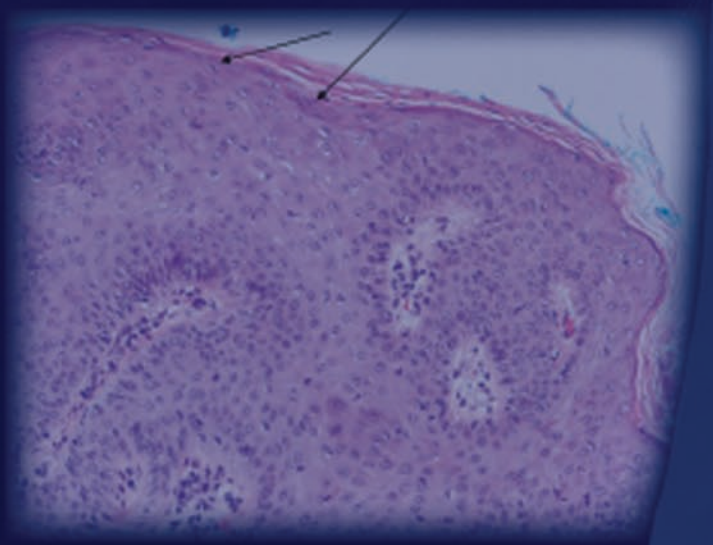
SECOND EDITION

THE VULVA

Physiology and Clinical Management



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CRC Press
Taylor & Francis Group

The Vulva

Physiology and Clinical Management

Second Edition

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CRC Press
Taylor & Francis Group
Boca Raton London New York

CRC Press is an imprint of the
Taylor & Francis Group, an **informa** business

CRC Press
Taylor & Francis Group
6000 Broken Sound Parkway NW, Suite 300
Boca Raton, FL 33487-2742

Printed on acid-free paper

International Standard Book Number-13: 978-1-4987-5243-5 (Pack- Hardback and Ebook)

Library of Congress Cataloging-in-Publication Data

Names: Farage, Miranda A., editor. | Maibach, Howard I., editor.
Title: The vulva : physiology and clinical management / edited by Miranda A.
Farage, Howard I. Maibach.
Other titles: Vulva (Farage)
Description: Second edition. | Boca Raton, FL : CRC Press, [2018] | Includes
bibliographical references and index.
Identifiers: LCCN 2016034849| ISBN 9781498752435 (pack : hardback : alk. paper) | ISBN
9781498752459 (ebook (Vitalbook)) | ISBN 9781498752442 (ebook (PDF))
Subjects: | MESH: Vulva--physiology | Vulvar Diseases--therapy
Classification: LCC RG261 | NLM WP 200 | DDC 618.1/6--dc23
LC record available at https://lccn.loc.gov/2016034849

Visit the Taylor & Francis Web site at
http://www.taylorandfrancis.com

and the CRC Press Web site at
http://www.crcpress.com

For my adored Mother and Father: your countless sacrifices have formed my world and given me the gift of purpose and strength of will to succeed. Wherever you are, I am nourished and guided by your never-ending love.

Miranda A. Farage

Contents

Foreword

This is a much-needed book for the patient with vulvovaginal symptomatology who too often faces the prospect of an incomplete evaluation and misdirected therapies. There are many reasons for this. Physicians with practice time constraints magnified by an office full of waiting patients too often begin their physical examination with the introduction of the vaginal speculum, bypassing the vulva. In addition, the record of diagnostic accuracy of vaginal infections by physicians shows a high error rate, and inaccurate diagnoses lead to inappropriate therapeutic interventions, which only prolong and sometimes intensify a patient's symptomatology. Finally, to a large extent, the care of patients with vulvovaginal problems requires dermatologic insights that are too often lacking for many practitioners.

The editors of this second edition, Miranda A. Farage and Howard I. Maibach, attempt to address these shortcomings, and I applaud their efforts. They have selected experts who have both the knowledge and the ability to organize their prose that captures reader attention and accomplishes reader understanding. The underlying philosophy of this book is to provide an in-depth exposé of the anatomy and physiology of the vulva: a basis for the understanding of the pathophysiology and one that sets a goal to be achieved with appropriate therapy. This is followed by an exposition of the myriad presentations of patients with a wide range of vulvovaginal diseases and current scientifically accepted treatment regimens. There is an excellent analysis of the menstrual cycle, lochia, and the range of health care products that are now available to women. Since medicine is not practiced in a vacuum, the influences of race and societal norms on women are provided in detail. Finally, there is a fascinating section that provides an in-depth review of newer investigational techniques that will influence the future care of women.

This second edition is for all readers. For me, it is a cover-to-cover joy to read. For others, it will be a valuable office reference to be opened every day in order to address the problems of individual patient care. My congratulations to both the editors and the authors. Obviously, this is a labor of love that hits the mark.

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Preface

Few books are devoted exclusively to the vulva. We have been in pursuit to break the menstrual and genital area taboos that still exist today on a global basis and move to scientific empowerments. Researchers studying the vulva and clinicians treating patients with vulvar conditions know that there is a paucity of information about the vulva in the medical/scientific literature. Consequently, the unique physiology of the vulva, its normal and diseased states, pertinent cultural and hygiene practices that affect vulvar health, menstrual cycles, and the direction of current investigative research are not widely recognized. This insufficient body of information is responsible for the existing deficiencies in knowledge of the vulva, education and training of physicians about vulvar conditions, and appropriate diagnosis and treatment of vulvar pathology. In addition, the assumption that vulva skin is exactly like the skin of external body surfaces is wrong. Vulvar tissue has many unique physiological properties and characteristics that differentiate it from the skin and tissue of other body sites.

We attempt to redress these deficiencies with this second edition volume, *The Vulva*, and strengthening the compilation of up-to-date clinical, physiological, sensorial, disease states, symptomology and research information collected in one comprehensive 2nd edition work.

