

Chapter 4

Anatomy and physiology of genital organs – women

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INTRODUCTION

“Anatomy is destiny” (Wallace, 1983; Freud, 1895): Sigmund Freud’s intense consideration has a rich symbolic and clinical meaning. It does not simply refer to the gender issues, which is the more frequent reading of his sentence. It can be appropriately applied to the importance that human anatomy has in predetermining functions, dysfunctions, and related vulnerabilities, particularly in the elusive domain of women’s sexuality. Freud, a skilled physician and neurologist himself, knew and stressed the importance of basic anatomy and physiology for perceiving the full meaning of what clinicians see and may read from human’s behavior. Son of his time, and with the scientific limits of his historic period, he was nevertheless trying to bridge the anatomy of the brain with complex mental functions, emotions, and dreams.

The quote is pertinent as a reminder that women’s sexuality is deeply rooted in the anatomy and physiology of their whole bodies, with a specific focus here on their genital organs – a sexuality whose biologic anatomic and functional basis is then modulated and reshaped throughout life by personal, relational, and context-dependent events and affective dynamics (Graziottin et al., 2009; Lukasiewicz and Graziottin, 2014).

The goal of this chapter is to offer an updated view of women’s genital anatomy and physiology, with a clinically oriented perspective.

EMBRYOLOGY OF WOMEN’S GENITAL ORGANS

The female genital organs differentiate in the feminine phenotype during the embryonic period without particular hormonal influences. Indeed, the “female” is the “default” program, that can be differentiated into the “male” only in

the presence of androgens at male physiologic levels for the gestational age. The genital organs are comprised of gonads, reproductive ducts, and external genitalia (Standing, 2008). The process of sexual differentiation is central for sexuality and reproduction. In sex development, it encompasses first the processes of sex determination, that is, the developmental decision that directs the undifferentiated embryo into a sexually dimorphic individual. Sex determination equals gonadal development, in human beings as in all mammals. The second process, known as sex differentiation, takes place once the sex determination decision has been made through factors produced by the gonads that determine the development of the phenotypic sex. Generally, factors influencing sex determination are transcriptional regulators, whereas factors important for sex differentiation are secreted hormones and their receptors (Biaison-Lauber, 2010).

Anatomically and morphologically, fetal sex development consists of three sequential stages:

1. the undifferentiated stage, when identical primitive structures develop in the XY and XX embryos
2. gonadal differentiation into testes or ovaries (key for sex determination)
3. the sexual differentiation of internal and external genitalia, which depends on the action of testicular hormones.

Disorders of sex development, of the highest importance for their sexual consequences, may result from defects in any of these stages (Rey and Grinspon, 2011).

The gonads

The gonads develop from primitive germ cells, the mesothelium of the posterior abdominal wall and

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mesenchyme during the fifth fetal week, counting from the first day of the last period (Netter, 2010). There are three key directors of male gonad differentiation:

1. the sex-determining region Y (SRY) protein, also known as testis-determining factor (Harley et al., 2003). It is a protein that in humans is encoded by the SRY gene, located in the Y chromosome. Its expression causes the development of primary sex cords, which later develop into seminiferous tubules. These cords form in the central part of the as yet undifferentiated gonad, turning it into a testis. The now induced Leydig cells of the testis then start secreting testosterone, while the Sertoli cells produce anti-müllerian hormone (AMH)
2. androgens, secreted by Leydig cells, further “force” the basic program into the progressively male fenotype
3. AMH, produced by Sertoli cells in men and by granulosa cells of the ovary in women.

In summary, the gonadal differentiation takes place in the second month of fetal life: the female phenotype depends therefore on the absence of sexual SRY protein, androgens, and AMH, leading to gonads composed of an inner medulla (ovarian stroma) and an outer cortex (parenchyma) (Stranding, 2008).

Internal genital organs: tubes, uterus, and upper vagina

In male mammals, AMH blocks the female “default” program, as it prevents the development of the müllerian ducts (MD) into the uterus and other müllerian structures (Matuszczak et al., 2013). The effect is ipsilateral, that is, each testis suppresses müllerian development only on its own side. In humans, this action takes place during the first 8 weeks of gestation. If the process is only ipsilateral, the co-presence of mixed internal genitalia may result (AlJurayyan, 2013). If no AMH is produced from the gonads, as normally happens in female subjects, or as happens in Turner syndrome (45,X0), the MD develop (Sajjad, 2010). Meanwhile the wolffian ducts, which are responsible for male reproductive ducts, are progressively reabsorbed, occasionally leaving only small cystic remnants (usually 1 cm in diameter or less) without any clinical meaning, that can be palpated/visualized with the ecographic probe or magnetic resonance imaging in the vaginal lateral wall, on either side.

The fallopian tubes, the uterus, and the upper part (two-thirds) of the vagina originate from the mesodermal paramesonephric ducts (of Müller). This process is referred to as müllerian organogenesis: the paired paramesonephric ducts (MD) fuse to form a confluence;

the cranial end of the fused ducts yields the future uterus which contains mesoderm that will form the uterine endometrium and myometrium. The unfused cranial ends assume a funnel-shaped configuration (the fimbrial portions of the fallopian tubes) and remain open to the future peritoneal cavity. The caudal end of the fused ducts gives origin to the upper two-thirds of the vagina (Healey, 2012). The lower part of the vagina, urethra, vaginal vestibule, and glands (urethral, paraurethral and vestibular) arises from the urogenital sinus (endoderm).

