Vulvar Pathology

Mai P. Hoang
Maria Angelica Selim
Editors

Springer

Vulvar Pathology

Mai P. Hoang • Maria Angelica Selim
Editors

Vulvar Pathology

Springer

Editors
Mai P. Hoang
Harvard Medical School
Massachusetts General Hospital
Department of Pathology
Boston, MA, USA

Maria Angelica Selim, MD
Duke University Medical Center
Department of Pathology
Durham, NC, USA

ISBN 978-1-4939-1806-5 ISBN 978-1-4939-1807-2 (eBook)
DOI 10.1007/978-1-4939-1807-2
Springer New York Heidelberg Dordrecht London

Library of Congress Control Number: 2014955477

To Carol and Hulse Wagner

—Mai P. Hoang, MD

To my family for always being there with unending support and wisdom; to my mentors who are a source of professional encouragement and inspiration; and to my colleagues and patients from whom I continue to learn. Finally, I would like to dedicate this book to you, the reader, committed to the care of women.

—Maria Angelica Selim, MD

Foreword

The time is now. Of all major body areas that the medical literature covers, the vulva is the one most neglected. Despite a long history of fascination since the beginning of humanity and its prominent display in the artwork of our early ancestors, the medical writings are less than might be anticipated by the seriousness and frequency of disease and the conditions that arise. To a large part, the cause may be that the diseases encountered fall outside the exclusive domain of any specific medical specialty. For example, the general pathologist and even the specialist in gynecologic pathology rarely see the dermatoses and other infectious disease processes afflicting the vulva. In turn, the general dermatopathologist typically sees the melanocytic lesions, but often not the other neoplasms, especially sarcomas, and other soft tissue conditions typically seen there. The average gynecologist and sometimes the dermatologist may initially be the first physicians the patient encounters with any condition involving the vulva, but to whom does the biopsy specimen go: To the general pathologist, to the gynecologic pathologist, or to the dermatopathologist?

Consequently and all too often, vulvar disease is not diagnosed or treated with the care it deserves. One manifestation of this contention is that few books have been written about the vulva – far fewer than textbooks on gynecologic pathology or dermatopathology – and few presented comprehensively. Within the last 3 years, only one other book listed in the Library of Congress on-line Catalogue has been written exclusively about vulvar pathology. It is therefore refreshing to see a new textbook written and edited by two experienced dermatopathologists who have spent much of their professional lives dealing with lesions found in the vulva. Their team includes dermatopathologists, gynecologic pathologists, dermatologists, and soft tissue experts, all of whom specialize in this area and have pooled their collective experience and wisdom.

Readers will enjoy that this book encompasses in-depth normal anatomy and embryology, inflammatory dermatoses, melanocytic and squamous proliferative lesions, squamous preneoplasia and cancer, cysts and glandular

lesions, and, finally, mesenchymal proliferations. Further, these major headings subdivide into 15 separate chapters presenting what are common to the not-so-common diagnostic challenges. The book is highly illustrated and easy to read, and should form a solid basis for someone involved in understanding vulvar disease.

Stanley J. Robboy, MD, FCAP, FFPath, RCPI, FRCPath, UK
Department of Pathology
Duke University Medical Center
Durham, NC, USA

Introduction

The word "vulva" originates from the Middle Latin word "*volva*" referring to the *"womb"* or *"female sexual organ."* This organ has been featured in rituals, Paleolithic art and mentioned in ancient texts like the Egyptian papyri from the second millennium BC, the Talmud, and the Bible. The first detailed medical description of vulvar diseases was rendered by Avicenna (Ibn Sina), illustrious philosopher-scientist of the pre-modern era. Through time, no single medical specialty has claimed vulvar diseases as its unique area of expertise. The most frequent diseases affecting the vulva are dermatologic, but most of such patients are cared for by family practitioners and gynecologists lacking sophisticated diagnostic and therapeutic skills in skin disorders. Conversely, dermatologists may have interest and expertise in the vulva, but only in a subset of its diseases. The challenge of diagnosing vulvar disorders is highlighted by considering three intersecting elements involved by a health care encounter with a patient with vulvar complaints:

- The *patient*'s social and cultural background colors how she perceives the problem. Reticence commonly leads to delay and/or attempted self-treatment, either of which may change or exacerbate the clinical appearance of the disease, adding to the diagnostic difficulty. This problem is of particular concern in sexually transmitted diseases, where the patient's partner(s) is/are at risk.
- The *vulva* is susceptible to the effects of friction, trauma, and maceration, all frequently encountered in this anatomic location. Itching is a common symptom in numerous disorders of the vulva; scratching in turn can produce secondary changes that obscure the original disease for the clinician and pathologist. In addition, the native vulvar environment, as well as secondary alterations, facilitates growth of microorganisms, making a large proportion of vulvar diseases multifactorial.
- The *physician* is typically not fully trained to care for the broad spectrum of vulvar diseases. Furthermore, skin diseases appear different when they occur in skin folds and on genital skin. It comes as no surprise, then, that vulvar diseases are frequently underreported, underinvestigated, or misdiagnosed. Delay in diagnosis and therapy is frustrating for both the patient and her physician. A multidisciplinary approach involving more than one specialist can minimize these problems and enable the patient to be seen, studied, and managed in one visit.

In response to the complexity of vulvar disorders, the *International Society for the Study of Vulvovaginal Disease* (ISSVD, http://www.issvd.org) was

founded with the objective of standardizing terminology and promulgating classifications that facilitate clear communication among different physicians caring for patients who suffer from non-neoplastic and neoplastic vulvar disease. A classification of inflammatory disorders based on histologic patterns (Table 1) was published on 2006 [1]. In 2011, a new classification incorporating the lesion type was presented in Paris (Table 2) [2] to assist in clinical diagnosis. Currently, the ISSVD considers the histologic and clinical classifications as complementary.

