, vitamin D, bisphosphonates, or calcitonin.

Délot EC, Vilain EJ. Nonsyndromic. 2003 Oct 30 [Updated 2015 May 7]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews

Management

- Affected individuals are typically infertile.
- Tumorigenic risk is low
- Psychological support
- Referral to an assisted conception service should be offered

Genetic counseling

- SRY positive cases are **generally not inherited** because this is usually associated with infertility.
- The inheritance pattern of SRY-negative 46,XX testicular disorder of sex development is unknown. A few families with unaffected parents have had more than one child with the condition, suggesting the possibility of autosomal recessive inheritance.

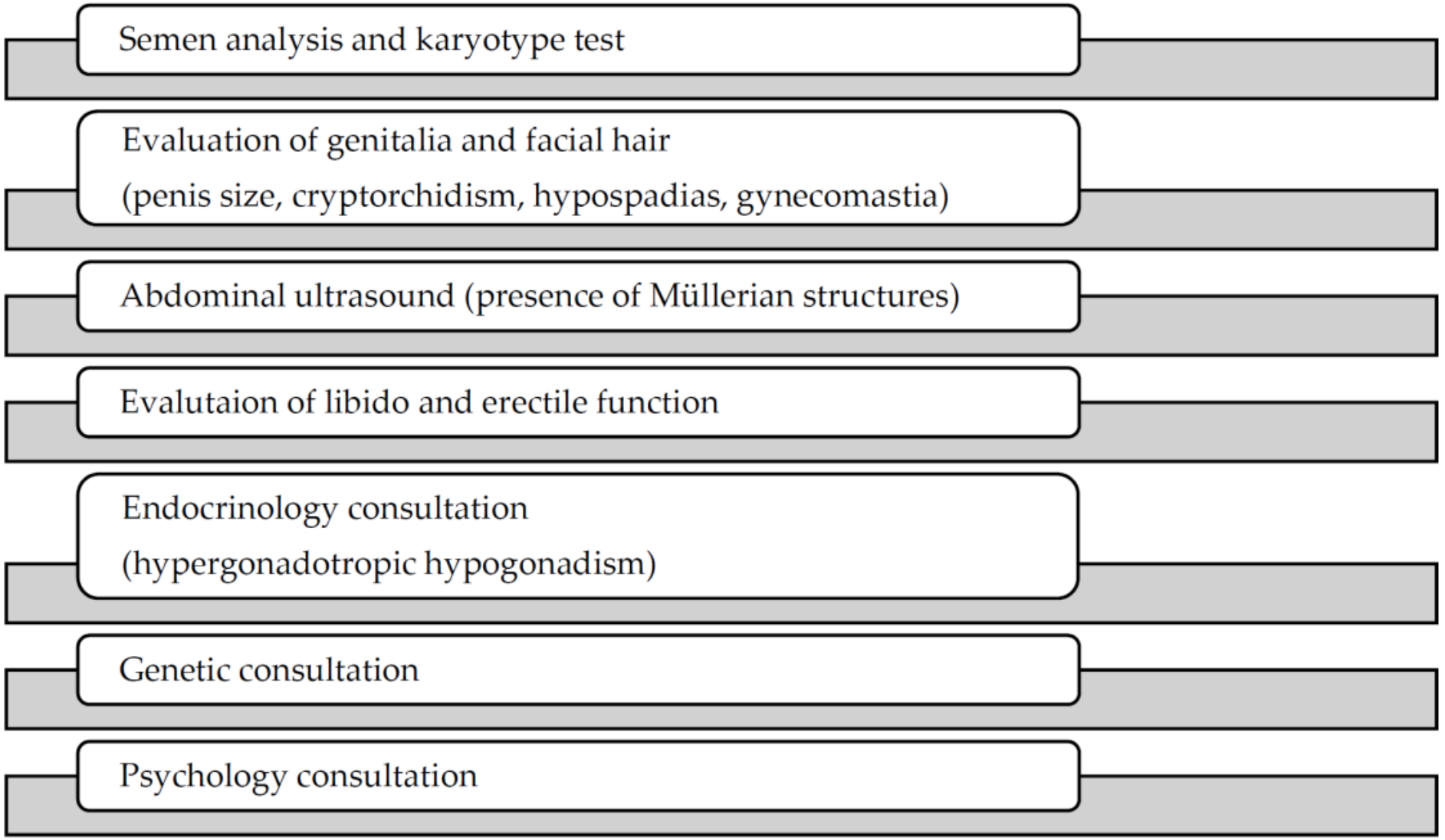


Figure 2. Diagnostic management for 46,XX male syndrome.