

Hermaphroditism and Pseudohermaphroditism

Developmental mechanisms, pathology, and current DSD classification

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Learning objectives

- Distinguish chromosomal, gonadal, ductal and external genital development.
- Translate historical labels into current DSD terminology without conflating categories.
- Explain androgen synthesis/action and gonadal differentiation disorders.
- Apply a safe, systematic diagnostic and pathology-oriented approach.

Scope: Textbook definition and clinical expansion

- Robbins supplies the four-level model and historical distinctions in a short passage.
- The following developmental mechanisms and disease examples are expanded from specialist references.
- Contemporary DSD terms are used for clinical interpretation; Historic names appear only for comparison.
- Not every DSD presents with atypical genitalia.

Four levels of sex-related development

Chromosomal

Sex chromosome constitution, including mosaicism and gene-level exceptions

Gonadal

Ovarian, testicular, dysgenetic or combined gonadal tissue

Ductal

Müllerian and Wolffian derivative development

External anatomy

Genital morphology shaped by local endocrine signals

Chromosomal constitution is one level—not a diagnosis

- 46,XX and 46,XY are common chromosomal complements.
- Mosaicism and structural rearrangements can produce discordant tissue lineages.
- SRY translocation or loss of function can uncouple a simple X/Y prediction from gonadal differentiation.
- Chromosome analysis is necessary in many evaluations but not sufficient alone.

From gonadal primordium to tissue phenotype

- Embryonic gonadal tissue starts in a bipotential state.
- Gene regulatory programs promote testicular or ovarian pathways.
- Mosaic or altered signaling can yield dysgenetic or mixed tissue.

Bipotential gonad



Sex-determining gene networks



Differentiated or dysgenetic gonad

Gonadal sex is defined histologically

- Testicular tissue is identified by seminiferous tubules and supporting cell lineages.
- Ovarian tissue is characterized by ovarian stroma and follicles when present.
- A streak gonad is dysgenetic tissue, not equivalent to a functioning ovary or testis.
- Gonadal histology can differ between sides and within a single gonad.

Ductal sex: Two embryologic systems

Primordium	Differentiates toward	Key regulator
Müllerian duct	Uterus, fallopian tubes, upper vagina	Regression induced by AMH from Sertoli cells
Wolffian duct	Epididymis, vas deferens, seminal vesicles	Maintenance promoted by testosterone

Phenotypic sex: External genital anatomy

- External genital appearance represents one endpoint of prenatal differentiation.
- Androgen exposure, conversion to DHT and androgen receptor activity influence virilization.
- Similar external phenotypes may arise through distinct molecular defects.
- Atypical genital anatomy does not establish chromosomal or gonadal constitution.

Discordance can occur at different levels

Chromosomes

46,XX or 46,XY constitution



Gonadal tissue

Ovary, testis, ovotestis or
dysgenesis



Anatomy

Ductal and genital structures
may be discordant

Presentation varies by life stage

- Prenatal: Unexpected chromosome–ultrasound discordance.
- Newborn: Atypical external genitalia or bilateral nonpalpable gonads.
- Childhood: Inguinal gonad, hernia, unusual endocrine features.
- Adolescence/adulthood: Primary amenorrhea, atypical puberty or infertility.

Historical terminology: What Robbins means

Historical term	Source-defining feature	Current interpretation
“True hermaphroditism”	Both ovarian and testicular tissue	Ovotesticular DSD
“Female pseudohermaphroditism”	Ovarian gonads with masculinized genitalia	Historically overlaps part of 46,XX DSD
“Male pseudohermaphroditism”	Testicular gonads with under-virilized genitalia	Historically overlaps part of 46,XY DSD