Table 1 ISSVD classification of vulvar dermatoses: pathologic subsets and their clinical correlates

Spongiotic pattern
Atopic dermatitis
Contact dermatitis
Allergic
Irritant
Acanthotic pattern
Lichen simplex chronicus
Primary (idiopathic)
Secondary (superimposed on other vulvar disease)
Psoriasis
Reiter's syndrome
Lichenoid pattern
Lichen sclerosus
Lichen planus
Dermal homogenization/sclerosis pattern
Lichen sclerosus
Vesiculobullous pattern
Bullous pemphigoid
Mucous membrane pemphigoid
Linear IgA disease
Pemphigus vulgaris
Pemphigus vegetans
Acantholytic pattern
Hailey-Hailey disease
Darier disease
Papular genitocrural acantholysis
Acantholytic acanthoma
Granulomatous pattern
Crohn disease
Melkersson-Rosenthal syndrome
Sarcoidosis
Vasculopathic pattern
Aphthous ulcers
Behcet disease
Plasma cell vulvitis

Used with permission from Lynch et al. [1] and from http://issvd.org/wordpress/wp-content/uploads/2014/02/2014-BIBLIOGRAPHY-CURRENT-ISSVD-TERMINOLOGYrev.pdf

Table 2 The 2011 ISSVD clinical classification of vulvar dermatological disorders

(A) Skin colored lesions
Papules and nodules
1. Papillomatosis of the vestibule and medial labia minora
2. Molluscum contagiosum
3. Warts (HPV infection)
4. Scar
5. Vulvar intraepithelial neoplasia
6. Skin tag
7. Nevus, intradermal type
8. Mucinous cysts of the vestibule and medial labia minora
9. Epidermal cyst
10. Anogenital mammary-like gland tumor (hidradenoma papilliferum)
11. Bartholin gland cyst and tumor
12. Syringoma
13. Basal cell carcinoma
Plaques
1. Lichen simplex chronicus (LSC) and other lichenified disease
2. Vulvar intraepithelial neoplasia
(B) Red lesions
Patches and plaques
Eczematous and lichenified diseases
1. Contact dermatitis, allergic and irritant
2. Atopic dermatitis (rarely seen as a vulvar presentation)
3. Eczematous changes superimposed on other vulvar disorders
4. Diseases clinically mimicking eczematous disease (e.g. candidiasis, Hailey-Hailey disease and extramammary Paget's disease)
5. Lichen simplex chronicus (lichenification with no preceding skin lesions)
6. Lichenification superimposed on an underlying preceding pruritic disease
Red patches and plaques with no epithelial disruption
1. Candidiasis
2. Psoriasis
3. Vulvar intraepithelial neoplasia
4. Lichen planus
5. Plasma cell (Zoon's) vulvitis
6. Bacterial soft-tissue infection (cellulitis and early necrotizing fasciitis)
7. Extramammary Paget's disease
Papules and nodules
Red papules
1. Folliculitis
2. Wart (HPV infection)
3. Angiokeratoma
4. Molluscum contagiosum (inflamed)
5. Hidradenitis suppurativa (early lesions)
6. Hailey-Hailey disease
Red nodules
1. Furuncles ("boils")
2. Wart (HPV infection)
3. Prurigo nodularis
4. Vulvar intraepithelial neoplasia

(continued)

Table 2 (continued)

5. Molluscum contagiosum (inflamed)
6. Urethral caruncle and prolapse
7. Hidradenitis suppurativa
8. Anogenital mammary-like gland adenoma (hidradenoma papilliferum)
9. Inflamed epidermal cyst
10. Bartholin duct abscess
11. Squamous cell carcinoma
12. Melanoma (amelanotic type)
(C) White lesions
Patches and plaques
1. Vitiligo
2. Lichen sclerosus
3. Post-inflammatory hypopigmentation
4. Lichenified diseases (when the surface is moist)
5. Lichen planus
6. Vulvar intraepithelial neoplasia
7. Squamous cell carcinoma
Papule and nodules
1. Fordyce spots
2. Molluscum contagiosum
3. Wart
4. Scar
5. Vulvar intraepithelial neoplasia
6. Squamous cell carcinoma
7. Milium (pl. milia)
8. Epidermal cyst
9. Hailey-Hailey disease
(D) Dark colored (brown, blue, gray or black) lesions
Patches
1. Melanocytic nevus
2. Vulvar melanosis (vulvar lentiginosis)
3. Post-inflammatory hyperpigmentation
4. Lichen planus
5. Acanthosis nigricans
6. Melanoma-in-situ
Papules and nodules
1. Melanocytic nevus (includes those with clinical and/or histologic atypia)
2. Warts (HPV infection)
3. Vulvar intraepithelial neoplasia
4. Seborrheic keratosis
5. Angiokeratoma (capillary angioma, cherry angioma)
6. Anogenital mammary-like gland adenoma (hidradenoma papilliferum)
7. Melanoma
(E) Blisters
Vesicles and bullae
1. Herpesvirus infections (herpes simplex, herpes zoster)
2. Acute eczema (see definitions in Part IV above)
3. Bullous lichen sclerosus
4. Lymphangioma circumscriptum (lymphangiectasia)

Table 2 (continued)

5. Immune blistering disorders (e.g. cicatricial pemphigoid, fixed drug eruption, Steven-Johnson syndrome, pemphigus)
Pustules
1. Candidiasis
2. Folliculitis
(F) Erosions and ulcers
Erosions
1. Excoriations
2. Erosive lichen planus
3. Fissures arising on normal tissue (idiopathic, intercourse related)
4. Fissures arising on abnormal tissue (candidiasis, lichen simplex chronicus, psoriasis, Crohn's disease, etc.)
5. Vulvar intraepithelial neoplasia, eroded variant
6. Ruptured vesicles, bullae and pustules
7. Extramammary Paget's disease
Ulcers
1. Excoriations (related to eczema, lichen simplex chronicus)
2. Aphthous ulcers (syn. aphthous minor, aphthous major, Lipschütz ulcer, occurring either as an idiopathic process or secondary to other diseases such as Crohn's, Behçet's, various viral infections)
3. Crohn's disease
4. Herpesvirus infection
5. Ulcerated squamous cell carcinoma
6. Primary syphilis (chancre)
(G) Edema
Skin-colored
1. Crohn's disease
2. Idiopathic lymphatic abnormality (congenital Milroy's disease)
3. Post-radiation and post-surgical lymphatic obstruction
4. Post-infectious edema (esp. staphylococcal and streptococcal cellulitis)
5. Post-inflammatory edema (esp. hidradenitis suppurativa)
Pink or red
Venous obstruction (e.g. pregnancy, parturition)
2. Cellulitis (primary or superimposed on already existing edema)
3. Inflamed Bartholin duct cyst/abscess
4. Crohn's disease
5. Mild vulvar edema may occur with any inflammatory vulvar disease