The Vulva, *Second Edition*, was updated primarily for medical and scientific audiences to underscore unique aspects of vulvar physiology, menstruation, to highlight possible ethnic differences, to review vulvar diseases, to alert researchers and clinicians to cultural and hygiene practices that affect vulvar health, to share the latest techniques in investigative research on vulvar tissue, and most importantly to break the taboo and move the science forward. *The Vulva* includes chapters on vulvar anatomy, physiology, microbiology, age-related changes, ethnicity, diseases, symptoms, current therapies, global cultural and hygiene practices, vulvar care, personal products used on the vulva, and toxicological and bioengineering research methods applied to vulvar research.

The information included in this second edition book presents the current knowledge and understanding of vulvology and its clinical management. Although this work attempts to be a comprehensive and up-to-date resource, we acknowledge that research on the vulva still lags other fields study. Researchers and clinicians who have contributed to this volume hope to continue promoting a better understanding of the unique physiology of the vulva and to encourage needed research.

This book is intended to continue to increase awareness of the unique health concerns of the genital and vulva areas and to be a valuable resource on the vulva region for the medical and scientific communities.

The editors welcome any suggestions and ideas for the third edition.

Miranda A. Farage and Howard I. Maibach

Acknowledgments

Many appreciations and thanks are gratefully owed to the many people who contributed knowingly and indirectly to this book.

The following readers generously offered their time and expertise to peer-review relevant chapters: Drs. Kenneth W. Miller, G. Collier, Ms. Lisa Lennon, Drs. Tom Osborn, Brian Gray, Ray Warren, Mr. Ron Visscher, Mr. J. Cooper, Mr. Kevin Johnson, and Dr. Ninah Enane-Anderson. Their collective recommendations have vastly improved the texts assembled here. Many thanks go to the efforts, valuable time, and help of all the contributors of this book.

This book represents the fruits of a jointly conceived and executed venture and has benefited from partners. Our deepest gratefulness and appreciations go to Dr. Sharon Mitchell and Dr. Ninah Enane-Anderson for their genuine support and encouragements. No praise is excessive from Ms. Lisa Lennon's help and efforts for which she has our heartfelt gratitude. Our deepest and most sincere debt is owed to an exceptional person who shepherded the book from start to finish, Dr. Kenneth W. Miller without whose belief, support, help, encouragement, guidance and understanding, this book would not have seen the light of day.

We would also like to single out Mr. Robert Peden, acquisitions editor, for a special recognition. His great efforts, time, discipline, and dedication helped moved this book forward on a timely and organized manner.

Above all, our everlasting gratitude, thanks and love go to our families, children, and spouses who supported, helped, and encouraged us all the way with their incredible patience. Your continuous care, unconditional love, and sacrifice made all this possible, and easier to achieve.

Miranda A. Farage and Howard I. Maibach

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PART 1

Anatomy and Physiology

Anatomy of the vulva

Aikaterini Deliveliotou and George Creatsas

INTRODUCTION

The vulva, or pudendum, is a collective term for the external female genital organs that are visible in the perineal area. Knowledge of the basic anatomy of the vulva is necessary in order to understand its physiology and appropriately recognize the wide spectrum of vulvar pathology. To achieve these goals, the vulvar embryology is first presented, before describing the anatomy of the vulva in women of reproductive age. Lifetime changes in the vulva from birth to adulthood are described in Chapter 3.

EMBRYOLOGY OF VULVA

Early in the fifth week of embryonic life, the cloaca is divided by the urorectal septum, which gives rise to the perineum. Folds of tissue form on either side of the cloaca: the anterior folds are urogenital and the posterior folds are anal. The anterior folds meet at the midline to form the genital tubercle. The genital tubercle enlarges. In the male embryo, under the influence of androgens, the genital tubercle becomes the penis; in the female embryo, growth slows and it becomes the clitoris. On either side of the tubercle, the urogenital folds form the labia minora. In the indifferent stage, the labioscrotal swellings develop on either side of the urogenital folds. In the male embryo, under the influence of androgens, they differentiate into the scrotum; in the female, lacking androgenic stimulation, they remain largely unfused to become the labia majora. The definitive urogenital sinus gives rise to the vaginal vestibule, into which the urethra, vagina, and greater vestibular glands open.

ANATOMY OF THE VULVA

The vulva consists of the mons pubis, the labia majora, the labia minora, the clitoris, the hymen, the vestibule of the vagina, the urethral orifice, Skene's glands, Bartholin's glands, and the vestibular bulbs (Figure 1.1).

Anatomy of the Vulva

The anterior and posterior boundaries of the vulva extend from the mons pubis to the anus, respectively; its lateral boundaries lie at the genitocrural folds. The vulvar epithelium exhibits regional differences in tissue structure based on embryonic derivation. The skin-bearing mons pubis, perineum, and labia are derived from the embryonic ectoderm. Vulvar skin, like skin at other sites, has a keratinized, stratified, squamous epithelial structure with hair follicles, sebaceous glands, and sweat glands. The thickness of the degree of keratinization of vulvar skin decreases progressively from the labia majora, over the clitoris, to the labia minora. The vulvar vestibule, derived from the embryonic endoderm, is nonkeratinized. Chapter 2 describes in detail the regional tissue structure of the vulva.

Mons Pubis

The mons pubis (mons Veneris) is the rounded eminence in front of the pubic symphysis, which is formed by a collection of adipose tissue beneath the integument. During puberty, it becomes covered with hair up to its junction with the abdominal wall. The hair pattern, or escutcheon, of most women is triangular. Genetic and racial differences produce a variety of normal hair patterns, with approximately one in four women having a modified escutcheon with a diamond pattern.

Labia Majora

The labia majora are a pair of prominent longitudinal, cutaneous folds of fibro-adipose tissue that are homologous to the scrotum in the male. The structures bear epidermal tissue resembling the dartos tunic of the scrotum, as well as adipose tissue, areolar tissue, blood vessels, nerves, and glands. The labia majora also include the terminal extension of the round ligament and, occasionally, a peritoneal diverticulum, the canal of Nuck.