During development, the MDs undergo a dynamic morphogenetic transformation from simple tubes consisting of homogeneous epithelium and surrounding mesenchyme into several distinct organs – the oviduct, uterus, cervix, and vagina. Following the formation of anatomically distinctive organs, the uniform MD epithelium (MDE) differentiates into diverse epithelial cell types with unique morphology and functions in each organ. Classic tissue recombination studies, in which the epithelium and mesenchyme isolated from the newborn mouse were recombined, have established that the organ-specific epithelial cell fate of MDE is dictated by the underlying mesenchyme (Kurita, 2011). Tissue recombination studies have also demonstrated that there is a narrow developmental window for determination of the epithelial cell fate in MD-derived organs. If the signaling that controls epithelial differentiation is disrupted at the critical developmental stage, the cell fate of MD-derived epithelial tissues will be permanently altered and can result in epithelial lesions in adult life. Cervical/vaginal adenoses and uterine squamous epithelium are examples of such incidences (Kurita, 2011).

Adenomyosis, i.e., the presence of endometrium, the inner mucosal layer of the uterus, within the myometrium, could be the result of a disrupted epithelial differentiation, with serious clinical consequences, in terms of incapacitating dysmenorrhea, deep dyspareunia, and chronic pelvic pain (Graziottin et al., 2013).

The external genitalia

The external genitalia remain sexually undifferentiated until the seventh fetal week and then begin to develop from the urogenital sinus, genital tubercle, and labioscrotal swellings. The corpora cavernosa of the clitoris and the glands are formed from the genital tubercle; the vestibule of the vagina, the labia minora, the vestibular bulbs, and the female corpus spongiosum are formed by the urogenital sinus and from the urogenital folds which do not fuse together (O’Connell and De Lancey, 2005). The labioscrotal swelling does not fuse either and forms the labia majora.

A knowledge of the embryonic differentiation of sexual apparatus is important to understand congenital malformations, so-called müllerian anomalies. They have a prevalence of 4–7% (Chan et al., 2011) and result from an altered fusion of the MD, leading to different abnormalities of the uterus and upper vagina (Lin et al., 2002). From the same embryologic origin, congenital genital/sexual malformations are often associated with renal abnormalities: comorbidity may be as high as 40%. The common associated anomalies are unilateral agenesis, ectopia, renal hypoplasia, multicystic dysplastic kidney, and hydronephrosis (Morcel et al., 2007). Therefore, the urologic system should always be evaluated when müllerian anomalies are documented (Jaramillo et al., 1990).

According to the gravity of failure of fusion of the two paramesonephric ducts, it is possible to identify different anomalies such as the Mayer–Rokitansky–Kuster–Hauser syndrome (characterized by congenital vaginal agenesis and an absent or rudimentary uterus in genotypic females), uterus bicornis, either unicollis or bicollis, uterus septus and vaginal septum (Epelman et al., 2013). The septum can be longitudinal, when it derives from an incomplete fusion of the caudal end of the two MDs. In its extreme form, it may lead to two distinct parallel vaginas, two cervixes and two uteri.

The vaginal septum can be transverse, complete or incomplete, single or multiple, when it results from incomplete cavitation of the vagina that initially is a solid organ. The hymen is generated when the still solid vagina connects with the cloacal tissue which leads to the external genitalia: it is just an embryonic remnant of the former fusion line, incompletely separating the lower end of the vagina with the vulvar vestibule. It is a circumferential skin structure composed of non-hair-bearing skin (O’Connell et al., 2008). It may have different shapes (e.g., annular, cribrous, septate) and thickness: it may be very elastic and/or subtle (“complacent”) or so fibrotic and thick as to constitute an anatomic, mechanical barrier to penetration, causing introital dyspareunia (Graziottin and Murina, 2011). In the most severe cases a tight fibrotic hymen may require surgical incision with topical analgesia, to allow painless penetration. Due to its strategic position at the entrance of the vagina, it had (and still has, in some cultures) an enormous symbolic meaning (proof of virginity) that far outweighs its otherwise irrelevant function as a simple embryonic remnant. The vestibule and the outer part of the basis of the hymen are densely innervated (Bohm-Starke et al., 1999; Bornstein et al., 2004): they are among the critical sites of coital pain (“introital dyspareunia”) and of genital pain (“provoked vestibulodynia”) in premenopausal women.

THE ADULT GENITAL ORGANS

The external genitalia

The external genitalia consist of the mons pubis, labia majora, labia minora, clitoris, and the vestibule of the vagina; they are supported by superficial and deep muscles of the perineum and their fasciae (Yavagal et al., 2011).

THE MONS PUBIS

The mons pubis is an inverted triangular area of fatty tissue, covered by hair-bearing skin lying on top of the pubic bone; it extends from the pubic hairline (the base of the triangle) to the glands of clitoris inferiorly (Standring, 2008). The labia majora are two prominent longitudinal cutaneous folds situated between the mons pubis and the perineum. They fuse together forming the anterior labial commissure; posteriorly, they are not really joint, but fuse with the surrounding tissue into the posterior labial commissure. Each labium has two surfaces: an outer one, covered with pigmented skin and pubic hair; and an inner surface, which is smooth and has sebaceous follicles (Williams and Bannister, 2008).

