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Blaustein's Pathology of the Female Genital Tract

Sixth Edition

Springer

Robert J. Kurman, Lora Hedrick Ellenson and Brigitte M. Ronnett (Eds.)

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With 1446 Figures and 125 Tables

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ISBN 978-1-4419-0488-1 e-ISBN 978-1-4419-0489-8
Print and electronic bundle ISBN 978-1-4419-0490-4
DOI 10.1007/978-1-4419-0489-8
Springer New York Dodrecht Heidelberg London

Library of Congress Control Number: 2010928122

Printed on acid-free paper

Springer is part of Springer Science+Business Media (www.springer.com)

To Carole C. Kurman for her constant support and encouragement
To my ultimate mentors, Donald Ward Hedrick and Pauline Gray Hedrick
In memory of my parents, Alexander and Helga Ronnett, for their value of education

Preface

The advances in the field of gynecologic pathology since the publication of the last edition of this text in 2001 have been significant and the progress that the senior editor has witnessed since the first edition of this book appeared in 1977 has been truly remarkable. To cite just one example, in the first edition, Herpes virus type 2 was thought to cause cervical cancer and the nomenclature for cervical cancer precursors was cervical dysplasia and carcinoma in situ (CIS), with the emphasis placed on the distinction of severe dysplasia from CIS since a diagnosis of severe dysplasia resulted in a cone biopsy whereas the diagnosis of CIS resulted in a hysterectomy. Since then, the terminology and, in turn, the management of the precursor lesions has evolved to cervical intraepithelial neoplasia 1-3 (CIN 1-3) with treatment of all grades of CIN, to low- and high-grade squamous intraepithelial lesions (LSIL and HSIL respectively) in which LSIL is generally not treated, as it is recognized as a manifestation of human papillomavirus (HPV) infection, whereas HSIL is managed by LEEP excision, as it is recognized as the immediate precursor of cervical cancer. Along with these changes in terminology and treatment, the recognition that high-risk human HPVs represent the etiologic agents that cause essentially all cervical and vaginal cancers and a substantial fraction of vulvar carcinomas led to the development of prophylactic vaccines in preventing HPV infections. As a consequence the management of this disease will change again. In fact, the efficacy of these vaccines in preventing cervical cancer precursors has the potential, in the future, of eradicating a cancer that affects over 500,000 women yearly worldwide and the recent award of the Nobel Prize in Medicine to Professor zur Hausen for his identification of HPV 16 DNA in cervical cancer specimens is testimony to this truly remarkable achievement.

Examination of the trajectory of advances in gynecologic pathology over the last 35 years since the first edition of *Blaustein's Pathology of the Female Genital Tract* highlights the significant contributions made by a number of different disciplines including molecular biology and epidemiology. In fact, the application of molecular biologic methods in conjunction with histopathologic classifications based on the natural history of disease ushers in a new approach for surgical pathology in general and gynecologic pathology in particular, which undoubtedly will continue to evolve in the future. Thus, the publication of this 6th edition of the Blaustein text marks the transition in diagnosis from a largely morphological activity to one based upon an integrated assessment using microscopy, immunohistochemistry and molecular biology. Finally, the emerging role of digital technology that makes an ever-increasing amount of data available at our fingertips will undoubtedly change the way we access information in the future. It is not difficult to envision that the next edition of this text will be on an electronic reader of some type instead of in the form of a textbook.