Used with permission from Lynch et al. [2] and from http://issvd.org/wordpress/wp-content/uploads/2014/02/2014-BIBLIOGRAPHY-CURRENT-ISSVD-TERMINOLOGYrev.pdf

The female genital tract is a complex system with multiple organs. Most textbooks of pathology, dermatopathology, and gynecologic pathology dedicate restricted space to vulvar diseases, with an understandable emphasis on neoplastic disorders due to their life-threatening nature. Yet, the demand for specialists in inflammatory and infectious vulvar disorders is increasing. This book focuses on setting forth our current knowledge of the full spectrum of vulvar pathology, utilizing a multidisciplinary approach. Our introductory chapter lays the groundwork for an understanding of vulvar diseases by

describing its embryologic development, normal anatomy, and histology. Inflammatory diseases are presented, organized by structures affected and histopathologic patterns. Mesenchymal processes are categorized based on cell of origin. Melanocytic and glandular lesions are reviewed in detail, so as to assist in diagnosis and classification. The changing and contending categorizations of squamous lesions are discussed, and the arguments for each are set out to assist the reader in understanding the logic behind each of the proposed classifications. The clinical presentation of each entity is described with emphasis of the peculiarities of presentation of each disease in the vulva. Extragenital manifestations of each disorder are enumerated, because not uncommonly they are the key to a correct diagnosis. Recent advances in understanding of the physiopathology, genetic, and molecular basis of vulvar diseases are thoroughly discussed. The histopathology of vulvar disease is presented in detail, with an emphasis on pathologic differential diagnosis and histopathologic mimickers.

To further enhance this book, we have included "take-away essentials," a section to which the reader can turn for a summary of practical points. Case vignettes at the end of each chapter provide an opportunity to observe how knowledge can be applied in actual cases. Each of these additions should be useful tools for professional development.

We hope the reader will find this book a useful, practical reference for the daily practice of vulvar disease diagnosis, an area of rapidly expanding knowledge and clinical need.

Duke University Medical Center
Department of Pathology
Durham, NC, USA

Maria Angelica Selim, MD

References

1. Lynch PJ, Moyal-Barracco M, Bogliatto F, Micheletti L, Scurry J 2006 ISSVD classification of vulvar dermatoses: pathologic subsets and their clinical correlates. J Reprod Med. 2007;52(1):3–9.
2. Lynch PJ, Moyal-Barracco M, Scurry J, Stockdale C 2011 ISSVD terminology and classification of vulvar dermatological disorders: an approach to clinical diagnosis. J Low Genit Tract Dis. 2012;16(4):339–44.

Acknowledgments

Special thanks to all authors for their exceptional efforts in putting together this book.

Many thanks to the Springer team – senior editor Richard Hruska, this book's developmental editor Elizabeth Corra, and Silembarasanh Panneerselvam and Arokianathan Vinita at SPi Global, for their patience and invaluable help.

We sincerely hope that this book will serve as a useful resource for the readers.

Contents

Contributors

Russell A. Ball Ball Dermpath, Greensboro, NC, USA

Sarah M. Bean Department of Pathology, Duke University Health System, Durham, NC, USA

Rex C. Bentley Department of Pathology, Duke University Health System, Durham, NC, USA

J. Andrew Carlson Department of Pathology, Albany Medical College, Albany, NY, USA

Libby Edwards Department of Internal Medicine, Carolinas Medical Center, Charlotte, NC, USA

Maria Teresa Fernández-Figueras Department of Anatomic Pathology, Hospital Universitari Germans Trias i Pujol, Badalona, Spain

Allison H.S. Hall Department of Pathology, Duke University Medical Center, Durham, NC, USA

Mai P. Hoang Department of Pathology, Harvard Medical School, Massachusetts General Hospital, Boston, MA, USA

Doina Ivan Department of Pathology, University of Texas MD Anderson Cancer Center, Houston, TX, USA

Dmitry V. Kazakov Department of Pathology, Charles University Medical Faculty Hospital, Pilsen, Czech Republic

Konstantinos Linos Department of Pathology, Dartmouth-Hitchcock Medical Center, Geisel School of Medicine at Dartmouth, Lebanon, NH, USA

Cesar A. Llanos Department of Pathology, Miller School of Medicine, University of Miami, Miami, FL, USA

Martin C. Mihm Jr. Department of Dermatology, Brigham and Women's Hospital, Boston, MA, USA

Kristen M. Paral Department of Pathology, The University of Chicago Medical Center, Chicago, IL, USA

Viviana Parra Facultad de Ciencias Medicas Uncuyo, Hospital Luis Lagomaggioer, Mendoza, Argentina

Victor G. Prieto Department of Pathology and Dermatology, University of Texas MD Anderson Cancer Center, Houston, TX, USA

Jason C. Reutter Department of Dermatopathology, Piedmont Pathology Associates, Hickory, NC, USA

Luis Requena Fundacion Jimenez Diaz, Madrid, Spain

Stanley J. Robboy Department of Pathology, Duke University Medical Center, Durham, NC, USA

Andrew E. Rosenberg Department of Pathology, University of Miami Hospital, Miami, FL, USA

Demaretta S. Rush Department of Pathology, Immunology, and Laboratory Medicine, University of Florida College of Medicine, Gainesville, FL, USA

Martin A. Sangueza Department of Pathology, Caja Nacional de Salud, La Paz, Bolivia

Omar P. Sangueza Departments of Pathology and Dermatology, Wake Forest Baptist Medical Center, Wake Forest University School of Medicine, Winston Salem, NC, USA

Maria Angelica Selim Department of Pathology, Duke University Medical Center, Durham, NC, USA

Christopher R. Shea Department of Medicine, The University of Chicago Medicine, Chicago, IL, USA

Bruce Smoller Department of Pathology, University of Rochester School of Medicine and Dentistry, Rochester, NY, USA

Tien Anh Nguyen Tran Department of Pathology, Florida Hospital Orlando, Orlando, FL, USA