THE LABIA MINORA

The labia minora are two small cutaneous folds 3–4 cm long, situated between the labia majora and extending from the clitoris anteriorly to the fourchette posteriorly (Putz and Pabst, 2008). Anteriorly each labium is divided into two portions: the upper division passes above the glans of the clitoris to fuse with the opposite part and forms the preputium clitoridis; the lower division passes under the clitoris, forming the frenulum of the clitoris with its contralateral part. The labia minora are rich in sebaceous glands, connective tissue, and vascular erectile tissue, with a considerable number of sensory nerve endings and receptors (Netter, 2010).

THE CLITORIS

The clitoris is an erectile structure, homolog to the male penis, formed by two corpora cavernosa and the glans, covered by the prepuce. Only a fifth (or less) is visible (glans) while the rest is hidden under the skin (O’Connell and De Lancey, 2005). The corpora cavernosa are made of cavernous erectile tissue and diverge and follow the pubic rami on each side, forming the crura. It represents the hidden part of the clitoris which is covered by the ischiocavernosus muscle: it may reach 7 cm or more in length. The glans of the clitoris is the free extreme of it: it is 4–7 mm long and covers the distal part of the corpora cavernosa, from which it is not dependent

(Williams and Bannister, 2008). It represents the most innervated part of the clitoris, full of free nerve endings, Krause-finger corpuscles, corpuscles of Pacini and Meissner (Yang et al., 2006).

The clitoris is connected to the mons pubis and pubic symphysis by the suspensory ligament which influences the stability of the clitoris during sexual intercourse (Rees et al., 2000). The urethra lies surrounded by this complex with the body directly anterior to it, flanked superficially by the bulbs and deeply by the crura. In anatomy texts the bulbs are referred to as the bulbs of the vestibule and appear as if they form an erectile structure of the labia minora (Standing, 2008; Netter, 2010). However, according to most studies, the bulbs relate most closely to the clitoris and urethra (O'Connell et al., 1998), so that they should be renamed the bulbs of the clitoris (O'Connell and De Lancey, 2005).

THE G SPOT

The G spot represents the most controversial area of the female genitalia (Jannini and Whipple, 2010), caused above all by lack of knowledge of the anatomy and innervation of this area (Foldes and Buisson, 2009). The G spot name is given in recognition of the researcher who found its existence and relationship to female ejaculation (Grafenberg's spot) (Grafenberg, 1950). Considered to be a prostate remnant, it may have consistent dimensional variations in different women: from being almost non-existent in some women, to covering an area that can be dynamically visualized through a vaginal ecographic probe in others (Hines, 2001). According to some authors, physical anatomic differences in G-spot size should be taken into account as a source of physiologic variability in female sexual response.

An interesting sonographic finding correlates with the presence of a thicker urethra vaginal space in women who have vaginal orgasms (Gravina et al., 2008). The close contact between the internal roots of the clitoris and the anterior vaginal wall during vaginal penetration could explain the special sensitivity of the lower anterior vaginal wall (Foldes and Buisson, 2009). O'Connell refers to the clitoral complex, composed of the distal vagina, urethra, and clitoris, as "the" location of female sexual activity (O'Connell et al., 2008). Another study supplies the evidence for the idea that the so-called G spot is a complex anatomic area encompassing the anterior vaginal wall and the embedded structures, so that it would be better to use the term clitoral-urethral-vaginal complex (Jannini and d'Amati, 2006). Different innervation has recently been demonstrated in the clitoral-urethral complex. Increased density of small nerves in the glans suggests that this is the location of the highest

sensation. Opposite to that, the area closer to the urethra is characterized by a reduced number of nerves so that it can be hypothesized that this zone is less important for sexual sensation (Oakley et al., 2013).

THE VESTIBULE OF THE VAGINA

The vestibule of the vagina extends from the glans clitoridis to the posterior fourchette between the labia minora, up to their internal border. It contains the vaginal orifice, external urethral meatus, vestibular bulbs, and the openings of the greater vestibular glands (also known as Bartholin's glands). The vaginal orifice is below the opening of the urethra and is characterized by the presence of the hymen (a circumferential hairless skin with variable shape) (Standing, 2008). The urethral orifice (lower third of the urethra) is surrounded by erectile tissue of the clitoral bulbs, partly considered the equivalent of the male urethral corpus spongiosum (O'Connell et al., 1998; O'Connell and De Lancey, 2005). It has both a sexual and protective function. It becomes very congested during physiologic sexual arousal, contributing to genital congestion and the formation of the so-called "orgasmic platform" (Masters et al., 1986). Meanwhile, it constitutes a kind of physiologic air bag, protecting the urethra from the "mechanic" trauma of repeated sexual thrusting at intercourse. When women suffer from vaginal dryness and/or inadequate genital arousal due to different etiologies, including low desire, poor foreplay, and/or vestibular pain with dyspareunia, and/or hyperactive pelvic floor mechanically narrowing the vaginal entrance, the lack of this protective cuff increases urethral and bladder vulnerability to the "mechanic" trauma of intercourse, contributing to recurrent cystitis. Sixty percent of recurrent urinary tract infections are reported 24–72 hours after intercourse and are referred to as "postcoital cystitis," a powerful contributor to chronic bladder pain syndrome (Graziottin, 2014).