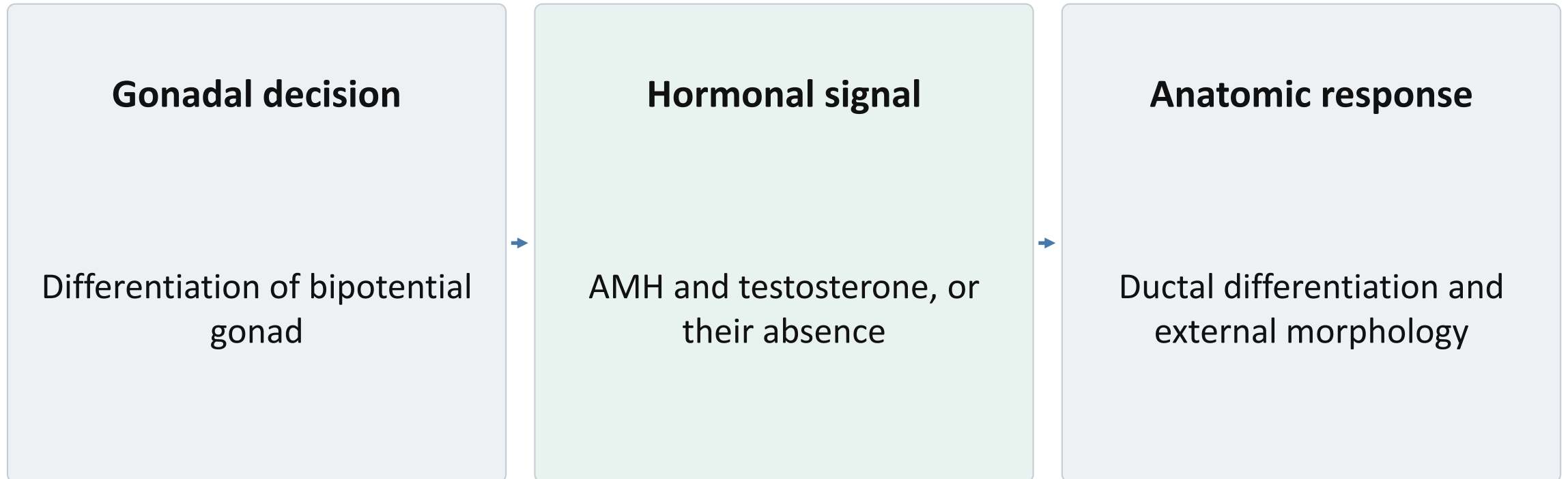
Why historical labels are no longer preferred

- The terms emphasize a binary “true/pseudo” scheme instead of mechanism.
- They do not describe the full chromosomal, gonadal and anatomical spectrum.
- Modern care favors the specific diagnosis and terminology acceptable to the individual.
- Historical nomenclature remains relevant when interpreting older textbooks.

Anatomical findings and identity are distinct

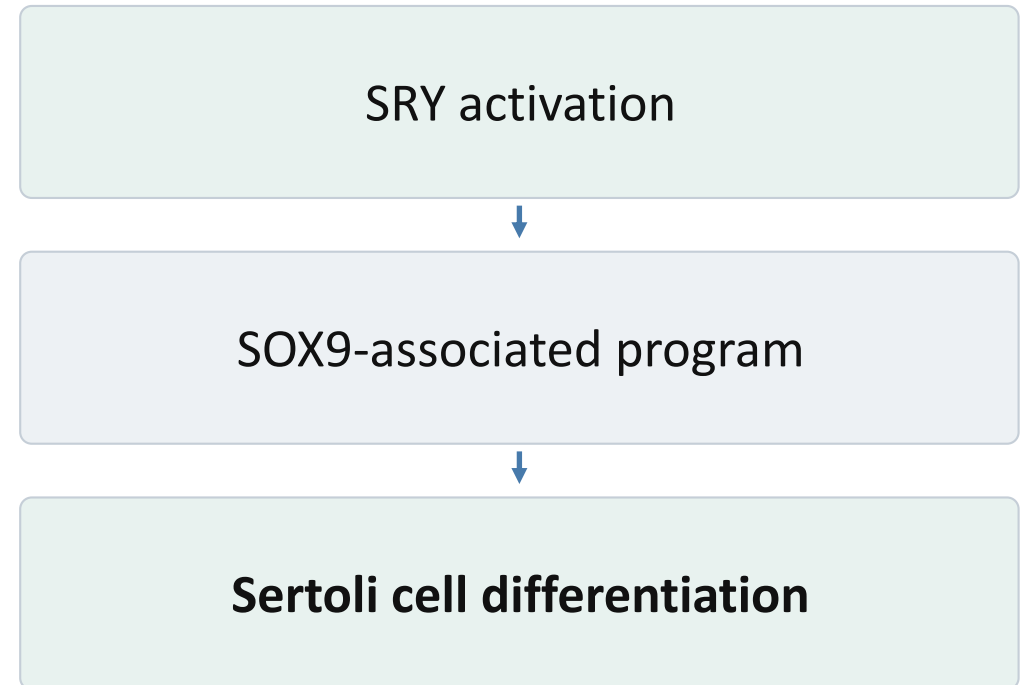
- Chromosomal/gonadal/anatomical characteristics are biological observations.
- Gender identity and lived experience cannot be inferred from karyotype or histology.
- Clinical communication should avoid prejudging future identity or goals.
- An individual's preferred terminology may vary.