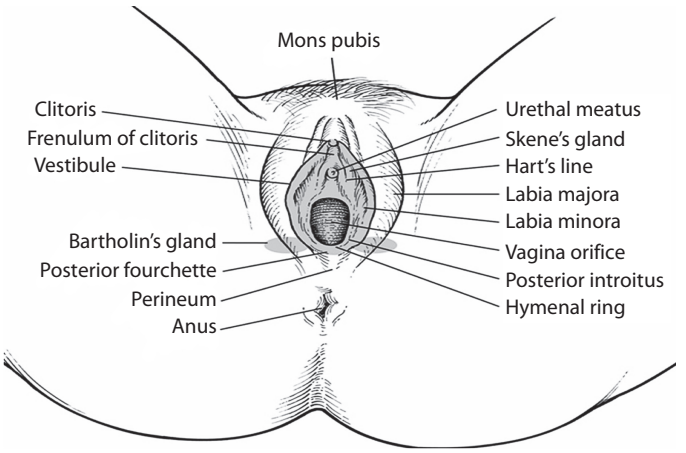

Figure 1.1 Anatomy of the adult vulva. (With kind permission from Libertas Academica Ltd, from Farage MA et al. *Clin Med Womens Health* 2010; 3: 1–13.)

The size of the labia majora is related to fat content. Each is approximately 7–8 cm in length and 2–3 cm in width. The labia majora extend downward and backward from the mons pubis, thus forming the lateral boundaries of a fissure or cleft (the pudendal cleft or rima) into which the vagina and urethra open.

Each labium majus has two surfaces: the outer surface is pigmented, rugose, and bears pubic hair, sebaceous glands, apocrine glands, and eccrine glands. The inner surface is smooth; it bears sebaceous, apocrine, and eccrine glands but no hair follicles. Vulvar apocrine glands are similar to those of the breast and axillary areas.

The labia majora are thicker in front. Anterior to the clitoris, they join to form the anterior boundary of the pudendal cleft, known as the anterior labial commissure. The labia majora do not surround the pudendal cleft fully; laterally, they remain approximately parallel to it and posteriorly, they gradually merge with the neighboring integument below the juncture of the labia minora (fourchette). The posterior ends of the labia majora and the connecting skin between them form the posterior boundary of the pudendum, known as the posterior labial commissure. The interval between the posterior commissure and the anus is 2.5–3 cm in length and constitutes the perineum.

Labia Minora

The labia minora (nymphae) are two small cutaneous folds that are situated between the labia majora and the vaginal orifice. The labia minora are homologous to the penile urethra and part of the skin of the penis in males. Laterally, they extend obliquely from the clitoris toward the rear for approximately 4 cm on either side of the vaginal orifice. They are shorter and thinner than the labia majora. At the clitoris, the anterior portion of each labium minus divides into two segments. Each upper segment passes anteriorly to the clitoris to meet its fellow of the opposite side, forming a fold, the preputium clitoridis, which overhangs the glans of the clitoris. Each lower segment passes beneath the clitoris, joining with its fellow to form the frenulum, which is attached to the inferior surface of the clitoris. The posterior portions of the labia minora surround the vestibule of the vagina. Their posterior juncture is the fourchette.

Histologically, the labia minora are composed of dense connective tissue, erectile tissue, and elastic fibers. Unlike the labia majora, they do not contain adipose tissue. The skin of the opposed surfaces of the labia minora has numerous sebaceous glands but no hair follicles or sweat glands. Among women of reproductive age, there is significant variation in the size of the labia minora. They are relatively more prominent in children and postmenopausal women.

Clitoris

The clitoris is a short, cylindrical, erectile structure that is 2–3 cm in length at the superior portion of the vestibule. It is the female homologue of the penis. It is situated beneath the anterior labial commissure, partially hidden between the anterior segments of the labia minora. The clitoris consists of a base of two crura that attach to the periosteum of the symphysis pubis. Like the penis, the clitoris has a suspensory ligament and two small muscles, the ischiocavernosi, which are inserted into the crura of the clitoris. The body of the clitoris consists of two cylindrical corpora cavernosa composed of thin-walled, vascular channels that function as erectile tissue. The distal third of the clitoris is a small rounded tubercle (glans clitoridis) that consists of spongy erectile tissue with many nerve endings. Usually, only the glans is visible, with the body of the clitoris positioned beneath the skin surface. The normal glans clitoridis in adult women has a width of less than 1 cm, with an average length of 1.5–2 cm. Age, weight, and oral contraceptive use do not change its anatomic dimensions. Childbearing may influence the size of the clitoris.

Hymen

The hymen is a thin fold of mucous membrane situated at the entrance to the vagina. Between the hymen and the frenulum of the labia minora is a shallow depression, the navicular fossa. The inner edges of the hymen may be in contact with each other, such that the vaginal orifice appears as a cleft between them. The hymen is usually perforated, with many variations in its structure and shape. The most common forms are that of a ring, which is broadest posteriorly, or that of a semilunar fold, with a hollow margin turned toward the pubes. The hymen is rarely cribriform or has inner edges that form a membranous fringe. It can be completely absent or can appear as a complete septum across the lower end of the vagina, a condition known as an imperforate hymen. Small tags or nodules of firm fibrous material, termed carunculae myrtiformes, are the remnants of the hymen in sexually active women. However, the hymen can persist after the first sexual intercourse, so its presence cannot be considered a sign of virginity. Histologically, the hymen is covered by stratified squamous epithelium on both sides and consists of fibrous tissue with a few small blood vessels.

Vestibule

The vestibule is derived from the endoderm, the lowest portion of the embryonic urogenital sinus. It is the cleft posterior to the glans clitoridis and between the labia minora. It can be visualized by holding the labia minora apart. The vestibule extends from the clitoris to the posterior fourchette. Hart's line marks the juncture of the nonkeratinized epithelium of the vulvar vestibule and the keratinized epithelium of the inner surface of the labia minora. The urethral and vaginal orifices as well as the ducts of the greater vestibular glands open into the vestibule. The remnants of the hymen and numerous small mucinous glands are located within the area of the vestibule.

Urethra

The female urethra, a membranous conduit for urine, runs from the urinary bladder to the vestibule and measures 3.5–5 cm in length. The mucosa of the distal third of the urethra is lined with stratified squamous epithelium, whereas the proximal two-thirds are lined with stratified transitional epithelium. The external urethral orifice is 4–6 mm in diameter and is immediately anterior to the vaginal orifice, approximately 2–3 cm beneath the glans clitoridis. Its mucosal edges grossly appear slightly everted, forming a short, sagittal cleft.