Recent data from an observational study on recurrent urinary tract infections indicate that comorbidity with vulvar vestibulopathy/provoked vestibulodynia/introital dyspareunia is as high as 60% (Salonia et al., 2013). During sexual arousal urethral secretions derive through distal urethral glands (Skene's).

VESTIBULAR BULBS

The vestibular bulbs (recently renamed "bulbs of the clitoris": O'Connell and De Lancey, 2005) are two erectile organs situated laterally to the vaginal orifice directly beneath the skin of the labia minora and joined together (pars intermedia) and extended to the base of the glans. They are in contact with the greater vestibular glands posteriorly and covered by the bulbocavernosus muscles

superficially. The greater vestibular glands (Bartolini's) are two small glands situated one on either side of the vaginal orifice, and through a 2-cm-long duct opening between the hymen and the labia minora (Standring, 2008).

The internal genitalia

The internal genital organs consist of the vagina, uterus and cervix, fallopian tubes, and ovaries.

THE VAGINA

The vagina is a fibromuscular tubular structure (length range 6–12 cm) extended between the vulva and the cervix. It represents a potential space, with anterior and posterior walls collapsed so that in a transverse section it results in an “H” shape, while in the longitudinal axis it is like a greatly stretched “S” (Netter, 2010). The entrance of the vagina is partially hidden by the labia minora and its back ends in a cul-de-sac penetrated by the uterine cervix. The recess formed by the presence of the cervix is called the fornix: anterior, posterior and lateral, left and right (Standring, 2008). The vagina is related anteriorly to the base of urinary bladder and urethra, so closely that some anatomists recently wrote that “the urethra is embedded in the vaginal wall” (O'Connell and De Lancey, 2005; Furness et al., 2011). Laterally the vagina is connected to the levator ani muscle and endopelvic fascia, and posteriorly to the perineal body and anal canal. The vaginal wall consists of three layers: (1) the inner mucosal layer (tunica mucosa) is a non-keratinized stratified squamous epithelium based on an extremely richly vascular network embedded in connective tissue called lamina propria (Fig. 4.1); (2) a middle muscular layer (tunica muscularis), divided into an external longitudinal and

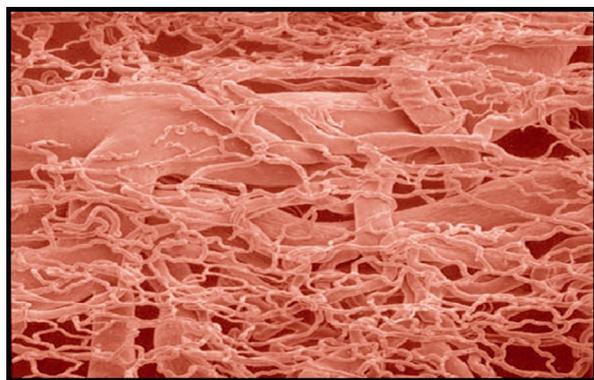


Fig. 4.1. Female sexual function *in vitro* studies of vaginal microvascular architecture. To become congested and give lubrication, the vessels need estrogens and testosterone. (Reproduced from Shabsigh et al., 1999.)

an internal circular layer of smooth muscle; and (3) an outer adventitial layer of collagen and elastin (Standring, 2008; Yavagal et al., 2011).

The vagina is surrounded by different striated pelvic muscles, forming two main parallel layers: the most superficial is composed of three muscles, laid out in two triangles: bulbocavernosus, ischiocavernosus, and superficial transverse perineal muscles (Standring, 2008). In particular the bulbocavernosus, which is laterally closer to the vaginal entrance, was defined as “constrictor cunni” by old anatomists, as it was considered to modulate the anatomic entrance door of the vagina, but it is too small and weak to play such a role. This role is more appropriately pertinent to the much stronger pubococcygeus part of the levator ani, just deeper to the bulbocavernosus (Netter, 2010).

The normal vaginal ecosystem or microbiota (the microorganisms living in a specific organ or tissue) defends the host against pathogen invasion, more so in the fertile age, when the specialized population of lactobacilli maintains the ecosystem (Graziottin and Murina, 2011). The first anatomic element important for vaginal microbiota is the vaginal epithelium, which proliferates and thickens in response to estrogens. Also vaginal transudation is controlled by estrogen levels and is composed of water, salts, mucins, carbohydrates, immunoglobulins, lysozyme, and other substances (Boris and Barne, 2000). The normal vaginal microbiota consists of a pool of anaerobic and aerobic microorganisms (Mehta and Talwalkar, 1995). Lactobacilli, Gram-positive bacilli, and so-called Döderlein's bacilli, represent the most prevalent microorganism (up to 90%) in the normal vaginal ecosystem and they present two mechanisms to interfere with pathogens: (1) adherence to the mucus, forming a barrier which prevents colonization by pathogens; and (2) the production of antimicrobial compounds such as lactic acid, hydrogen peroxide, and bacteriocin-like substances (Boris and Barne, 2000).

The vaginal acid system is facilitated by lactobacilli, which metabolize glycogen into lactic acid, lowering vaginal pH to a normal value of 4.2. In physiologic conditions, lactobacilli include 90% of the vaginal ecosystem during the fertile age; the remaining 10% is composed of different commensal germs. The ecosystem is important for limiting the growth of pathogenic bacteria (Stumpf et al., 2013). The concept of “pathogenic biofilms” currently refers to structured germ communities living inside a self-produced polysaccharide network adhering to the vaginal mucosa and/or to inert medical devices. They can contribute to recurrent vaginitis and cystitis with their associated sexual comorbidities, such as introital dyspareunia and postcoital cystitis.