Sex differentiation: Simplified timeline



Testis-determining molecular cascade

- SRY commonly initiates a testis-promoting program in 46,XY embryos.
- SOX9 is a major downstream regulator of Sertoli cell differentiation.
- This is a gene network: Chromosomal complement alone is not deterministic.

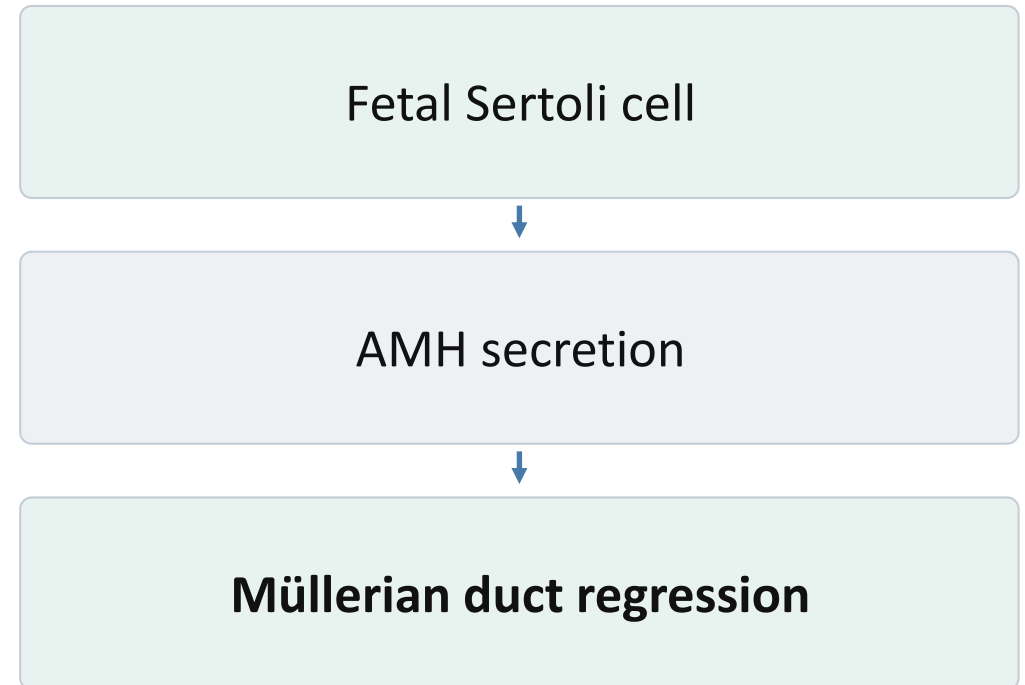


Ovarian differentiation is an active process

- Ovarian development is not simply a passive fallback from absent Y chromosome.
- Multiple ovarian-promoting and testis-antagonizing pathways participate.
- Gonadal phenotype reflects a balance of regulatory networks.
- Disruption may produce partial gonadal differentiation or ovotesticular tissue.

Sertoli cells drive Müllerian regression

- Differentiated fetal Sertoli cells produce anti-Müllerian hormone (AMH).
- AMH signaling promotes Müllerian duct regression.
- Failure of production or receptor signaling can preserve Müllerian derivatives despite testes.



Leydig-cell testosterone stabilizes Wolffian ducts

- Fetal Leydig cells synthesize testosterone.
- Testosterone maintains Wolffian ducts, leading to internal male-typical derivatives.
- Absent testosterone action permits duct regression even if testes are present.