As with previous editions of the Blaustein text, the 6th edition maintains our commitment to producing a comprehensive text that covers the field of gynecologic pathology in depth while not sacrificing its utility as a "desk-side" text that can be referred to in every day practice. Accordingly, significant changes have been made to inform the reader of advances in research that have occurred since the last edition while at the same time enhancing its usefulness in the everyday practice of gynecologic pathology. To accomplish this latter goal we have increased the number of photomicrographs, nearly all of which are now in color. Discussions of differential diagnosis have also been significantly expanded. Both the text and the photomicrographs emphasize the importance of immunohistochemistry and newly emerging molecular techniques as adjuncts to morphology in routine clinical diagnosis. To avoid the text becoming too ponderous we have reduced its size by asking contributors to delete sections they deemed no longer relevant while retaining older material that they regarded as "classic" or that described large series of cases with clinicopathologic data that are still relevant today. Similarly, given the ability to obtain references easily on the Internet, many older references have been deleted with emphasis on including those published since 2000. Unlike the last edition in which embryology, anatomy, epidemiology, immunohistochemistry, molecular biology and gross processing were separate chapters, these subjects have been incorporated into the individual chapters by organ site. This has resulted in a more streamlined format that integrates these various disciplines with the histopathology. Finally, two separate chapters, one on soft tissue tumors and the other on hematologic disorders involving the female reproductive organs, have been added because these are subspecialty areas in their own right and are authored by experts in these fields.

The publication of this text has depended on the assistance of many individuals to whom the authors are greatly indebted. In particular, in an effort to achieve a degree of uniformity in the quality of the images among the various

chapters, Mr. Norman Barker, Associate Professor and Director of Pathology, Digital Imaging and Computer Graphics at Johns Hopkins reviewed and digitally edited all of the photomicrographs, many of which required his considerable expertise (particularly those images that were scanned from Kodachrome slides). We feel this has been successfully accomplished and are grateful for his efforts. Finally, there are many people, including fellows, our colleagues in the Divisions of Gynecologic Pathology at Johns Hopkins and Cornell and individuals from other disciplines who, through our collaboration with them, have enhanced our understanding of the pathobiology of neoplasms of the female reproductive organs. They are far too numerous to specifically mention but their influence on us has been considerable. To all these people we wish to express our thanks.

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Blaustein's Pathology of the Female Genital Tract

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1 Benign Diseases of the Vulva

Edward J. Wilkinson · Nicole A. Massoll

R. J. Kurman, L. Hedrick Ellenson, B. M. Ronnett (eds.), *Blaustein's Pathology of the Female Genital Tract (6th ed.)*, DOI 10.1007/978-1-4419-0489-8_1,

Anatomy

The external female genitalia include the mons pubis, labia majora and minora, prepuce, frenulum, clitoris, and vestibule. The orifices of the paraurethral (Skene) and Bartholin glands, as well as those of the minor vestibular glands and the urethral meatus, open into the vestibule (*Fig. 1.1*). After menarche, the mons pubis and lateral aspects of the labia majora acquire increased amounts of subcutaneous fat and develop the coarse, curly pubic hair. During adolescence, the labia develop pigmentation and the clitoris undergoes some enlargement. Histologically, the entire vulva, with the exception of the vulvar vestibule, is covered by keratinized, stratified squamous epithelium [245]. The labia majora contain both smooth muscle and fat, whereas the labia minora are devoid of adipose tissue but are rich in elastic fibers and blood vessels [167]. Within the lateral aspects of the labia majora, sebaceous glands are associated with hair follicles but open directly to the surface epithelium toward the medial aspect. Similar sebaceous glands are seen on the perineum posterior to the vestibule. The labia minora typically do not contain glandular elements, except sebaceous glands near the junction with the interlabial sulcus and near the inferior and lateral aspects. The apocrine glands of the labia majora, prepuce, posterior vestibule, and perineal body, like the apocrine glands of the axilla, are activated at menarche, whereas the eccrine sweat glands, primarily involved in heat regulation, function before puberty [189]. The vestibule is bounded medially by the external portion of the hymen ring, posteriorly and laterally by the line of Hart, and anteriorly by the frenulum of the clitoris. The mucosa of the vestibule is glycogenated in women of reproductive age, or under estrogen influence, and resembles vaginal mucosa. The linea vestibularis, seen in approximately one quarter of newborn female infants, is located in the posterior portion of the vestibule, and is a white streak or spot in the midline of the posterior vestibule extending nearly to the posterior commissure [109]. The squamous epithelium of the vestibule merges with the transitional epithelium at the urethral meatus, and with the duct openings of the paraurethral glands (Skene), the major vestibular (Bartholin) glands, and the minor vestibular glands.