THE UTERUS

The uterus is a muscular organ situated in the pelvis between the bladder and the rectum; its cavity communicates with the vagina inferiorly and with the fallopian tubes with its upper part. It consists of two portions separated by the isthmus, an upper fibromuscular body and a lower cervix (Netter, 2010). The cervix (neck) is the lower part of the uterus which projects through the anterior wall of the vagina. It can be distinguished in a supravaginal and an intravaginal portion. The cavity of the cervix communicates with that of the vagina through a circular aperture, the external orifice of the uterus. The form, size, anatomic and functional characteristics of the uterus vary in different periods of life and circumstances (prepubertal, menstruation, pregnancy, menopause). Levels of estrogens, progesterone, and testosterone in different life phases modulate its anatomic and functional changes (see Chapter 10).

The body uterus wall is composed of three layers: an external or serous, a middle muscular and an internal or mucous (Standring, 2008). The serous coat derives from the peritoneum which invests the fundus, all of the posterior surface, and the anterior surface only as far as the junction of the body and cervix. The muscular layer is the most representative coat of the uterus and consists of a longitudinal external, a middle (whose fibers do not present in a regular direction), and circular internal layer. The mucous membrane in the body of the uterus is lined by columnar ciliated epithelium. It differs from that of the cervix, which is rich in deep glandular follicles, producing an alkaline mucus under hormonal estrogenic stimulation. The mucosal layer of the vagina is pluristratified, with a clear pink soft color; the columnar monolayer epithelium of the inner cervix has a bright red/purple color (Kurita, 2011). The cells that give origin to both types of epithelium are called “metaplastic” and are the most vulnerable from an oncogenic point of view, specifically to the oncogenic strains of papillomaviruses.

The cervical squamocolumnar (SC) junction is the site of a recently discovered “embryonic” cell population that was proposed as the cell of origin for cervical cancer and its precursors. Early in life, embryonic cervical epithelial cells were seen throughout the cervix and subsequently diminished in number to become concentrated at the SC junction in the adult. Cuboidal embryonic/SC junction cells give rise to subjacent metaplastic basal/reserve cells with a switch from the SC junction positive to negative immunophenotype (Herfs and Vargas, 2013).

THE SALPINGES

The salpinges (fallopian tubes) are tubular structures about 10 cm long situated from the upper lateral end

of the uterus to the ovary. They are divided into four parts: interstitial, isthmic, ampullary, and infundibulum with the fimbria (Standring, 2008). Sperm and egg meet at the external third of the salpinges, where fertilization occurs. The salpinges wall is made up of three coats: a serous peritoneal, a middle muscular, and an internal mucous coat, with a columnar and ciliated epithelium (Kurita, 2011). The cilia of the mucous coat, like moving fingers, are responsible for the transport of the fertilized egg, together with the waveform movements of the salpinges muscular layer.

Transport from the outer third of the salpinges to the uterine cavity requires on average 3 days. If the ciliary epithelium has been damaged by inflammatory processes, usually as a consequence of sexually transmitted disease or endometriosis, the fertilized egg will not be transported within the proper time window. It will then start early placental differentiation in the salpinges, resulting in an ectopic pregnancy.

THE OVARIES

The ovaries are two oval organs situated in the ovarian fossa on the lateral wall of the pelvis, connected to the uterus by the utero-ovarian ligament and to the pelvic side wall by the infundibulum pelvic ligament. Each ovary consists of an inner medulla and an outer cortex with follicles and stroma. The surface of the ovary is covered by the germinal epithelium of Waldeyer, a layer of columnar cells, and just immediately beneath it lies the stroma, with a large number of follicles in earliest condition (cortex). Going deep inside the ovary to the center of the organ (medulla), other large and mature follicles are found surrounded by a great amount of vessels. The follicular cells are responsible for the production of estradiol; after ovulation, the corpus luteum (the residual part of the follicle after the oocyte was delivered) produces progesterone for up to 14 days, unless a new pregnancy has started. Deep in the ovary (hilum ovarii) are located the Leydig cells, responsible for the ovarian production of testosterone, androstenedione, and dehydroepiandrosterone in women (Standring, 2008).

Recent findings in stem cell biology have presented new perspectives and opportunities for the understanding and treatment of reproductive diseases. In a departure from the long-held dogma of embryologically fixed numbers of oocytes, current literature suggests that human ovaries contain stem cells which form new oocytes even in adulthood and that these stem cells can be cultured *in vitro* to develop into mature oocytes. These findings have provided new hope and broader options for fertility preservation (Duke and Taylor, 2013).

The implications that fertility preservation may have for women's sexual identity, sexual function, and sexual relationships are countless, thanks to ovarian stem cell discovery and therapeutic use.

On a more general functional note, the high level of plasticity recently demonstrated in human stem cells challenges the old dogma of fixed and rigid evolution of tissues of genital organs. Evidence of endometrial regeneration by bone marrow stem cells in endometrial tissue of women who received bone marrow transplant highlights the potential for the novel treatments of uterine disorders and supports new theories for the etiology of endometriosis as an ectopic transdifferentiation of stem cells (Duke and Taylor, 2013).