Testicular steroidogenesis



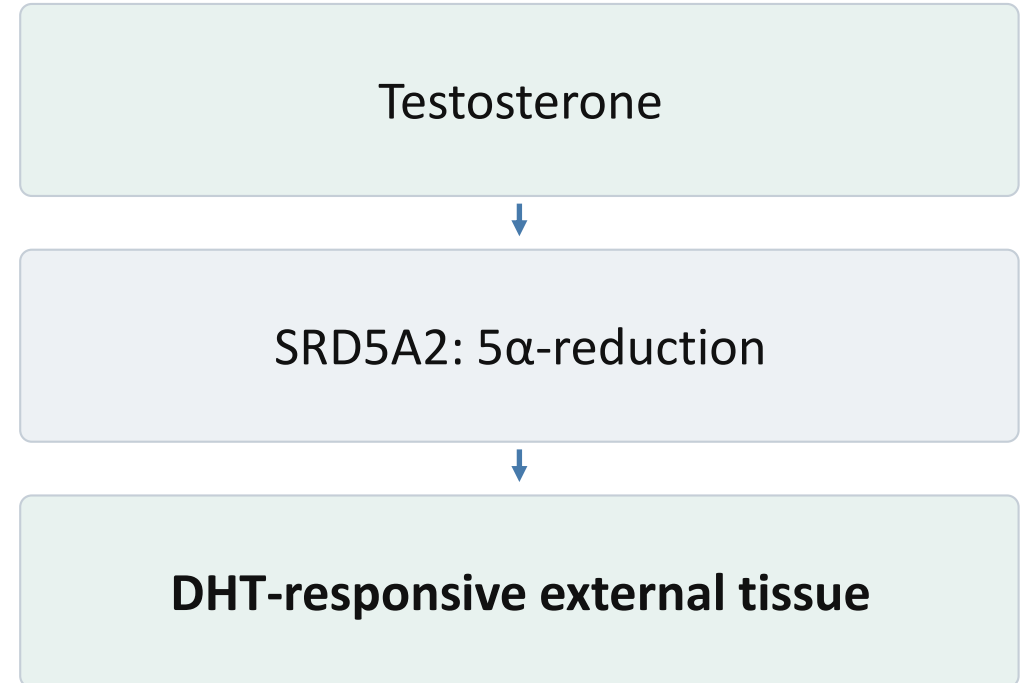
Testosterone reaches tissue



Wolffian duct maintenance

DHT is crucial for external virilization

- 5 α -reductase type 2 converts testosterone into dihydrotestosterone (DHT).
- DHT is important for male-typical external genital differentiation.
- Impaired DHT production may spare Wolffian structures while changing external morphology.



Distinct hormones, distinct anatomic outcomes

Signal	Main developmental target	If signaling is deficient
AMH	Müllerian structures	Persistence of Müllerian derivatives
Testosterone	Wolffian derivatives	Reduced or absent Wolffian development
DHT + androgen receptor	External genital virilization	Under-virilization despite testicular tissue

Absence of testicular signals: Expected pattern

- Without AMH, Müllerian structures can persist.
- Without sufficient testosterone, Wolffian derivatives regress.
- Without substantial prenatal androgen action, external genitalia generally develop along a female-typical pathway.
- These are developmental tendencies—not guarantees in complex DSD.

Four-level integration: Two simplified pathways

Common 46,XX pattern

46,XX



Ovarian differentiation



No testicular AMH/T



Müllerian derivatives



Female-typical external anatomy

Common 46,XY pattern

46,XY with functional SRY



Testicular differentiation



AMH + testosterone



Wolffian derivatives



DHT-dependent virilization

Teaching schematic: Exceptions exist at every level

Contemporary classification framework

46,XX DSD

Androgen excess; Gonadal or developmental variations

46,XY DSD

Gonadal differentiation, steroidogenesis or androgen-action conditions

Sex chromosome DSD

Mosaic or aneuploid complements with variable phenotypes

Ovotesticular DSD

Both ovarian and testicular tissue in the same individual

46,XX DSD: More than virilization

- Common mechanism: Fetal androgen excess with ovarian gonads.
- Less common mechanisms include altered gonadal differentiation.
- The presence of an XX karyotype alone does not establish ovarian tissue.
- The exact cause requires clinical, biochemical and genetic correlation.

46,XY DSD: Mechanisms at three levels

- Gonadal formation may be impaired despite 46,XY constitution.
- Testosterone/DHT synthesis or conversion may be altered.
- Androgen receptor function may be reduced or absent.
- The same broad genital appearance can arise through different defects.

Sex chromosome variation and mosaicism

45,X/46,XY

Can involve asymmetric gonadal development and mixed gonadal dysgenesis

46,XX/46,XY

Rare mosaic/chimeric complements may coexist with ovotesticular tissue

Structural Y variants

Loss or relocation of relevant genomic segments alters differentiation

Phenotypic variability

Tissue mosaicism may not match a single peripheral blood result

Historical versus modern organizing questions

Historical question	Modern diagnostic question
“Which sex is real?”	Which chromosomal, gonadal, hormonal and anatomical features are present?
“True or pseudo?”	Is ovarian tissue, testicular tissue, or both demonstrable?
“Male or female pseudo?”	What underlying developmental mechanism and specific diagnosis explain the phenotype?
“Correct the phenotype?”	What health needs, preferences, options and longitudinal support apply?

Ovotesticular DSD: Defining criterion

- Both ovarian and testicular tissue must occur in one individual.
- Tissues may be separate gonads or coexist in one ovotestis.
- External genitalia range widely; No single appearance is diagnostic.
- The gonadal-tissue definition corresponds to Robbins' historical "true hermaphroditism."