J. Matthew Velkey Department of Cell Biology, Duke University School of Medicine, Durham, NC, USA

Kelly L. West Ball Dermpath, Greensboro, NC, USA

Edward J. Wilkinson Department of Pathology, Immunology, and Laboratory Medicine, Shands Hospital, University of Florida College of Medicine, Gainesville, FL, USA

Part I

The Normal Vulva

Normal Vulva: Embryology, Anatomy, and Histology

1

J. Matthew Velkey, Allison H.S. Hall, and Stanley J. Robboy

Overview

The vulva consists of the female genital structures external to the vaginal opening—the introitus. Anatomically, the vulva lies within the perineum, which is a diamond-shaped region bounded anteriorly by the pubic symphysis, laterally by the left and right ischial tuberosities of the pelvic bones, and posteriorly by the coccyx (Figs. 1.1 and 1.2) [1]. The perineum further subdivides into an anterior urogenital triangle with the vulva and a posterior anal triangle with the anus and its external sphincter. The vulva comprises the mons pubis, the labia majora, the labia minora, the clitoris, and the vestibule. The vestibule itself is the specific region demarcated anteriorly by the clitoral prepuce, laterally by the labia minora, and posteriorly by the fourchette, which is a fold of skin where the labia minora join. Within this region are the clitoris, the vestibulovaginal bulbs and associated vestibular (Bartholin's) glands, the urethral meatus and associated periurethral (Skene's) glands, and the vaginal introitus. Before considering the anatomy and histology of these structures in more detail, however, it will be beneficial to first consider the development of the female reproductive tract.

J.M. Velkey (✉)
Department of Cell Biology, Duke University School of Medicine, Durham, NC, USA
e-mail: Matt.velkey@duke.edu

Embryology of the Female Reproductive Tract and External Genitalia

The urinary and reproductive systems in both males and females are embryologically and anatomically interrelated in that both develop from a urogenital ridge of intermediate mesoderm located along the posterior body wall in the developing abdominal cavity and both open into an endoderm-lined cloaca at the caudal end of the embryo (Table 1.1, Fig. 1.3). During the 4th week of development, excretory tubules of the mesonephros arise within the lateral, or mesonephric, portion of the urogenital ridge along the body axis extending from the thoracic to upper lumbar body segments [2]. The excretory tubules elongate into S-shaped loops encapsulating a rudimentary glomerular capillary tuft located along their medial portion. The lateral end of each excretory tubule attaches to a collecting duct running longitudinally known as the mesonephric or Wolffian duct, which opens into a portion of the cloaca that will invaginate to form the urogenital sinus. As the name implies, the urogenital sinus contributes to the lower urinary tract, namely, the bladder and urethra, as well as a portion of the reproductive tracts in both the male (prostate and prostatic urethra) and female (vagina and vestibule). Initially, the segmental nephrons of the mesonephros provide functional urine output but then regress as the definitive,

M.P. Hoang and M.A. Selim (eds.), *Vulvar Pathology*,
DOI 10.1007/978-1-4939-1807-2_1,

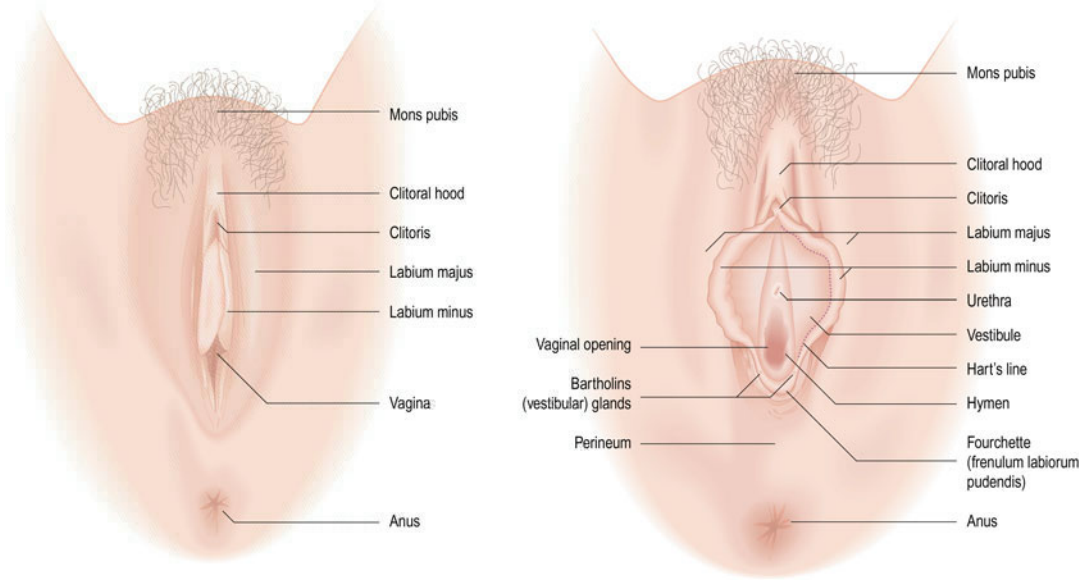

Fig. 1.1 External genitalia of the vulva (Used with permission from Robboy et al. [22]

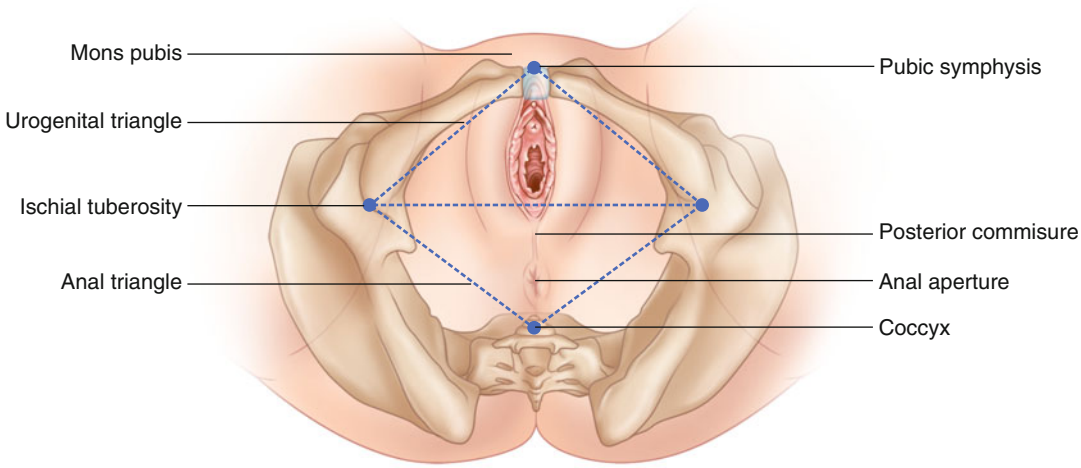

Fig. 1.2 Perineal surface anatomy

metanephric kidneys arise from the caudal intermediate mesoderm. The longitudinal mesonephric duct on each side persists and becomes part of a paired set of genital ducts that contribute significantly to the male reproductive tract. As described below, the mesonephric ducts largely regress in the female and normally only contribute to rudimentary structures.