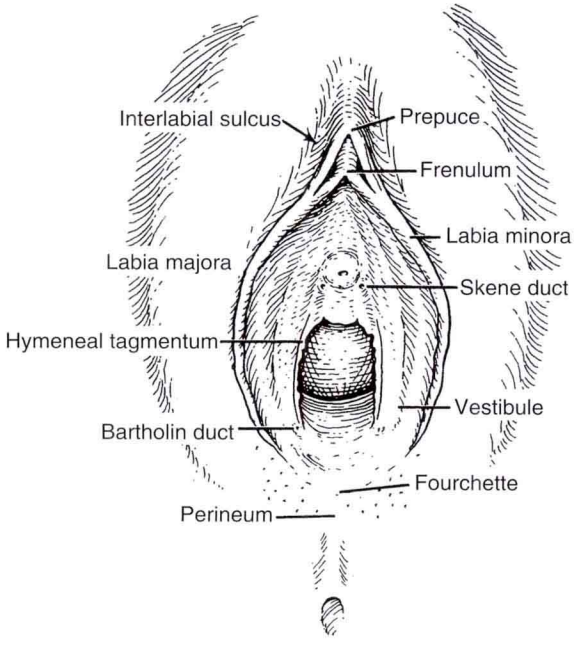

Fig. 1.1
External anatomy of the vulva and the Hart's line. The line of Hart is the junction between the nonkeratinized mucous membrane epithelium of the vestibule, the thinly keratinized epithelium of the medial aspects of the labia minora, the posterior aspects of the labia majora, and the perineal body

The paired Skene's glands, homologous of the prostate in females [80], are composed of pseudostratified mucus-secreting columnar epithelium, open to the external surface on both sides of the urethral meatus and along the posterior and lateral aspects of the urethra itself. The ducts are lined by transitional epithelium. The major vestibular glands of Bartholin are bilateral racemose, tubuloalveolar glands, with acini composed of simple, columnar, mucus-secreting epithelium (*Fig. 1.2*). Each gland is drained just external to the hymen ring of the vestibule posterolaterally. The Bartholin duct, approximately 2.5 cm in length, has three types of epithelial linings depending on the location within the duct. It is lined proximally by mucus-secreting epithelium, distally by transitional epithelium, and, at its exit, by squamous epithelium. The minor vestibular glands are composed of acini lined by simple columnar mucus-secreting epithelium. They lie within 1–2.5 mm of the superficial epithelium and communicate with the vestibular surface. Squamous metaplasia often occurs within these glands and may obliterate them completely, resulting in the formation of a vestibular cleft. These minor glands ring the vestibule and extend from the frenulum on both sides of the meatus, around the external base of the hymenal ring, to the fourchette [38]. Specialized anogenital sweat glands (mammary-like) have been found within the vulvar interlabial sulcus, in the medial aspects of the labia majora, and in lesser numbers within the perineum and about the anus. These glands, with long and wide coiled ducts that

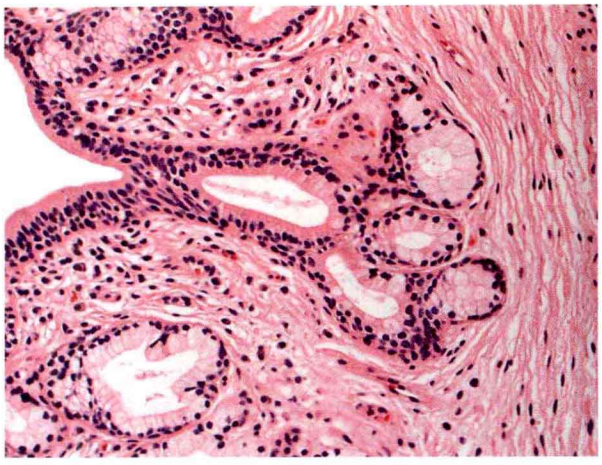

Fig. 1.2
Bartholin duct and gland. The terminal Bartholin duct has a transitional epithelial-type lining that merges with the simple columnar mucus-secreting epithelium of the Bartholin gland acini. The glands are tubuloalveolar and racemose and the surrounding fibrous stroma is somewhat more cellular than the peripheral stroma

open to the surface, have a simple columnar epithelium with apical snouts and myoepithelium beneath the glandular epithelium [232, 233].