Ovotesticular DSD: Anatomic arrangements

Unilateral ovotestis

Combined tissue on one side, with varying contralateral tissue

Bilateral ovotestes

Ovarian and testicular components in both gonads

Separate gonads

An ovary on one side and a testis on the other

Internal anatomy

Müllerian structures may be present, absent or asymmetric

Ovotesticular DSD: Tissue-level distinction

Tissue finding	Diagnostic implication
Ovarian follicles within gonadal tissue	Supports an ovarian component
Seminiferous tubules / testicular architecture	Supports a testicular component
Both tissue types in one gonad	Supports an ovotestis
Streak or indeterminate gonad alone	Insufficient to designate ovotesticular DSD

Why a gonadal biopsy can be misleading

- Ovarian and testicular components may be spatially heterogeneous.
- A limited core can sample only one component.
- Morphologic interpretation depends on age and tissue preservation.
- Histology, imaging, cytogenetics and molecular findings must be integrated.

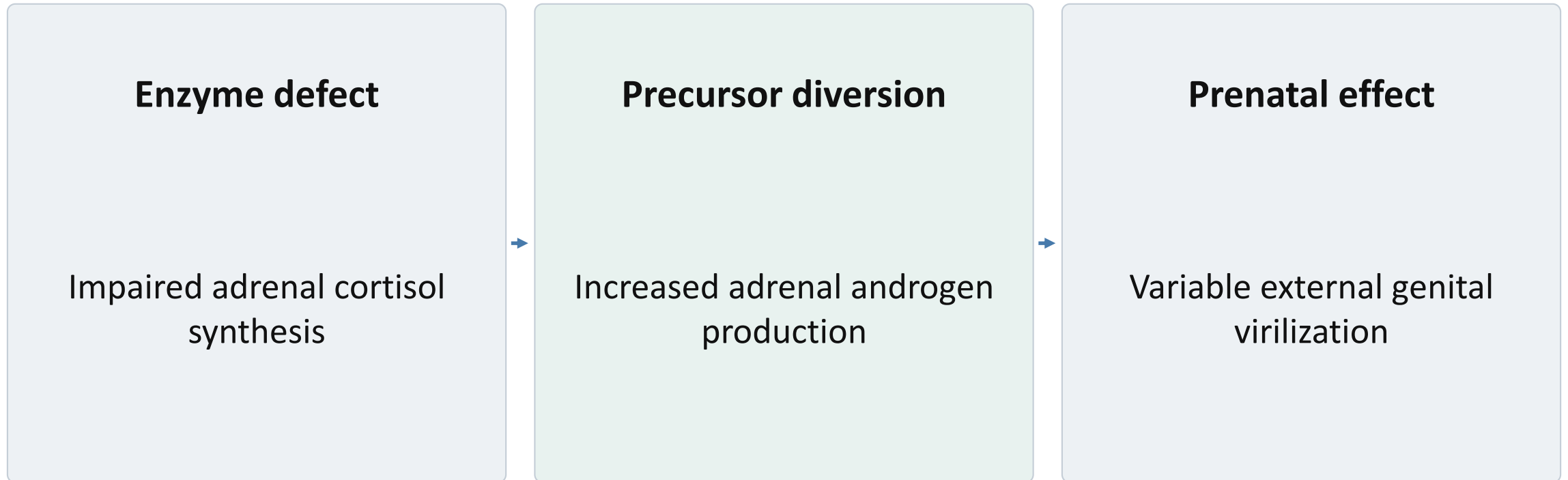
Genetic diversity in ovotesticular DSD

- 46,XX is a documented chromosomal background, but not the only one.
- Some cases involve SRY-associated rearrangements.
- Alterations affecting SOX9 regulation, NR5A1 and other pathways are reported.
- A negative single-gene result does not exclude the tissue-defined condition.

Ovotesticular DSD: Practical clinical implications

- Gonadal endocrine function may be asymmetric or change with age.
- Puberty, menstrual function, fertility potential and anatomy vary widely.
- Gonadal tumor considerations depend on specific tissue and genetic context.
- Care requires individualized counseling rather than label-based assumptions.

46,XX virilization: Common causal chain



21-hydroxylase deficiency: Central mechanism

- CYP21A2 encodes adrenal 21-hydroxylase.
- Impaired cortisol synthesis increases ACTH drive.
- 17-hydroxyprogesterone accumulates upstream of the enzymatic block.
- Steroid precursors enter active androgen-producing pathways.

Cortisol feedback explains adrenal hyperplasia

- Reduced cortisol weakens negative feedback.
- Pituitary ACTH secretion rises.
- Sustained ACTH drive stimulates the adrenal cortex and excess steroid precursors.