Vaginal Orifice

The vaginal orifice is a median slit below and posterior to the opening of the urethra; the hymen surrounds it, so that its size varies inversely with that of the hymen. It opens into the vagina, a neuromuscular vault connecting to the cervix of the

uterus that unsheathes the penis during sexual intercourse, and allows passage of the newborn infant during birth.

Skene's Glands

Skene's or paraurethral glands are homologous to the prostate in the male. They are branched, tubular glands, adjacent to the distal urethra. Usually, Skene's ducts run parallel to the long axis of the urethra for approximately 1 cm before opening into the distal urethra. Sometimes they open into the area just outside the urethral orifice. The duct of the Skene's gland presents an opening on its posterior surface. Skene's glands are the largest of the paraurethral glands; however, many smaller glands empty into the urethra.

Bartholin's Glands

The greater vestibular glands, or Bartholin's glands, are the homologues of the bulbourethral glands (Cowper's glands) in the male. They consist of two small, roundish, reddish–yellow bodies. Bartholin's glands are situated on the posterolateral aspect of the vaginal orifice, in contact with the posterior end of each lateral mass of the bulb of the vestibule. Histologically, the gland is composed of cuboidal epithelium. The duct from each gland is approximately 2 cm in length and is lined by transitional epithelium. Bartholin's ducts open immediately lateral to the hymen into the groove between the hymen and the labia minora. Their mucus secretion helps maintain adequate lubrication. Infection of these glands can result in an abscess.

Vestibular Bulbs

The vestibular bulbs are the homologues of the bulb and adjoining part of the corpus cavernosum urethrae of the male. They consist of two elongated masses of erectile tissue situated on either side of the vaginal orifice and are united to each other in front by a narrow median band termed the pars intermedia. Each lateral mass measures approximately 2.5 cm in length. The distal ends of the vestibular bulbs are adjacent to Bartholin's glands, whereas the proximal ends are tapered and joined to one another by the pars intermedia. Their deep surfaces are in contact with the inferior fascia of the urogenital diaphragm. Each bulb is immediately below the bulbocavernosus muscle.

Muscles of the Vulva

Three types of muscle exist in the vulva:

1. The ischiocavernosus muscle compresses the crura and lowers the clitoris. It originates from the ischial tuberosity and inserts at the ischiopubic bone.
2. The bulbocavernosus muscle compresses the vestibular bulb and dorsal vein of the clitoris. It originates from the perineal body and inserts into the posterior aspect of the clitoris; some fibers pass above the dorsal vein of the clitoris in a sling-like fashion.
3. The superficial transverse perineal muscle holds the perineal body fixed. It originates from the ischial tuberosity and inserts at the central perineal tendon.

Blood Supply of the Vulva

The vulva derives its blood supply from the femoral artery via the external and internal pudendal arteries. Venous drainage occurs via the internal pudendal veins.

Lymphatic Drainage of the Vulva

The vulva drains primarily to the superficial and deep inguinal nodes and along the dorsal vein of the clitoris, directly to the iliac nodes.

Innervation of the Vulva

The innervation of the vulva derives from branches of several nerves, including the ilioinguinal nerve, the genital branch of the genitofemoral nerve, the perineal branch of the lateral femoral cutaneous nerve of the thigh, and the perineal branch of the pudendal nerve.

CONCLUSION

This chapter provided a review of the embryology and anatomy of the vulva in women of reproductive age. This knowledge is necessary in order to understand the vulva's physiology and recognize the wide spectrum of vulvar pathology.

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2

Tissue structure and physiology of the vulva*

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INTRODUCTION

The vulva is composed of specialized tissue with regional differences in embryonic derivation, structure, and morphology. The vulva comprises the mons pubis, the labia majora and minora, the clitoris, the vulvar vestibule surrounding the urethral orifice and vaginal introitus, and the hymen, a membrane at the juncture of the vulvar vestibule and the vagina. This chapter describes variations in epithelial structure, blood flow, hormonal and immune responsiveness, barrier function, permeability, irritant susceptibility, and microbial colonization of the vulva in women of reproductive age (Table 2.1).

VARIATIONS IN EPITHELIAL STRUCTURE

The lower urogenital tract is the only portion of the female anatomy derived from all three embryologic layers (ectoderm, endoderm, and mesoderm) (Table 2.2). In the vulva, cutaneous epithelium derived from the embryonic ectoderm is juxtaposed closely with nonkeratinized epithelium derived from the embryonic endoderm (6,17).

The embryonic ectoderm gives rise to the keratinized cutaneous epithelium of the mons pubis, labia majora, clitoris, labia minora, and perineum. Like skin at other anatomical sites, the epidermis of the mons pubis, labia majora, and perineum has a keratinized, stratified squamous structure with sweat glands, sebaceous glands, and hair follicles (Figure 2.1) (18). The cutaneous thickness and the degree of keratinization are relatively high on the mons pubis and labia majora, but decrease over the anterior portions of the clitoris and decline progressively from the outer surface to the inner surface of the labia minora (19).

The cutaneous epithelium consists of four layers:

1. A basal germinative layer (stratum basale), which rests on the basal lamina between the epidermis and the dermis
2. A spinous or prickle cell layer, forming the bulk of the epidermal thickness (stratum spinosum)
3. A granular layer (stratum granulosum)
4. A surface layer of flattened, keratinized cells embedded in hydrophobic intercellular lipid (stratum corneum)

Three specialized cells—melanocytes, Langerhans cells, and Merkel cells—also reside in the epidermis. Melanocytes represent a tenth to a fifth of the cells in the cutaneous basal layer (20). They convert tyrosine to melanin pigment, which protects the basal cells from ultraviolet damage. Melanocytes respond regionally to hormones: at puberty, pigmentation of the mons pubis and labia majora increases; during pregnancy, steroid hormones stimulate melanogenesis in the areola, nipples, and perineum and on the midline of the anterior abdominal wall.