Further, endometrial-derived stem cells have been demonstrated to be useful in the treatment of several chronic and often debilitating diseases, including Parkinson's disease and diabetes. Other cells that may present future therapeutic benefits for a myriad of disease states include placental and fetal cells which enter maternal circulation during pregnancy and can later promote parenchymal regeneration in maternal tissue. These findings highlight novel functions of the uterus and ovaries. They demonstrate that the uterus is a dynamic organ permeable to fetal stem cells that are capable of transdifferentiation as well as a renewable source of multipotent stem cells (Duke and Taylor, 2013). While we still have much to understand about stem cells, their potential applications in reproductive biology and women's sexuality are consistent.

The bony pelvis

The pelvis is a ring composed of the two innominate or hip bones which are joined anteriorly at the symphysis pubis and posteriorly to the sacrum and coccyx (Fig. 4.2: Standring, 2008). The pubic symphysis is a unique joint consisting of a fibrocartilaginous disc sandwiched between the articular surfaces of the pubic bones. It resists tensile, shearing, and compressive forces and is capable of a small amount of movement under physiologic conditions in most adults (up to 2 mm shift and 1° rotation). During pregnancy, circulating hormones such as relaxin induce resorption of the symphyseal margins and structural changes in the fibrocartilaginous disc, increasing symphyseal width and mobility (Becker et al., 2010).

Each innominate bone is formed by the fusion of ilium, ischium, and pubis, and on its lateral surface there is an acetabulum, which articulates with the femoral head. In front and below it, ischium and pubis form the obturator foramen covered by the obturator membrane and pertinent muscles. The pelvis is divided into the greater and lesser pelvis by an oblique plane that

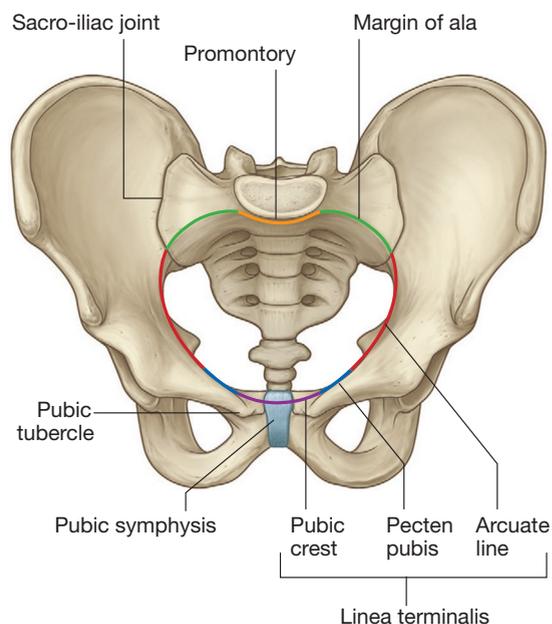


Fig. 4.2. The pelvis. (Reproduced from Standring, 2008.)

passes through the prominence of the sacrum, the arcuate and pectineal lines, and the upper margin of the symphysis pubis (Netter, 2010). The circumference of this plane is named the linea terminalis or pelvic brim. The greater pelvis (pelvis major) is situated above the pelvic brim, and bounded on either side by the ilium, while in front it is incomplete. The lesser pelvis (pelvis minor), situated below and behind the pelvic brim, is divided into an inlet and outlet part. The superior aperture or inlet is formed laterally by the pectineal and arcuate lines, in front by the crests of the pubis, and behind by the anterior margin of the base of the sacrum and sacrovertebral angle. It has three diameters: anteroposterior (from the sacrovertebral angle to the symphysis pubis), transverse (connecting the middle of the brim on each side), and oblique (from the iliopectineal eminence of one side to the sacroiliac articulation of the opposite side) (Standring, 2008). The cavity of the lesser pelvis is a short, curved canal deeper on its posterior than on its anterior wall. The inferior aperture or outlet is bounded by the point of the coccyx and laterally by the ischial tuberosities. It has two diameters, an anteroposterior (from the tip of the coccyx to the lower part of the pubic symphysis) and a transverse one (between the ischial tuberosities). The pelvis allows transfer of weight-bearing forces between the trunk and lower limbs, protects the pelvic organs, gives insertion for muscles, fascia, and ligaments and plays an important role during sex and labor (Standring, 2008).

The sacrum is a triangular bone, situated in the lower part of the vertebral column and at the upper and back part of the pelvic cavity, inserted between the two hip bones. Inferiorly it articulates with the coccyx in a movable articulation (Standring, 2008). Physiologic mobility of the coccyx is important for sexual and reproductive reasons, as it allows higher mobility and elasticity of the levator ani, partially inserted to the coccyx. When rigid or lesioned, it may contribute to chronic pelvic pain and dyspareunia. Physiologic retropulsion of the coccyx increases the diameter of the lower pelvic and gives more room to permit the passage of the fetus during labor (Edmonds, 2012).

The pelvic floor muscles

“There is no considerable muscle in the body whose form and function are more difficult to understand than those of the levator ani, and about which such nebulous impressions prevail” (Dickinson, 1889). Despite over a century of medical progress since Dickinson offered this observation, the details of levator ani muscle anatomy remain poorly understood (Lawson Tait, 1974; Bustami, 1988; DeLancey and Starr, 1990; Kearney et al., 2004).