The clitoris, which has no glands, is covered by thinly keratinized stratified squamous epithelium. Within the stroma of the clitoris are two conjoined corpora cavernosa, which branch near the base of the clitoris and lie along the pubic rami as divided crura. They are invested in a loose fibrous sheath containing abundant nerves and with an incomplete center septum. The dermis, subepithelium, and stroma of the vulva are rich in collagen, blood vessels, and myofibroblastic-type cells that are frequently immunoreactive for desmin [242]. Myxoid-like changes are present within the subepithelial stroma and have been reported extending from the ectocervix to the vulva. Atypical-appearing multinucleated cells may be observed in this subepithelial myxoid area [1]. Sparse numbers of inflammatory cells including lymphocytes, a few plasma cells, and mast cells are normally present in the perivascular spaces and interstitium.

The femoral and inguinal lymph nodes receive lymphatic drainage from the entire vulva except the clitoris, which has a minor secondary lymphatic pathway [97, 135]. Delicate intercommunicating lymphatic vessels extend to the labia minora, clitoral prepuce, and vestibule, bypassing the clitoris. The lymphatic bed of the labia majora drains in an anterosuperior direction toward the mons, joining the lymphatic vessels from the labia minora and prepuce, and then into the ipsilateral inguinal and femoral nodes. Some contralateral flow also may occur into the superior medial nodes of the femoral group. The superficial inguinal lymph nodes, consisting of 8–10 nodes on each side, divided into a superior oblique and an inferior ventral group, are the major nodes that drain the vulva and therefore are included in a radical vulvectomy [150]. The superior oblique group is found about the Poupart ligament, and the inferior ventral group lies above the junction of the saphenous vein and fascia lata. Lymphatic drainage from the clitoris and midline perineum proceeds bilaterally in more than 67% of cases and may bypass the superficial nodes [94]. A second minor lymphatic pathway from the glans clitoris joins the lymphatics of the urethra, traverses the urogenital diaphragm, and merges with the lymphatic plexus on the anterior surface of the bladder. From there, drainage is into the internal iliac, obturator, and external iliac nodes. No direct pathway of lymphatic flow from the clitoris to the pelvic nodes could be demonstrated by in vivo colloid injection [94]. Lymphatic flow from other sites on the vulva usually proceeds to the ipsilateral groin and pelvic lymph nodes. This finding correlates with the observation that in cases of clitoral carcinoma, in which the inguinofemoral lymph nodes are free of tumor, it is highly unlikely that the pelvic nodes are involved.

The superficial and deep external pudendal arteries branch from the femoral artery. The internal pudendal arteries branch from the internal iliac arteries. These branches from the femoral and internal iliac arteries provide the major blood supply to the vulva via the anterior and posterior labial branches. The clitoris, including the crura and corpora cavernosa, is supplied separately by the deep arteries of the clitoris, whereas the anterior vaginal artery supplies blood flow to the vestibule and the Bartholin glands. The venous return parallels the arterial supply. The nerve supply to the vulva includes sensory nerves, special receptors, and autonomic nerves to the vessels and various glands. The major nerves of the vulva derive from the anterior (ilioinguinal) and posterior (pudendal) labial nerves [123]. The clitoris is innervated by the dorsal nerve of the clitoris and the cavernous nerves of the clitoris, which also supply the vestibule [212].

Developmental Abnormalities

The clitoris in an adult women measures 16.064 mm in length, with a transverse diameter of 3.46 mm and longitudinal diameter of 5.161.4 mm. It is slightly larger in parous