During the 6th week, primordial germ cells appear within the medial, or genital, portion of the urogenital ridge. These germ cells initially arise in the embryo's epiblast, migrate through

Table 1.1 Homologues and origins of the human reproductive system

Indifferent	Germ layer	Female	Male
Gonad	Mesoderm	Ovary	Testis
Paramesonephric (Müllerian) duct	Mesoderm	Fallopian tubes	Appendix testis
Paramesonephric duct	Mesoderm	Uterus, vagina	Prostatic utricle
Mesonephric (Wolffian) duct	Mesoderm	Rete ovarii	Rete testis
Urogenital sinus	Endoderm	Skene's glands	Prostate
Urogenital sinus	Endoderm	Bladder, urethra	Bladder, urethra
Urogenital sinus	Endoderm	Bartholin's gland	Bulbourethral gland
Labioscrotal folds	Ectoderm	Labia majora	Scrotum
Urogenital folds	Mesoderm	Labia minora	Spongy urethra
Genital tubercle	Mixed	Vestibular bulbs	Bulb of the penis
Genital tubercle	Mixed	Clitoral glans	Glans penis
Genital tubercle	Mixed	Clitoral crura	Crus of the penis
Prepuce	Mixed	Clitoral hood	Foreskin
Gubernaculum	Mesoderm	Round ligament of the uterus	Gubernaculum testis

Modified from Ref. [21]

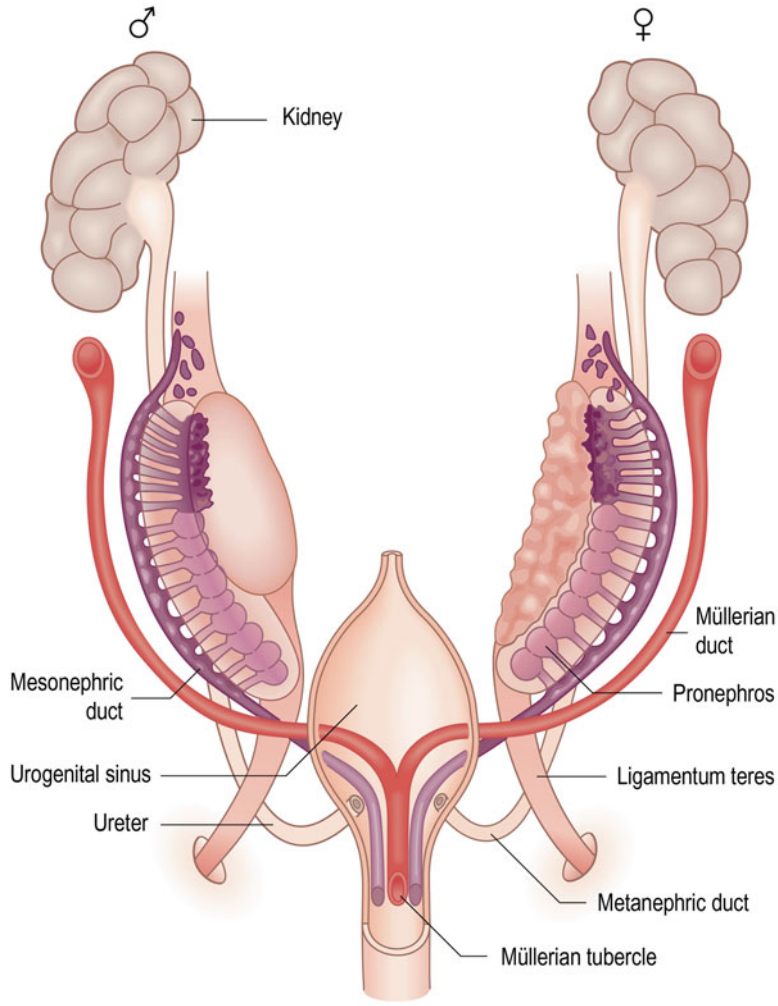

Fig. 1.3 Anlage of the genital organs in the indifferent, bisexual stage (Used with permission from Jaubert et al. [3]

the primitive streak during gastrulation in the 3rd week, and come to rest in the wall of the yolk sac near the forming allantois. Soon after gastrulation, the germ cells migrate back into the embryo along the dorsal mesentery of the hindgut and invade the medial edge of the urogenital ridge. In response to the germ cells, the overlying coelomic epithelium of the genital ridge proliferates and invades the mesenchymal tissue to form a series of irregularly shaped, primitive sex cords that remain connected to the surface epithelium and become closely associated with the germ cells. The surrounding mesenchymal cells, in turn, will develop into sex-specific interstitial cells of the gonads that contribute to the differentiation of the male or female phenotype.

During this same period, a second set of genital ducts, the paramesonephric (Müllerian) ducts, arise as the epithelium along the lateral edge of the genital ridge adjacent to the mesonephric ducts invaginates to form a longitudinal tube. At their cranial end, the paramesonephric ducts are lateral to the mesonephric ducts and end in a funnel-shaped opening into the abdominal cavity at about the same level as the superior aspect of the indifferent gonad. Caudally, the paramesonephric ducts continue lateral to the mesonephric ducts and then cross under (ventral to) the mesonephric ducts to course medially and partially fuse in the midline to form the uterine canal. The uterine canal projects caudally until it meets the wall of the urogenital sinus, where it causes a small swelling known as the paramesonephric, or Müllerian, tubercle to form [3].