Low cortisol



Increased ACTH



Adrenal growth + androgen excess

Salt-wasting CAH is a neonatal emergency

- Severe enzyme deficiency may also impair aldosterone synthesis.
- Sodium depletion and volume loss can lead to dehydration, shock and death.
- Potential presentations include vomiting, poor feeding and failure to thrive.

Low aldosterone



Renal sodium / water loss



Adrenal crisis risk

17-hydroxyprogesterone: Diagnostic significance

- Elevated 17-hydroxyprogesterone supports 21-hydroxylase deficiency.
- Interpretation is age-, gestation-, assay- and collection-time dependent.
- Electrolytes and glucose assess urgent physiological consequences.
- A positive newborn screen requires confirmatory clinical evaluation.

46,XX virilization: Alternative causes

Mechanism	Illustrative cause	Main clue
Adrenal androgen excess	21-hydroxylase deficiency	Elevated 17-hydroxyprogesterone
Other adrenal steroid defect	11 β -hydroxylase deficiency	Hypertension may occur
Exogenous androgen exposure	Maternal androgen medication / exposure	Prenatal history
Altered gonadal differentiation	46,XX testicular/ovotesticular DSD	Discordant gonadal tissue / molecular findings

Case: Neonate with virilized external genitalia

A newborn has labioscrotal fusion and a single perineal opening. Gonads are not palpable. On day 7, feeding worsens and vomiting begins.

- Which potentially life-threatening condition must be considered immediately?
- Which first-line physiology and biochemical measurements are urgent?

Case resolution: Prioritize adrenal physiology

- Classic salt-wasting congenital adrenal hyperplasia is a critical possibility.
- Assess hydration, blood pressure, glucose and electrolytes without delay.
- Collect endocrine tests as feasible without delaying stabilization.
- Refer urgently to neonatal/endocrine specialists.

46,XY DSD: Location of the primary defect

Gonadal differentiation

SRY/SOX9-related mechanisms; Complete or partial gonadal dysgenesis

Steroid production

Defects in Leydig-cell function or testosterone synthesis

Testosterone → DHT

5 α -reductase type 2 deficiency

Androgen response

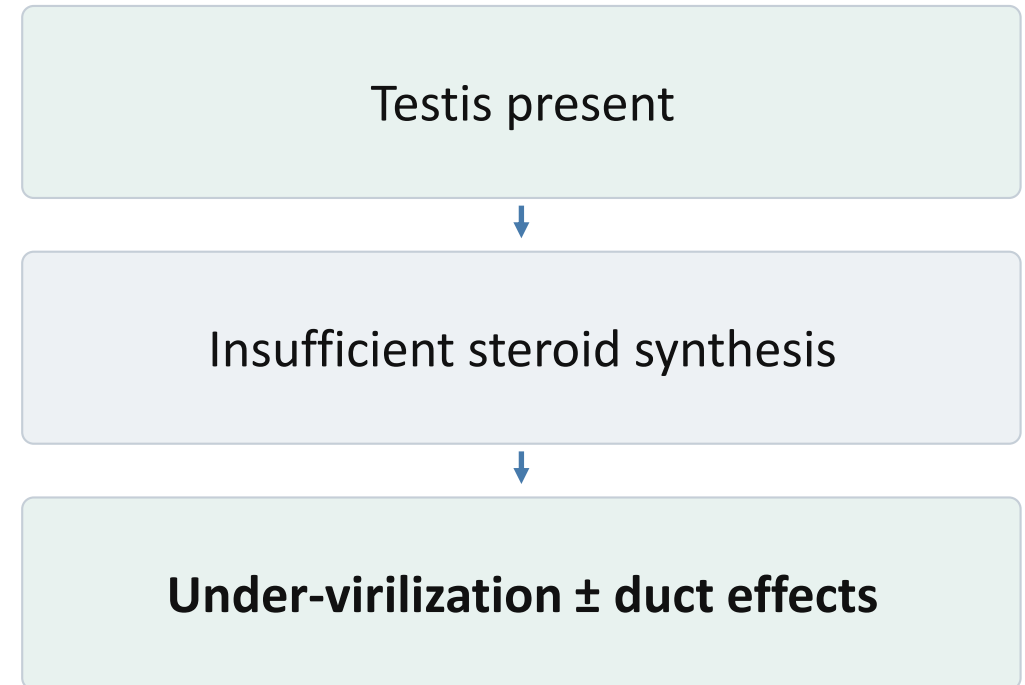
Androgen receptor defects: Complete or partial insensitivity

46,XY gonadal dysgenesis: Tissue failure

- Testicular differentiation may be absent or incomplete.
- Dysgenetic gonads may fail to produce appropriate AMH and androgens.
- Müllerian structures can persist when Sertoli-cell AMH action is absent.
- Tumor risk is higher in some dysgenetic gonads containing Y material.