Langerhans cells are dendritic cells found in the epidermis, in thymic and mucosal tissues, and in lymph nodes. Their chief functions are to sample antigens at the epithelial surface, process them, and present them to circulating T lymphocytes, the activation of which initiates the cell-mediated immune response.

Merkel cells are found in the basal epidermal layer. Their cell bodies form synapse-like contacts with the terminal endings of myelinated nerve fibers. They release neurotransmitters in response to sensory excitation (21). Merkel cells serve as skin mechanoreceptors that shape sensitivity to soft touch.

The nonkeratinized epithelium of the vulvar vestibule is the only portion of the female genital tract of endodermal origin (17,22). The epithelial structure of the vulvar vestibule resembles that of the vagina and buccal mucosa (Figure 2.2) (17,23). Its superficial stratum bears large, moderately flattened cells lacking keratin but containing glycogen granules and, frequently, pyknotic nuclei. Differentiation of the inner epithelial layers is indistinct: loosely packed, polyhedral cells alter in size and organelle density as they migrate upward from the generative basal layer, but do not form clearly demarcated strata as observed in the skin. Langerhans cells are present in the epithelium of the vulvar vestibule.

The vaginal mucosa, like the vestibule, is a nonkeratinized squamous epithelium.

BLOOD FLOW AND INNERVATION

The vulva is a highly vascularized and well-innervated structure (24). Arterial blood supplies the vulva bilaterally and derives from branches of the internal iliac and femoral arteries; venous drainage eventually reaches the femoral and internal iliac veins.

Blood flow in labia majora skin is more than twice that in forearm skin (Table 2.3) (25). Studies of vulvar skin have demonstrated increased blood flow in response to histamine at doses to which forearm skin is unresponsive (26).

Genital blood flow and innervation are central to the sexual response. The surge in genital and vaginal blood flow that accompanies sexual arousal results in genital vasocongestion, engorgement, and heightened lubrication (27,28). A nitric oxide/cyclic guanosine monophosphate pathway mediates smooth muscle relaxation and clitoral and vaginal blood flow during

* Portions of this review appeared in Farage, M. A. and Maibach, H. I., The vulvar epithelium differs from the skin: implications for cutaneous testing to address topical vulvar exposures, *Contact Dermatitis*, 51, 201–9, 2004. Reprinted with permission from Blackwell Publishing.

Table 2.1 Qualitative Differences between Exposed Skin and Vulvovaginal Epithelia

Characteristic	Exposed skin	Vulvar skin	Vulvar vestibule	Vaginal epithelium
Embryonic derivation	Ectodermal		Endodermal	Mesodermal (estrogen dependent)
Tissue structure	Keratinized, stratified squamous epithelium		Nonkeratinized epithelium with less distinct stratification	
Blood flow	Depends on anatomical site	Higher blood flow than exposed forearm skin	No data	
Hydration	Depends on anatomical site	More hydrated than forearm skin (1,2)	Hydrated by cervicovaginal secretions	
Occlusion	Depends on anatomical site	Greater occlusion than forearm skin	Greater occlusion than exposed skin	
Friction	Depends on anatomical site	Higher coefficient of friction than forearm skin (3)	Not determined	
Hormonal influences	Menstrual cycle variability in water barrier function and susceptibility to irritants (4,5)	Thickness unchanged over the course of menstrual cycle (6) Menstrual cycle variability in barrier function and irritant susceptibility unknown	Not determined	Menstrual cycle variability in epithelial thickness, glycogen content, and nuclear pyknosis (7,8)
Permeability	Varies by site; influenced by skin thickness (9)	Permeability affected by increased hydration and occlusion (10,11)	Significantly more permeable than keratinized skin (12)	
Immune cell densities	Diverse population of immune cells	Langerhans cells most common No difference in Langerhans' cell density between keratinized and nonkeratinized regions (13)		Langerhans' cell densities lowest at fornix, highest at introitus (14)
Microbiology	Diverse population includes *S. aureus*, coagulase-negative staphylococci, streptococci, diphtheroids, yeasts, etc.	Microflora affected by hydration, occlusion, and vaginal and perineal cross-colonization. Higher densities of *S. aureus,* streptococci, lactobacilli, and *Candida* than exposed skin (15)	Microflora influenced by cervicovaginal secretions and perineal and urethral cross-colonization	Highly diverse, mixed aerobic and anaerobic microflora. Acid-producing microbes are dominant in healthy women (16)

Table 2.2 Embryologic Derivation of the Female Lower Urogenital Tract

Origin	Structures
Ectoderm	Skin of the labia majora and part of the labia minora
Endoderm	Vulvar vestibule
	Bladder (except trigone)
	Anterior urethral wall
Mesoderm	Hymenal membrane
	Posterior urethral wall
	Bladder trigone

sexual arousal (28). The sex steroid hormones not only maintain epithelial tissue structure and function, but also sustain genital blood flow and vaginal lubrication in response to pelvic nerve stimulation. Estrogen exerts its vascular effects by regulating endothelial nitric oxide production (29).

The vulva has both somatic and autonomic innervation. Motor components mediate pelvic muscle contraction and vascular engorgement of clitoral and vaginal tissue. Sensory components convey touch, pain, itch, temperature, wetness, distention of the anal canal and vagina, and sensations related to sexual arousal. In the clitoris, nerve fibers from the small and large trunks of the dorsal nerve form extensive plexuses in the deeper regions of the dermis and subcutaneous layers (24). In the upper regions of the dermis, the nerve fibers display terminal fibrils with endings that penetrate the epidermis. These epidermal nerve endings vary from simple axon terminals to highly branched and encapsulated structures. Although such structures are found in other regions of the vulva, they decrease in number in a lateral direction from the clitoris.