The pelvic floor consists of different muscle layers: the pelvic diaphragm, the urogenital diaphragm, the superficial trigonal muscles, and the lateral muscles (Standring, 2008). The pelvic floor is important for the support of the pelvic organs, to assist fecal and urinary continence, and to improve pelvic and spinal stability; furthermore, it plays a key role in sexual pleasure. The pelvic diaphragm is formed by the levator ani and the

coccygeus muscles (International Anatomical Nomenclature Committee, 1983; Kearney et al., 2004).

The coccygeus muscle forms a triangular structure attached to the spine of the ischium and to the lateral surface of the coccyx and S5 (Fig. 4.3). This muscle does not contribute to active movement of the pelvic floor; in fact, the effective contractile support structure is represented by the levator ani muscle. The components of the levator ani muscle are the puborectal, iliococcygeal, and pubovisceral (pubococcygeus) muscles, further subdivided into pubovaginal, puboperineal, and puboanal. This terminology was accepted in 1998 by the Federative Committee on Anatomical Terminology (International Anatomical Nomenclature Committee 1983).

The iliococcygeus originates from the tendinous arch of levator ani and forms a diaphragm between the anus and the coccyx. The puborectalis originates from the pubic bone, forming a ring around the rectum. The pubococcygeus with its three branches originates from the pubic bone and inserts into the perineal body, the vaginal wall, and into the tissue between the internal and external anal sphincter. In the axial plane, the puborectal muscle can be seen lateral to the pubovisceral muscle and decussating dorsal to the rectum. The course of the puboperineal muscle near the perineal body is visualized in the axial plane. The coronal view is perpendicular to the fiber direction of the puborectal and pubovisceral muscles and shows them as “clusters” of muscle on either side of the vagina. The sagittal plane consistently demonstrates the puborectal muscle passing dorsal to the rectum to form a sling that can consistently be seen as a “bump.” This plane is also parallel to the pubovisceral muscle

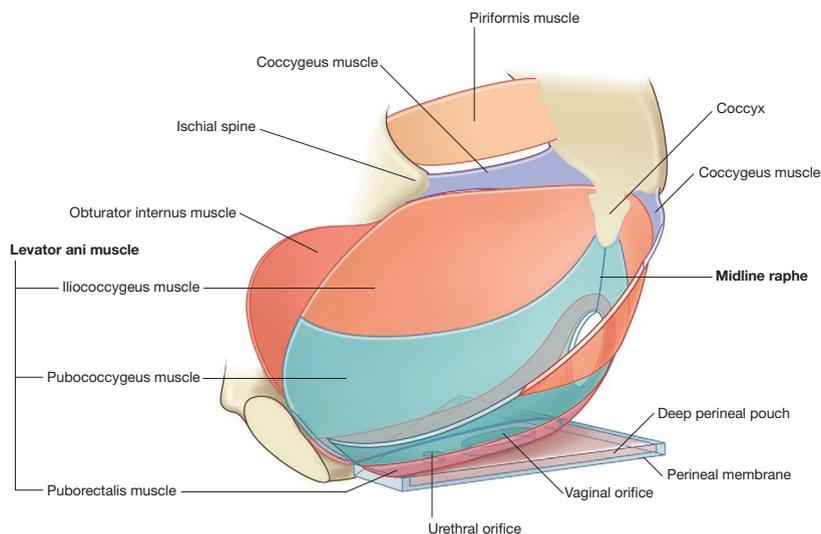


Fig. 4.3. The pelvic floor muscles. (Reproduced from Standring, 2008.)

fiber direction and shows the puboperineal muscle (Margulies et al., 2006).

APPEARANCE OF THE LEVATOR ANI MUSCLE SUBDIVISIONS IN MAGNETIC RESONANCE IMAGES

The urogenital diaphragm consists of the deep transverse perineal muscle with the superior and inferior fascia. The perineal membrane is composed of two regions, one dorsal and one ventral. The dorsal portion consists of bilateral transverse fibrous sheets that attach the lateral wall of the vagina and perineal body to the ischiopubic ramus. This portion is devoid of striated muscle. The ventral portion is part of a solid three-dimensional tissue mass in which several structures are embedded. It is intimately associated with the compressor urethrae and the urethrovaginal sphincter muscle of the distal urethra with the urethra and its surrounding connective tissue. In this region the perineal membrane is continuous with the insertion of the arcus tendineus fascia pelvis. The levator ani muscles are connected with the cranial surface of the perineal membrane. The vestibular bulb and clitoral crus are fused with the membrane's caudal surface (Stein and DeLancey, 2008).

The superficial trigonal muscle is composed of the bulbocavernosus, ischiocavernosus, and superficial transverse perineal muscles in the anterior triangle and the anal sphincter in the posterior triangle. The superficial transverse perineal originates from the ischial tuberosity and inserts on the perineal body (Stein and DeLancey, 2008). The ischiocavernosus muscle extends from the ischial tuberosity to the clitoral crura, inserting on to the body of the clitoris (this muscle compresses the crura of the clitoris and delays the return of blood through the veins, contributing to maintain the erection). The bulbocavernosus muscle occupies each lateral side of the vagina between the perineal body and the clitoris body (it diminishes the orifice of the vagina and with its anterior fibers contributes to the erection of the clitoris) (Strandring, 2008).