At this point, the gonads of males and females are indistinguishable. The ductal systems are distinguishable by location only, but not histologically. However, from the 7th week on, the male and female systems diverge greatly as the process of sexual differentiation ensues. In the male, the sex-determining region of the Y-chromosome gene (*SRY*) acts in conjunction with *SOX9* to upregulate the expression of steroidogenic factor 1 (*SF1*) [4]. SF1 stimulates the differentiation of the epithelial sex cord cells into Sertoli cells, which then secrete anti-Müllerian hormone (AMH, also known as Müllerian inhibiting substance, or MIS) [5]. AMH is a transforming growth factor-beta (TGF-β) family member which induces apoptosis and regression of the paramesonephric ducts. The Sertoli cells also express CYP26, which degrades local retinoic acid, thus inducing meiotic arrest in the germ cells. In this milieu, the germ cells are directed to become spermatogonia [6]. SF1 also directs the differentiation of the interstitial cells of the male gonad into Leydig cells that secrete testosterone, which promotes growth and differentiation of the mesonephric ducts into the efferent ductules, epididymis, vas deferens, and seminal vesicles [7]. Testosterone is further converted by 5-α reductase into dihydrotestosterone, which stimulates growth and differentiation of the prostate and external genitalia.

In the female, *SRY* expression is absent, and instead the dominant genetic program is directed by *WNT4*, which initiates differentiation of the female phenotype [8]. Under this program, the surface epithelium of the female gonad proliferates rapidly to give rise to a secondary generation of sex cords known as cortical cords which will then become follicular cells rather than Sertoli cells. As there are no Sertoli cells, AMH is absent and the paramesonephric ducts persist. Moreover, retinoic acid signaling within the gonad induces progression of the germ cells into oogonia that proliferate and enter into the first meiotic division to form primary oocytes. The oocytes, in turn, direct the differentiation of the epithelial cord cells into follicular cells and cells of the surrounding mesenchyme into theca cells. Without Leydig cells, there is not a significant source of testosterone (and therefore DHT) to support the growth of the mesonephric ducts or male external genitalia. Instead, the theca and follicular cells secrete estrogens which promote the growth and development of the paramesonephric ducts and female external genitalia.

The uterine (Fallopian) tubes, uterine corpus, and uterine cervix develop exclusively from the paramesonephric ducts, whereas the vagina has contributions also from the urogenital sinus. The cranial portion of the paramesonephric ducts develop into the uterine (Fallopian) tubes, retaining their funnel-shaped openings into the coelomic cavity, which develop into the infundibulum and fimbriae, while the caudal portion of the paramesonephric ducts, when fused, gives rise to the uterus (Fig. 1.3). At this period, the entire presumptive uterus is a simple canal, without any of the later structural changes found in the adult

uterine body or cervix. The uterine canal grows toward and contacts the urogenital sinus at about the 7th week and induces the formation of the paramesonephric tubercle. Concurrent with this process, the endodermal epithelium of the urogenital sinus at the point of contact forms a pair of swellings (sinovaginal bulbs) that fuse into a solid vaginal plate that proliferates and extends cranially, thus pushing the paramesonephric tubercle and forming uterus away from the urogenital sinus. The growth of the vaginal plate and paramesonephric tubercle continues during the 3rd and 4th months followed by a process of canalization that is completed by the 5th month such that the mesenchymal walls of the vaginal fornices are derived from the paramesonephric tubercle and the squamous epithelial surfaces and possibly some of the lowest vagina are of urogenital sinus origin [3]. The initial site where growth of the vaginal plate from the wall of the urogenital sinus commenced usually does not fully canalize, thus leaving a membranous hymen that separates the vaginal canal from the urogenital sinus. While the mesonephric ducts mostly regress in the female, some remnants may remain as rudimentary tubules or cysts found adjacent to the ovary (epoophoron), uterine tube (paroophoron), or along the lateral wall of the uterus and/or vagina (Gartner's ducts/cysts) (Fig. 1.4).

The development of the external genitalia is apparent by the 4th week of development as the tissue along the rim of the cloacal opening thickens into cloacal folds [9]. Division of the cloaca into urogenital and anal portions occurs during the 5th and 6th weeks by the growth of the urorectal septum, which is a block of mesoderm-derived tissue that grows in between the alimentary and urogenital tracts and eventually fuses with the cloacal folds at the site of the perineal body. Anteriorly, the tissues of the cloacal folds fuse to form the genital tubercle. Posterior to the genital tubercle, the tissue surrounding the opening into

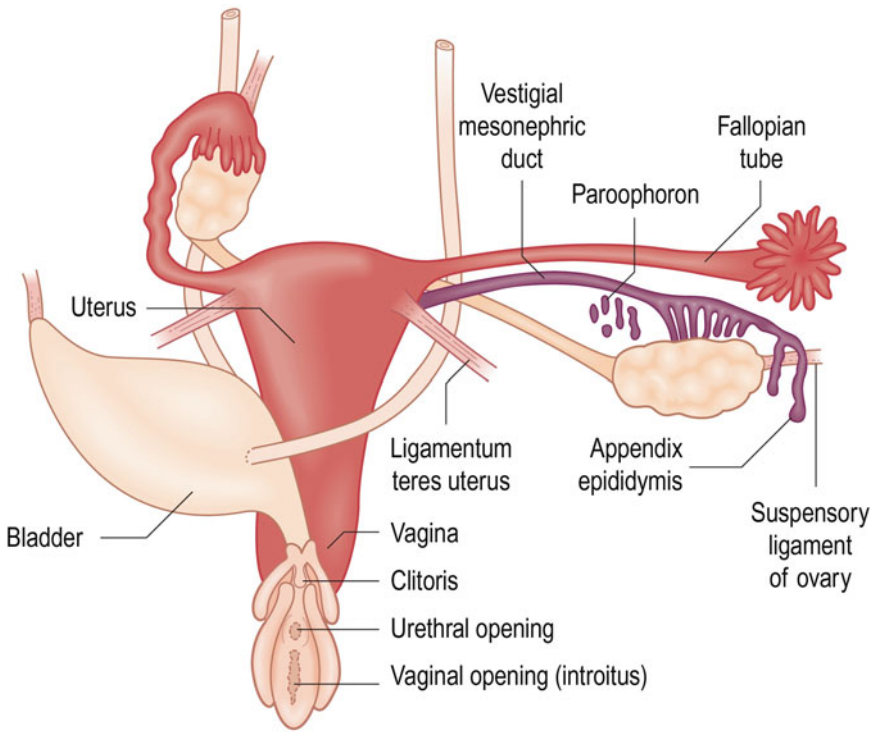

Fig. 1.4 Female differentiation of the genital organs (Used with permission from Jaubert et al. [3]