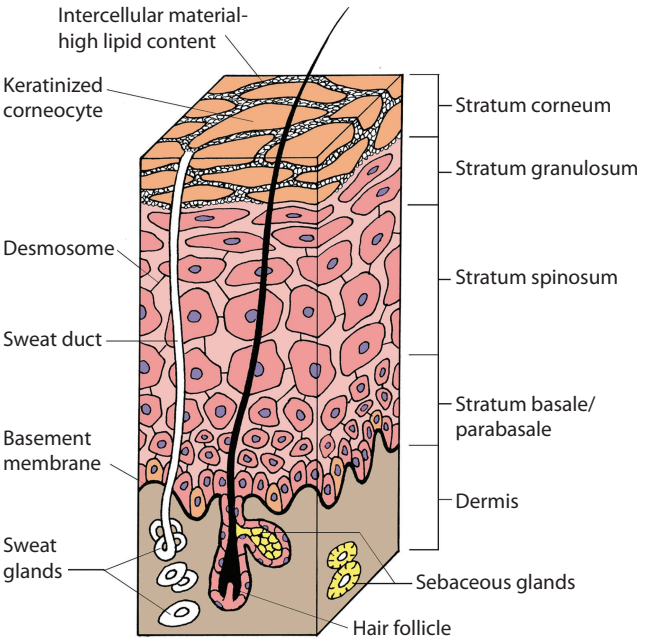

Figure 2.1 Epithelial structure of vulvar skin. (From Farage MA, Maibach HI. *Contact Dermatitis* 2004; 51(4): 201–9. Adapted with permission.)

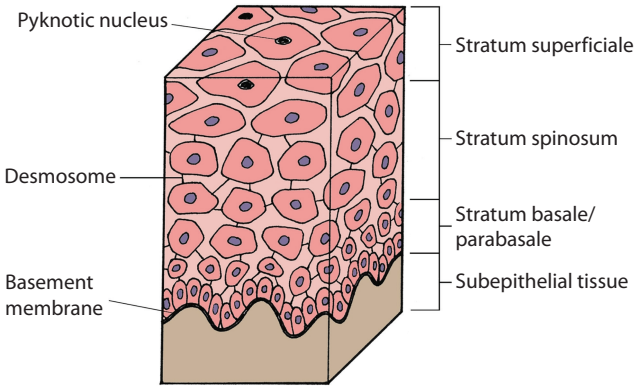

Figure 2.2 Epithelial structure of the vulvar vestibule. (From Farage MA, Maibach HI. *Contact Dermatitis* 2004; 51(4): 201–9. Adapted with permission.)

Innervation of the labia majora differs from that of the rest of the vulva: although both superficial and deep neural nets are present, superficial nerves are reduced markedly. Most nerve endings in the labia majora are parafollicular and do not extend into the epidermis (24).

HORMONAL RESPONSIVENESS

Vulvar skin has a higher concentration of epidermal androgen receptors than skin at nongenital sites (30). At puberty, androgens direct the maturation of vulvar sebaceous glands and hair follicles (31).

The vaginal epithelium has a high level of estrogen receptors and is responsive to ovarian hormone cycling. At midcycle, vaginal epithelial cell proliferation, glycogen content, and nuclear pyknosis increase in response to estrogen. A small but statistically significant increase in vaginal epithelial cell layers has been found at midcycle (8), but no significant difference in epithelial thickness has been observed between follicular and luteal phases (8,32). In postmenopausal women, the lack of ovarian estradiol secretion is associated with long-term thinning of the epithelium, reduced vaginal secretions, and increased pH (33), a condition known as vaginal atrophy.

The concentration of estrogen receptors decreases progressively from the vagina to the vulva, with the lowest levels on keratinized vulvar skin (30). The thickness of the vulvar epithelium remains constant over the course of the menstrual cycle, but its surface cells are predominantly orthokeratotic (lacking nuclei) at the beginning and end of the cycle, and increasingly parakeratotic (bearing a degenerated nucleus) at midcycle (6,7). Progesterone receptors are not found on vulvar skin; they are restricted to the transitional epithelium of the inner aspect of the labia minora and to the nonkeratinized epithelia of the vagina and vulvar vestibule (30).

IMMUNE CELL POPULATIONS

Immune cell infiltration of the vulva is most evident during the reproductive years (31). Langerhans cells are the most common immune cell type in the vulva; intraepithelial and perivascular lymphocytes are found infrequently (13). Langerhans cells are part of the dendritic cell system. They serve as sentinels, sampling antigen at the epithelial surface, then transporting and presenting it in immunogenic form to responsive T

Table 2.3 Quantitative Comparison of Biophysical Variables, Permeability, and Irritant Susceptibilities in Forearm and Labia Majora Skin

Parameter assessed (units)	Forearm	Vulva	Statistical significance (N = number of subjects)	Reference
Transepidermal water loss (g/m² · h)	3.5 ± 0.3	14.5 ± 1.3	$p < 0.001$[a] (N = 44)	(3)
Friction coefficient (μ, unitless)	0.48 ± 0.01	0.66 ± 0.03	$p < 0.001$[a] (N = 44)	(3)
Blood flow (absorbance units)	22.0 ± 3.0	59.5 ± 7.4	$p < 0.001$[a] (N = 9)	(25)
Hydrocortisone penetration (% of applied dose absorbed in 24 hours)	2.8 ± 2.4	8.1 ± 4.1	$p < 0.01$[b] (N = 9)	(11)
Testosterone penetration (% of applied dose absorbed in 24 hours)	20.2 ± 8.1	25.2 ± 6.8	NS[b,c] (N = 9)	(11)
Frequency of irritant reactions to 20% maleic acid solution (%)	62	76	– (N = 21)	(53)
Mean intensity of irritant reactions to 20% maleic acid at 24 hours postapplication (0–3 visual scale)	0.86 ± 0.36	1.29 ± 0.83	$p = 0.036$[a] (N = 21)	(53)
Frequency of irritant reactions to 17% benzalkonium chloride solution (%)	9	57	Not determined (N = 21)	(53)
Mean intensity of irritant reactions to 17% benzalkonium chloride solution at 24 hours postapplication (0–3 visual scale)	0.19 ± 0.33	1.00 ± 0.88	$p = 0.0003$[a] (N = 21)	(53)
Irritant reactions to 1% sodium lauryl sulfate at day 2 postapplication (proportion of scores >1 on a 0–4 scale)	9/10	0/10	$p < 0.05$[d] (N = 10)	(54,55)

[a] Student *t* test.
[b] One-way analysis of variance followed by Neuman–Keuls multiple range test.
[c] Not significant.
[d] Wald–Wolfowitz two-sample test.

lymphocytes in regional lymph nodes. In women, Langerhans cells play a major role in vaginally transmitted HIV infection. They are the first cells to encounter HIV particles, transferring them to their primary targets, the $CD4^+$ T lymphocytes (34). In the murine model, vaginal Langerhans cells are heterogeneous, and at least four populations have been identified by immunohistochemistry and flow cytometry (35). Whether these distinct populations are endowed with specific functions in the immune responses of the vagina is not known at this time.