Steroidogenic 46,XY DSD: Causal model

- Testes may form despite inadequate androgen synthesis.
- Reduced testosterone impairs Wolffian duct maintenance.
- Reduced androgen substrate also limits DHT-dependent virilization.



5 α -reductase type 2 deficiency

- Testosterone production can be adequate.
- SRD5A2-associated impairment reduces testosterone-to-DHT conversion.
- Internal Wolffian structures may be preserved while external genitalia are under-virilized.

Testosterone intact



Reduced DHT conversion



External genital under-virilization

Puberty in 5 α -reductase deficiency

- Testosterone-dependent virilization may become more pronounced at puberty.
- Severity and lived outcomes vary; The phenotype is not fixed by the neonatal examination.
- Hormone ratios require age-appropriate interpretation and sometimes stimulation.
- Molecular testing can establish the underlying enzymatic cause.

Androgen insensitivity: Target-tissue failure

- Testicular androgen production may be present.
- Altered androgen-receptor function reduces tissue responsiveness.
- Phenotype spans complete and partial androgen insensitivity.

Testosterone production



AR signaling impaired



Variable androgen target response

Complete androgen insensitivity syndrome

- 46,XY individuals commonly have testes and female-typical external genitalia.
- AMH action normally prevents uterine development.
- Androgen-dependent Wolffian derivatives are reduced or absent.
- Presentation may include inguinal gonad, absent uterus or primary amenorrhea.

Partial androgen insensitivity syndrome

- Residual androgen receptor activity produces a broad phenotypic spectrum.
- Hypospadias, cryptorchidism and variable genital virilization may occur.
- Morphology does not reliably quantify receptor function.
- Endocrine and molecular evaluation distinguishes PAIS from synthesis defects.

46,XY DSD: Mechanism–anatomy comparison

Condition	Müllerian structures	Androgen effect
Gonadal dysgenesis	May be present when AMH production is impaired	Variable/low
5 α -reductase type 2 deficiency	Usually absent if AMH is intact	DHT-dependent external effects reduced
Complete androgen insensitivity	Usually absent if AMH is intact	Absent target response
Testosterone biosynthetic defect	Usually absent if Sertoli function is intact	Reduced androgen availability

Persistent Müllerian duct syndrome: Different defect

- Testes and male-typical external genitalia may be present.
- AMH synthesis or AMH receptor signaling is defective.
- Müllerian structures persist despite otherwise masculinizing androgen action.
- Demonstrates independence of ductal and external genital differentiation.

Case: Adolescent with primary amenorrhea

A phenotypically female adolescent presents with primary amenorrhea. Pelvic imaging reports an absent uterus, and gonadal tissue is identified in the inguinal canal.

- Which disorders belong in the differential diagnosis?
- Which endocrine and genetic tests help distinguish them?

Case resolution: Classify the mechanism

- Complete androgen insensitivity is an important possibility, not a diagnosis from imaging alone.
- Establish chromosome complement and evaluate hormone synthesis/action.
- Review gonadal anatomy and any prior surgery or imaging.
- Provide coordinated endocrinology, genetics and psychosocial care.

Neonatal signs that warrant DSD assessment

- Atypical genital anatomy or a single perineal/urogenital opening.
- Severe hypospadias with a bifid scrotum or undescended testes.
- Bilateral nonpalpable testes in a term newborn.
- Discordance between prenatal genetic findings and genital anatomy.

First neonatal decision: Exclude a crisis

- Congenital adrenal hyperplasia can cause rapidly progressive salt loss.
- Careful review of feeding, vomiting, hydration and circulation is urgent.
- Investigations and specialist referral must not delay stabilizing treatment.

Recognize possible DSD



Check physiology / electrolytes



**Urgent referral and treatment if
unstable**

History: Targeted diagnostic clues

- Ask about familial DSD, infertility, amenorrhea or unexplained neonatal deaths.
- Record consanguinity and known pathogenic variants where applicable.
- Review prenatal screening, maternal androgen exposure and fetal imaging.
- Document neonatal symptoms of adrenal insufficiency.

Physical examination: Document, do not presume

- Document location and palpability of gonads.
- Describe genital structures precisely; Record openings and fusion.
- Assess hydration, blood pressure and other systemic features.
- Avoid making a diagnosis or sex assignment solely from genital appearance.