the forming urogenital sinus develops into urogenital folds. The posterior-most cloacal folds develop into anal folds that surround the forming anus. Lateral to the urogenital folds, a second set of swellings, the labioscrotal folds, appear. In the male (under androgenic influence, in particular dihydrotestosterone), the genital tubercle develops into the penile glans; the urogenital folds fuse and elongate to form the penile shaft; and the labioscrotal folds fuse to become the scrotum [8]. In the female (under the influence of estrogens rather than androgens), the genital tubercle develops into the clitoral glans, whereas the urogenital and labioscrotal folds give rise to the labia minora and majora, respectively [9] (Fig. 1.5). Anteriorly, the labia majora merge to form the mons pubis, and posteriorly, the labia majora fuse with the perineal body anterior to the anus. The remaining opening of the urogenital sinus exterior to the vaginal introitus (usually completely or partially covered by the hymen) and bounded by the labia minora expands to form the vestibule, the lining of which is thus endoderm derived. This is in contrast to the other structures of the vulva, which are of ectoderm and mesoderm origin and therefore respond differently to hormones or other stimuli evoked in either the normal or diseased state.

Overview of Vulvar Anatomy

As described above, the vulva consists of those structures within the urogenital triangle and external to the vaginal introitus, or hymen. Anteriorly, the most superficial vulvar structure is the mons pubis, which blends laterally with the labia majora found on either side of the vestibular opening. Posteriorly, the labia majora merge with the perineal body, which lies between the vaginal fourchette and the anus. The mons pubis and labia majora are of ectodermal origin and therefore are covered by hairy skin. Medial to the labia majora are the interlabial sulci, which separate the labia majora from the labia minora and also mark a transition point where the skin becomes hairless. The labia minora bound the opening into the vestibule. Anteriorly, each labium minus bifurcates into a medial and lateral fold. The medial folds from each labium minus unite posterior to the clitoris to form the frenulum of the clitoris, whereas the lateral folds unite anterior to the clitoris to form the hood or prepuce of the clitoris. Posteriorly, the labia minora merge to form the frenulum of the labia minora (or vaginal fourchette). Elements of the labia minora constitute an imaginary vestibular line (of Hart) that demarcates the vestibule, which is of endodermal origin, from the exterior elements of the vulva, which are of ectodermal origin. Hart's line, thus, is defined anteriorly by the prepuce of the clitoris, laterally by the labia minora, and posteriorly by the vaginal fourchette. Within the vestibule itself are the vaginal introitus, bounded by the hymen, the paired erectile vestibulovaginal bulbs and associated vestibular glands, and the urethral meatus and associated paraurethral glands.

Somatic innervation of the vulva is largely via the iliohypogastric, ilioinguinal, and genitofemoral nerves, which serve the mons pubis and anterolateral labia majora, and the pudendal nerve, which originates from the sacral plexus and carries fibers derived from sacral spinal cord segments S2 to S4 as well as sympathetic fibers derived from gray rami communicantes from the pelvic sympathetic chain and is the major nerve of the perineum [1]. The pudendal nerve enters the perineum by coursing along the lateral wall of the ischioanal fossa within the pudendal canal formed by the fascia associated with the obturator internus muscle. The pudendal nerve gives rise to three major branches:

1. The inferior rectal nerve, which serves the rectum and anus
2. The perineal nerve, which provides motor innervation to the muscles of the perineum, sensory innervation via the posterior labial nerve, and sympathetic innervation to blood vessels and sweat glands
3. The dorsal nerve of the clitoris, which passes through the perineal membrane just inferior to the pubic symphysis and courses along the dorsal body and glans of the clitoris to provide sensory innervation

Parasympathetic innervation of erectile tissue within the vestibular bulb and the clitoris occurs via pelvic splanchnic nerves that originate from the anterior rami of sacral spinal cord segments S2 to S4 and course into the inferior hypogastric plexus before then ramifying into fine branches that pierce the perineal membrane to enter into