A gradient in Langerhans cell density exists along the lower female genital tract. In Rhesus macaques, for example, cell densities are lowest at the vaginal fornix and highest at the introitus (14). Human studies demonstrate a higher density of Langerhans cells in the vulva than in the vagina, with no difference between keratinized and nonkeratinized regions (13). The deficit in Langerhans cells in the vagina relative to concentrations in the vulva may be one of several vaginal adaptations to the antigenic challenges posed by resident microbiota and foreign proteins encountered during intercourse. Seminal fluid also contains a variety of inhibitors that suppress immune function in the vagina and cervix.

Langerhans cell densities were estimated at 19 per 100 basal cells in the vulvar epithelium, 13 per 100 basal cells in the cervix, and 6 per 100 basal cells in the vagina. By contrast, lymphocytes predominate in the vagina. The $CD8^+$ subtype is the most common vaginal immune cell, the $CD4^+$ subtype constitutes the second largest population of vaginal immune cells, and tissue macrophages represent the third largest population (32).

Growing evidence suggests that immune responsiveness is modulated differentially along the reproductive tract. Transplantation studies suggest that the cervix is immunologically privileged in order to protect the fetus from maternal alloresponses to antigens in ejaculate (36). Cervical mucus, which protects the entry to the uterus, contains secretory antibodies, particularly IgA. These secretory antibodies inactivate antigens by forming nonabsorbable complexes with them. Cervical mucus is bacteriocidal in the presence of lysozyme and complement, and can agglutinate bacteria and opsonize them for phagocytosis by macrophages.

Different regions of the genital tract exhibit distinct responses to antigens. Antigen application to vulvar skin can result in sensitization; indeed, allergic contact dermatitis to topical agents is a prime contributor to persistent vulvar discomfort (37–39). By contrast, antigen application to nonkeratinized mucosa may induce tolerance. This phenomenon, best characterized in the oral mucosa, is not due to the phenotype of resident Langerhans cells, but results from altered responses at the level of the draining lymph nodes (40,41). Studies in animal models demonstrate that tolerance induction also occurs in the vagina, where the phenomenon is hormonally regulated (42). In mice, vaginally induced tolerance occurred only during the estrogen-dominant phase of the estrus cycle when sperm exposure would occur.

The number and distribution of vaginal immune cells are relatively stable throughout the menstrual cycle (8,32,43), although the thickness of the epithelium peaks at midcycle. However, administration of exogenous contraceptive hormones affects the functional capacity and distribution of vaginal immune cell populations. An increase in the density of vaginal Langerhans cells was observed in response to vaginally administered progesterone (44). The synthetic, long-acting progestin contraceptive depot medroxyprogesterone acetate (DMPA) increased vaginal densities of T cells and of immune cells bearing HLA-DR (a major histocompatibility complex class II receptor) and CCR5 (a chemokine receptor used by HIV to enter and infect host cells) (43). In a study of women using either DMPA, levonorgestrel, or combined oral contraceptives, DMPA caused a selective increase in $CD8^+$ T lymphocytes, levonorgestrel increased the $CD4^+$:$CD8^+$ ratio, and the combined oral contraceptive caused no cell population changes (32).

NuvaRing is a sustained-release, combined contraceptive ring inserted vaginally. It delivers a low dose of synthetic estrogen and etonogestrel (a progestin) to protect against pregnancy for 1 month. NuvaRing and combined oral contraceptive users, but not DMPA users, had lower densities of Langerhans cells in the vaginal epithelium. DMPA users had lower systemic levels of interferon-α (IFN-α). They also exhibited lower cervicovaginal fluid levels of IFN-α, the chemokine CXCL10, monocyte chemotactic protein-1, and granulocyte-colony stimulating factor (45).

Lastly, antimicrobial peptides and proteins, which are secreted by the epithelial tissues of the female genital tract, are increasingly being recognized for their microbicidal and immune modulating properties (reviewed in (46–48)). Among these are secretory leukocyte protease inhibitor, human β-defensin-2), surfactant protein A (SP-A), the cytokines interleukin (IL)-1α and IL-6, and transforming growth factor-β (49,50). SP-A, for example, is produced by a specific vaginal epithelial cell population in the intermediate layer and is also found in vaginal lavage fluid (50). Antimicrobial proteins have a broad spectrum of activity not only against bacteria, but also against fungi and viruses. They suppress bacterially induced cytokine production and induce macrophage chemotaxis and dendritic cell activation in the mucosal tissue.

TISSUE HYDRATION AND BARRIER FUNCTION

Vulvar tissue is more hydrated and has a lower barrier function than exposed skin, as assessed by transepidermal water loss (TEWL), a measure of skin hydration and water barrier function. Water diffuses across the stratum corneum of the labia majora at an elevated rate compared to its rate of diffusion across the stratum corneum of forearm skin (Table 2.3) (1,2). To a degree, this reflects elevated skin hydration due to occlusion. However, vulvar skin also presents an intrinsically lower barrier to water loss: steady-state TEWL values remain higher on the vulva than on the forearm after equilibration with the environment or after the prolonged drying of both sites with a desiccant (2,51). The comparatively greater hydration of occluded vulvar skin raises its friction coefficient (Table 2.3), which may make vulvar skin more susceptible to mechanical damage (3).

PERMEABILITY

Predicting tissue permeability is complex. The phenomenon depends on the extent to which the penetrant partitions into the tissue, the rate at which the penetrant diffuses through the tissue, and the distance to be traversed (52). Consequently, vulvar penetration of exogenous agents is influenced by regional differences in epithelial structure and lipid composition, the physicochemical characteristics of the penetrants, and the nature of the applied vehicle.

