

Contents

<i>Contributors</i>	vii
<i>Foreword: Brad Van Voorhis, MD</i>	xiii
<i>Preface</i>	xv
1. Sexual Differentiation: From Gonad to Phallus	1
2. Puberty	17
3. Pediatric and Adolescent Gynecology	29
4. Müllerian Agenesis	37
5. Septate Uterus	41
6. Turner Syndrome	49
7. Menstrual Cycle	59
8. Abnormal Uterine Bleeding	71
9. Oral Contraceptives	81
10. Amenorrhea	105
11. Exercise-Induced Amenorrhea	113
12. Ectopic Pregnancy	117
13. Sheehan Syndrome	129
14. Premenstrual Syndrome	133
15. Chronic Pelvic Pain	143
16. Endometriosis	151
17. Fibroids	175
18. Polycystic Ovary Syndrome	183
19. Female Subfertility	209

CONTENTS

20. Male Subfertility	229
21. Diminished Ovarian Reserve	255
22. Assisted Reproductive Technologies	263
23. Financially Efficient Fertility Care	283
24. Ovarian Hyperstimulation Syndrome	289
25. Hyperemesis in Pregnancy	299
26. Gamete Preservation	303
27. Luteal Phase Deficiency	309
28. Hyperprolactinemia and Galactorrhea	315
29. Hypothyroidism	331
30. Recurrent Pregnancy Loss	335
31. Management of Early Pregnancy Failure	357
32. Primary Ovarian Insufficiency/ Primary Ovarian Failure	365
33. Genetic Testing	371
34. Androgen Replacement Therapy	393
35. Postmenopausal Hormone Therapy	403
36. Postmenopausal Osteoporosis	421
37. Hot Flashes	437
38. Transvaginal Ultrasound in Reproductive Endocrinology and Infertility	445
39. Hysteroscopy	453
40. Laparoscopy	457
41. Journal Club Guide	469
Chapter Key Points	479
References	493
Index	539

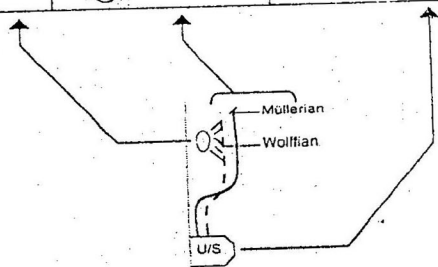
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Sexual Differentiation: From Gonad to Phallus

EMBRYOLOGY

- Bipotential: gonads and external genitalia (urogenital sinus; two labioscrotal swellings; genital tubercle)
- Unipotential: wolffian or müllerian ducts

	GONADS		INT. GENITALIA		EXT. GENITALIA	
	SRY		T AMH	Wolff Müllerian	DHT	Phallus/urogen. sinus labioscrotal folds
XX	⊖	ovaries	⊖ ⊖	regress oviducts/uterus upper vagina	⊖	clitoris/labia lower vagina
XY	⊕	testes	⊕ ⊕	epididymis/vas SVs regress	⊕	penis/scrotum prostate



T, testosterone
 AMH, anti-müllerian hormone
 SVs, seminal vesicles
 DHT, dihydrotestosterone
 SRY, sex-determining region of the Y-chromosome
 U/S, urogenital sinus

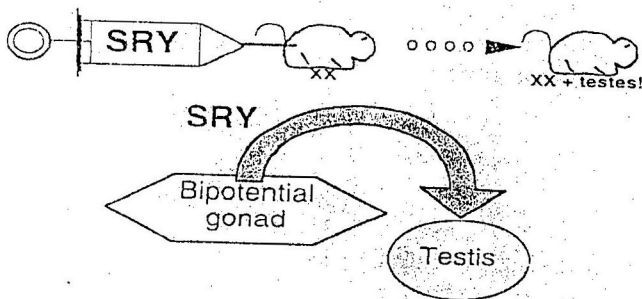
SEXUAL DIFFERENTIATION

Gonads

- Formation of a testis occurs in the presence of the Y chromosome (46,XY).
- Formation of an ovary occurs in the absence of the Y chromosome and the presence of a 2nd X chromosome (46,XX).
- Gonads begin development during weeks 5-6 of gestation.