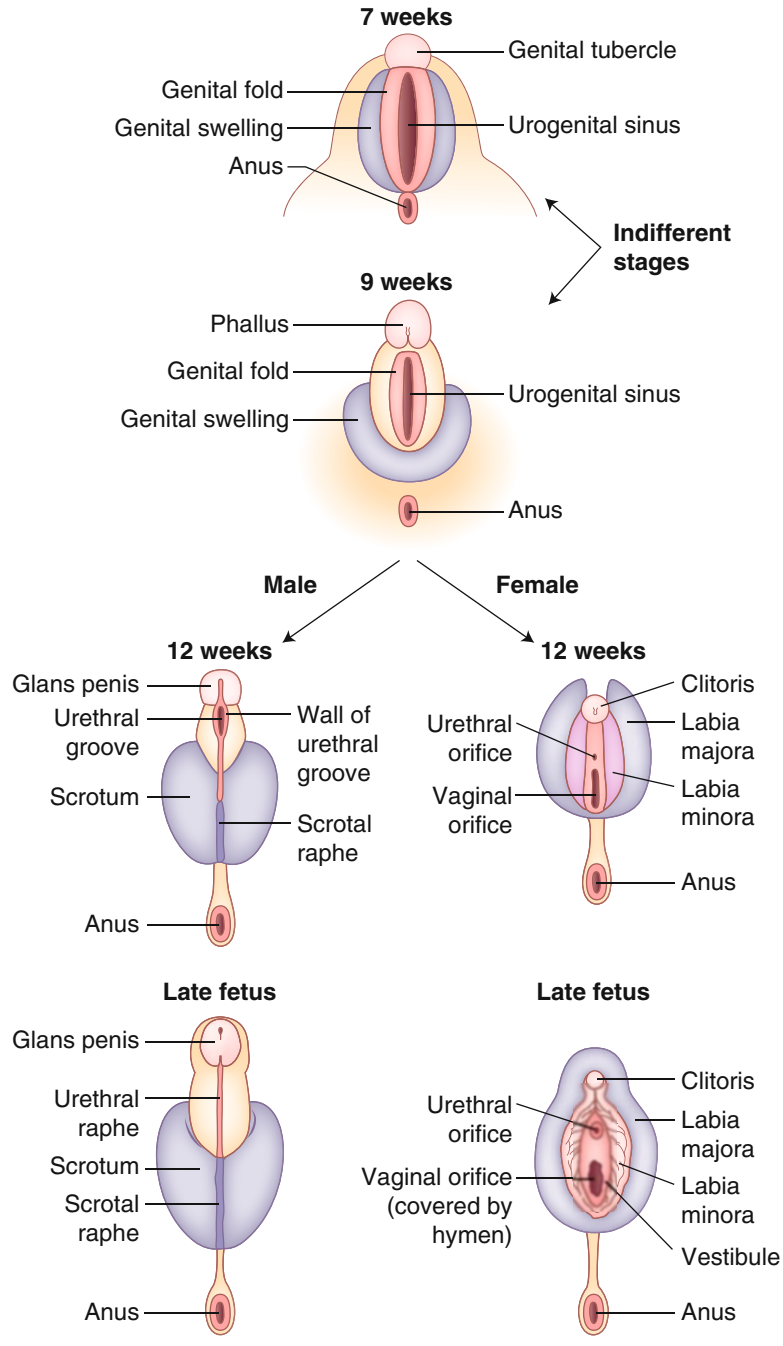

Fig. 1.5 Embryological development of the female and male external genitalia

the crura and glans of the clitoris and the bulbs of the vestibule [1].

Blood supply to the vulva is via the femoral artery, which sends both superficial and deep external branches that supply the mons pubis and anterolateral labia majora, respectively, and the internal iliac artery from which the internal pudendal artery derives [1]. The internal pudendal artery, in turn, branches in a similar pattern to the pudendal nerve to supply the rectum, anus, and perineal structures (via branches of the perineal artery such as the posterior and anterior labial

arteries that serve the labia minora and majora). The terminal internal pudendal artery gives rise to the arteries that serve the vestibular bulb as well as to the dorsal and deep arteries of the clitoris that supply erectile tissues within these organs. Venous drainage follows a similar pattern.

Lymphatic drainage from the perineal deep structures follows the internal pudendal artery into the internal iliac nodes in the pelvis [1]. Lymphatic drainage from the superficial tissues of the labia majora and mons pubis goes to the superficial inguinal nodes located superficial to the fascia lata near the emergence of the saphenous vein from the femoral vein. Lymphatic channels from the labia minora, clitoris, vestibule, and caudal-most vagina drain into deep inguinal nodes located deep to the fascia lata near the saphenous vein and external iliac nodes located along the external iliac artery. Lateral vulvar structures generally drain to the respective ipsilateral side, whereas medial structures drain centrally.

Regional Anatomy and Histology: Mons Pubis

The mons pubis overlies the pubic symphysis at the apex of the urogenital triangle. Being of ectodermal origin, it is covered by skin with a stratified squamous keratinized epithelium, hair follicles, sebaceous glands that empty into the hair follicles, eccrine sweat glands that empty onto the surface, and sensory receptors similar to other locations on the body. Touch receptors associated with the epithelium include Meissner's corpuscles and Merkel's tactile disks for vibratory sensation and free nerve endings for fine touch, pain, and temperature [10]. Vibratory sensation is further augmented by free nerve endings associated with hair follicles. Pacinian and Ruffini corpuscles for pressure sensation are present throughout the subcutaneous tissue, largely at the dermis-hypodermis interface, as are Dogiel-Krause receptors [10].

Substantial changes occur at puberty in the skin of the mons pubis. For one, the subcutaneous tissue becomes more prominent as the hypodermis progressively accumulates more adipose tissue. The hair follicles elongate and the hairs become coarser as puberty progresses up until about age 17 years when the final adult pubic hair pattern is set [11]. Racial and genetic factors affect the quality of pubic hair in terms of pigmentation, amount, and consistency.

Regional Anatomy and Histology: Labia Majora

The labia majora arise from the labioscrotal folds of the embryo, which, unlike those of the male, do not fuse but instead remain open as a pair of folds bounding the labia minora and the opening of the vulvar vestibule. The labia majora lie laterally to the labia minora, separated by the interlabial sulcus. Anteriorly, the labia majora merge with the mons pubis, whereas posteriorly, they join the perineal body located between the vaginal fourchette and the anus. Laterally, the labia majora merge with the inguinal-gluteal folds.

Like the mons pubis, the labia majora are of ectodermal origin and are therefore covered by skin with many of same features as those seen in the mons pubis (Fig. 1.6), although in addition to

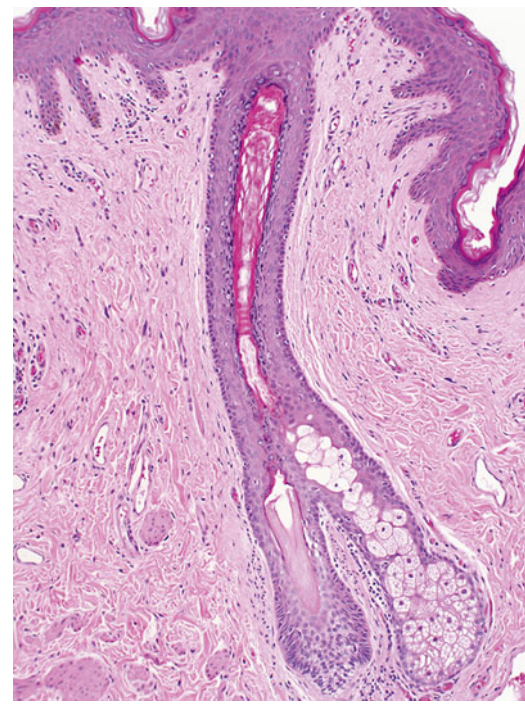

Fig. 1.6 The skin of the labium majus with hair follicle and sebaceous gland