Permeability of Labia Majora Skin

Table 2.4 illustrates skin permeability to hydrocortisone by anatomic site (9). Vulvar skin is substantially more permeable

Table 2.4 Relative Permeability to Hydrocortisone (% of Dose Absorbed) by Anatomical Site[a]

Site	Permeability relative to forearm skin
Forearm (ventral)	1.0×
Forearm (dorsal)	1.1×
Foot arch (plantar)	0.14×
Ankle (lateral)	0.42×
Palm	0.83×
Back	1.7×
Scalp	3.5×
Axilla	3.6×
Forehead	6.0×
Vulva (labia majora)[b]	2.8–7.0×
Jaw angle	13.0×
Scrotum	42×

[a] Adapted from Feldmann RJ, Maibach HI. *J Invest Dermatol* 1967; 48: 181–3.

[b] From Britz MB, Maibach HI, Anjo DM. *Arch Dermatol Res* 1980; 267(3): 313–6; Oriba HA, Bucks DA, Maibach HI. *Br J Dermatol* 1996; 134(2): 229–33.

than forearm skin to this agent (10,11). Probable contributing factors include elevated vulvar skin hydration, the higher concentration of hair follicles and sweat glands on vulvar skin, and increased cutaneous blood flow. Tissue penetration rates also depend on the properties of the penetrant. For example, there is no difference in the rate of testosterone penetration through vulvar and forearm skin (Table 2.3) (10,11). However, the skin at both sites is far more permeable to testosterone than to hydrocortisone. This is probably due to the greater hydrophobicity of testosterone and because of the presence of androgen receptors in the skin.

Permeability of the Vulvar Vestibule and Vaginal Epithelium

Nonkeratinized epithelia are more generally permeable to external penetrants. This has been described best in oral tissue, which, like the vulva, displays regional differences in structure and keratinization (56,57). The nonkeratinized buccal mucosa, which resembles the vaginal epithelium morphologically, is 10-fold more permeable to water than is keratinized skin (58). Buccal mucosa is more permeable than the skin to horseradish peroxidase, although absolute penetration rates of this large molecule are lower than those of water (57).

The heightened permeability of nonkeratinized tissue results from several factors. First, the absence of a stratum corneum removes a principal barrier to entry of external agents. Second, the more loosely packed cell layers create a structure with less resistance to paracellular movement, the principal route by which most penetrants traverse tissues (59,60). Third, such tissues have a less-structured lipid barrier with lower resistance to molecular diffusion (61,62).

Finally, thinner epithelia (such as the buccal mucosa and vulvar vestibule) present a shorter path length to be traversed.

Nonkeratinized tissue is also more vulnerable to breaches in tissue integrity, which can augment tissue penetration. For example, buccal tissue was 40-fold more permeable than keratinized skin to the organic base nicotine, an irritant that increases the penetration of coadministered compounds (63,64). The heightened permeability of the vulvar vestibule can be inferred from studies on vaginal and buccal epithelia, which serve as surrogate tissues. Vaginal and buccal epithelia have similar ultrastructural features and lipid compositions. Moreover, comparable tissue penetration rates at coadministration have been observed for a range of model penetrants, including water, estradiol, vasopressin, and low-molecular-weight dextrans (12,65–67). Like the epithelia, the thin, nonkeratinized vulvar vestibule may be more permeable than keratinized skin and more vulnerable to the effects of externally applied agents.

SKIN IRRITATION

Vulvar skin differs from exposed skin in its susceptibility to applied irritants. However, irritant effects are difficult to predict. The available evidence suggests that elevated skin hydration plays a role in vulvar susceptibility to polar irritants. For example, vulvar skin was more reactive than forearm skin to high aqueous concentrations of maleic acid (20% concentration) and benzalkonium chloride (17% concentration) (Table 2.3) (53). Because polar or charged materials do not penetrate the hydrophobic lipid barrier of the stratum corneum readily, the comparatively greater hydration of vulvar skin may have facilitated skin penetration of the polar irritants at this site.

The surfactant sodium lauryl sulfate (SLS) caused a different response. Vulvar skin was less reactive than forearm skin to low concentrations of this agent (Table 2.3) (54,55,68). This result may relate to the structure of the penetrant: the surfactant molecule bears both a charged head and a hydrophobic tail. Notably, hydrophobic molecules partition far more readily into the lipid barrier of the stratum corneum than do charged materials, and lipid partitioning is more favored when the applied medium is relatively polar. In the case of aqueous SLS, skin penetration of the charged head would be highly disfavored; therefore, lipid partitioning of the hydrophobic surfactant tail may have been a driving force for the heightened effects on less hydrated, forearm skin.

An effect of the menstrual cycle on vulvar skin reactions has not been documented. However, evidence from other anatomical sites suggests that skin barrier function and reactivity to irritants may exhibit cyclical variability. Water barrier function on the back and forearm (as measured by baseline TEWL values) was significantly lower on days just prior to menstruation compared to days just prior to ovulation (5). In women, forearm skin exhibited stronger reactions to SLS on day 1 than during days 9–11 of the menstrual cycle, while no difference was detected in a male control group evaluated over the same period (4).

MICROBIOLOGY

Historical studies of vulvar and vaginal microbial colonization have employed traditional culture techniques. Using these techniques, higher cell densities of *Staphylococcus aureus*, coagulase-negative staphylococci, streptococci, diphtheroids, lactobacilli, and yeasts have been measured on the labia majora than on exposed skin (Table 2.5) (15).

Culture-independent methods have recently been applied to characterize vulvar microbiota. A pilot study in five women found a diverse microbiota on the vulva, including populations known to be commensals of the microbiota of the skin, colon, and vagina (69). A greater diversity of microbes inhabited the labia majora compared with the labia minora, although both sites had appreciable numbers of lactobacilli and strict anaerobes. No single species was common to all women. A study in 10 Japanese women compared the microbiota on the labia minora before and during menstruation. Twenty-two genera