Testicular Determinants

- Sex-determining region of Y (SRY) is the gene involved in testis determination (short arm [p] of Y chromosome) (Sinclair 1990; Tilford 2001).



Ovarian Determinants

- Unless SRY and SOX9 are expressed, ovarian development ensues (assuming XX is present).
- 2nd X chromosome required for normal ovarian development.
- Autosomal genes (see diagram on page 4 regarding three facets of sexual differentiation).

Internal Genitalia

- Wolffian ducts (dependent on testosterone [T] from testes) → epididymis/vas deferens/seminal vesicles (internal genitalia)
- AMH = anti-müllerian hormone, produced by Sertoli cells
- Müllerian ducts (in absence of AMH) → fallopian tubes/uterus/upper vagina (internal genitalia)

SEXUAL DIFFERENTIATION

- Müllerian and wolffian development begin simultaneously; they are local phenomena (i.e., they occur *ipsilaterally* depending on presence/absence of T/AMH).

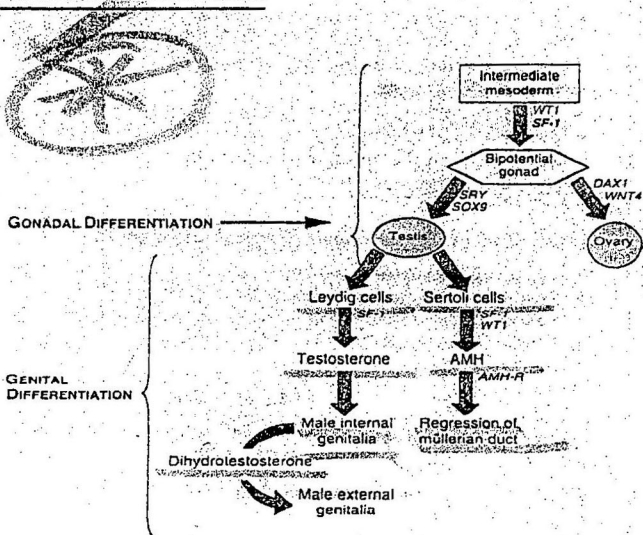
External Genitalia

- DHT is crucial in the development of external genitalia:
 - presence of DHT: male
 - absence of DHT: female
- DHT is produced in sufficient amounts from gestational weeks 7-8 until birth.
- Human chorionic gonadotropin (hCG) stimulates Leydig cells $\rightarrow \uparrow T$
- Feminization of external genitalia completed by approximately 14 weeks.
- Masculinization of external genitalia completed by approximately 16 weeks.
- T, insulin-like 3 ligand, and its receptor (Lgr3) mediate descent of testes.

THREE FACETS OF SEXUAL DIFFERENTIATION

1. Gonadal differentiation
2. Genital differentiation
3. Behavioral differentiation
 - Sexual or gender identity:
 - $\rightarrow$ Sense of oneself as man or woman
 - $\rightarrow$ Established by age 2 1/2 years
 - $\rightarrow$ Derived through internalization of social cues based on the external genitalia.
 - Patients with 5 α -reductase (5 α R) deficiency or 17 β -hydroxysteroid dehydrogenase (17 β HSD) deficiency may change from female to male gender identity at puberty; therefore, there is a *hormonal role* in sexualization of the brain.

SEXUAL DIFFERENTIATION



Factors involved in the determination of male sex. HOX, homeobox transcription factor; AMH-R, AMH-receptor; SF-1, steroidogenic factor 1; SOX9, SR homeobox gene (on autosome); SRY, sex-determining region of the Y chromosome, in Y chromosome, "testis-determining factor"; WT1, Wilms' tumor 1. (Source: Adapted from Federman DD. Three facets of sexual differentiation. *N Engl J Med* 350[4]:323, 2004.)