First-tier investigations: Purpose-driven

Investigation	Question addressed
Electrolytes / glucose	Is there life-threatening salt loss or hypoglycemia?
17-hydroxyprogesterone $\pm$ adrenal testing	Is classic CAH plausible?
Chromosome study and SRY assessment	What chromosomal constitution / gene status is present?
AMH, testosterone, gonadotropins	What is the evidence for gonadal and steroidogenic function?
Pelvic ultrasound	Are gonadal and Müllerian structures identified?

Imaging: Strengths and limitations

- Ultrasonography is commonly the initial examination of internal anatomy.
- A nonvisualized uterus or gonad is not always truly absent.
- MRI or targeted anatomical studies may clarify unresolved findings.
- Imaging does not replace endocrine, genetic or histopathologic evidence.

Genetic testing: An escalation strategy

- Chromosome analysis detects numerical and some structural variations.
- Directed SRY analysis may clarify atypical chromosomal–gonadal findings.
- Multigene panels or exome sequencing may identify disease mechanisms.
- Variants must be interpreted for pathogenicity and phenotype concordance.

When histopathology contributes

- Gonadal morphology can establish ovarian, testicular or dysgenetic tissue.
- Sampling is not routine for every person with DSD.
- A pathologist should consider maturation-related mimics of germ cell neoplasia.
- Biopsy or gonadectomy decisions require individualized risk–benefit review.

Integrated diagnostic reasoning

- Phenotype does not identify one unique cause.
- Combine clinical, hormonal, imaging and molecular findings.
- Use histology when it changes diagnosis or clinical management.

Anatomy + clinical presentation



Endocrine + chromosome studies



Mechanism-specific diagnosis

Gonadal tumor risk is subtype-dependent

- Risk is influenced by dysgenetic gonadal tissue, Y-derived material and gonadal location.
- Do not assign one cancer-risk percentage to all DSD conditions.
- The tumor potential of CAIS differs from that of some dysgenetic gonads.
- Surveillance and gonadal surgery decisions should be individualized.

Care: Multidisciplinary and longitudinal

- Paediatric endocrinology, genetics and relevant surgical specialists coordinate diagnostic care.
- Psychological support and age-appropriate disclosure are integral.
- Fertility, hormone needs and tumor surveillance vary by diagnosis.
- Transition to adult services supports lifelong health decisions.

Informed decisions and autonomy

- Urgent medical treatment should be distinguished from elective anatomic interventions.
- Current specialist guidance supports transparent shared decision-making.
- Irreversible nonurgent procedures warrant particular attention to future autonomy.
- Published evidence on long-term outcomes remains incomplete.

Five clinicopathologic distinctions to retain

Gonad ≠ chromosome

SRY and gonadal network alterations create exceptions

Duct ≠ external genitalia

AMH and androgen signals have different targets

Ovotesticular ≠ dysgenetic

Both ovarian and testicular tissues require evidence

Urgency ≠ cosmetic anatomy

Adrenal salt loss is urgent; Appearance alone is not

Integrated challenge: Classify before naming

A newborn has an undervirilized phallus and a palpable inguinal gonad. Pelvic ultrasound does not identify a uterus. Testosterone production appears adequate, but DHT action is uncertain.

- Which endocrine pathways remain plausible?
- What finding would distinguish inadequate DHT synthesis from AR dysfunction?

Integrated challenge: Mechanism first

- A palpable gonad and absent uterus suggest testicular tissue with Sertoli-cell AMH action.
- Evaluate testosterone, DHT, timing of sampling and stimulation requirements.
- Consider SRD5A2 deficiency versus partial androgen insensitivity and other causes.
- Interpret biochemical evidence alongside molecular testing and clinical context.

Final synthesis: Three rules for practice

- Use histology to define ovotesticular tissue—not genital appearance.
- Classify discordance along chromosome, gonad, duct and external anatomy.
- Rule out endocrine emergencies; Then pursue individualized, multidisciplinary evaluation.

Selected references

Foundational source	Supplementary specialist sources
Robbins, Cotran & Kumar. Pathologic Basis of Disease, 11th ed. (2026). Ch 5, p.152.	EAU Paediatric Urology Guidelines, section 20: DSD.
Historical terminology and four-level classification.	Ahmed et al. Clin Endocrinol. 2021;95:818–840.
	Domenice et al. 46,XY DSD. Endotext (2022).
	Endotext, Congenital Adrenal Hyperplasia; GeneReviews, 46,XX testicular DSD.