Female longitudinal anal muscles or conjoint longitudinal coats (CLCs) are attached to the subcutaneous tissue along the vaginal vestibule on the anterior side of the external anal sphincter. Lateral to the CLCs, the external anal sphincter also extends anteriorly towards the vaginal side walls. The anterior part of the CLCs originated from the perimysium of the levator ani muscle. In terms of topographic anatomy, the female anterior CLCs are likely to correspond to the lateral extension of the perineal body (a bulky subcutaneous smooth-muscle mass present in adult women), supporting the vaginal vestibule by transmission of force from the levator ani (Kinugasa et al., 2013).

FEMALE LONGITUDINAL ANAL MUSCLES EXTEND INTO THE SUBCUTANEOUS TISSUE ALONG THE VAGINAL VESTIBULE

The lateral walls of the pelvis are composed of the piriformis and obturator internus (muscles of the lower limb). The perineum is a diamond-shaped area limited by the pubic symphysis, ischiopubic rami, sacrotuberous ligaments, and the coccyx (Fig. 4.4). A line that passes through the two ischial tuberosities divides the perineum into two triangles: the anterior urogenital and the posterior anal triangle (Strandring, 2008).

The connective system

In addition to muscles, the pelvic organs are supported by connective tissue organized in different layers of fasciae and ligaments. Magnetic resonance studies offer new insights to the traditional anatomic readings (Tunn et al., 2001, 2003).

- The endopelvic fascia covers the pelvic organs and connects them to the lateral pelvic wall. It is made up of a combination of elastin, collagen, mucopolysaccharides, adipose, and neurovascular tissue. The fascia covering the levator ani muscle continues with the endopelvic fascia above, perineal fascia below, and obturator fascia laterally (Yavagal et al., 2011). The levator ani muscles and their superior and inferior fascia combined together form the so-called pelvic diaphragm (Ashton-Miller and De Lancey, 2007).
- The broad ligaments connect the uterus to the lateral pelvic walls on both side, and on its upper end it encases the fallopian tubes, round ligaments, utero-ovarian ligaments, and ovaries (Strandring, 2008).
- The round ligaments extend from the lateral side of the uterine body and, passing through the inguinal canal, insert into the labia majora (Strandring, 2008).
- The uterosacral ligaments support the cervix and the upper part of the vagina by their attachment to the sacrum, having also an important role of vaginal receptiveness in sexual intercourse (Campbell, 1950).
- The cardinal ligaments or Mackenrodt's ligaments extend from the cervix to the posterolateral pelvic wall (Ramanah et al., 2012).

THE OBTURATOR FASCIA

The fascia of the obturator internus covers the pelvic surface of the muscle; it arches beneath the obturator vessels and nerve, completing the obturator canal, and at the front of the pelvis is attached to the back of the superior ramus of the pubis. Below it is attached to the falciform process of the sacrotuberous ligament and to the pubic

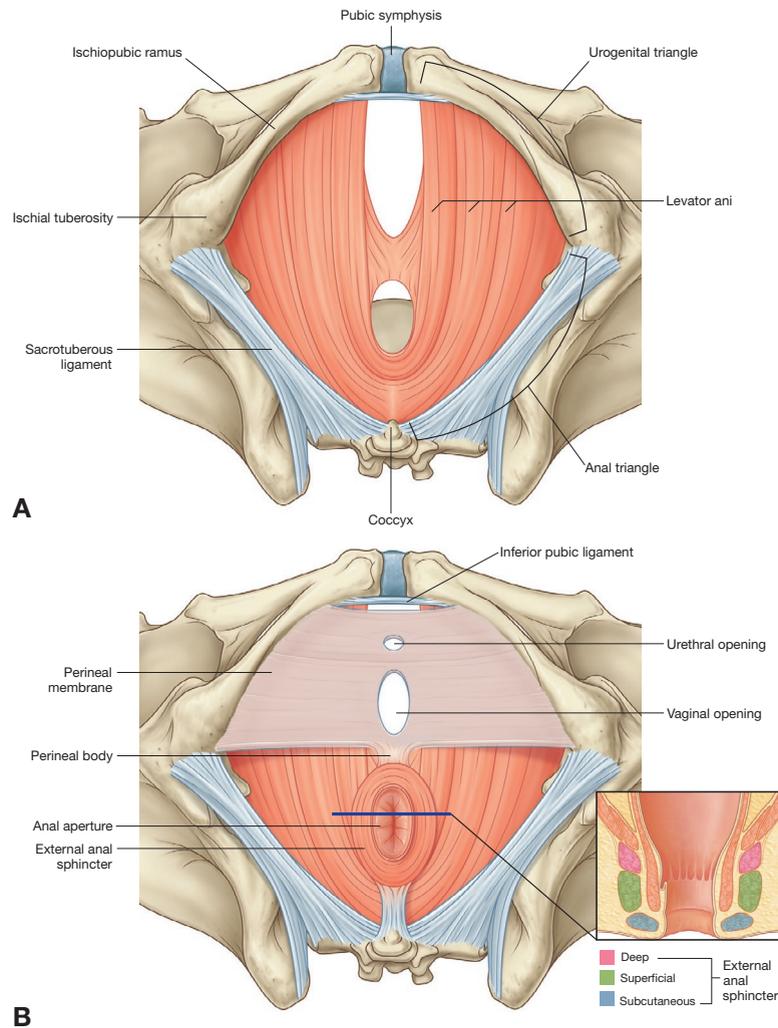


Fig. 4.4. (A, B) The perineum. (Reproduced from [Standring, 2008](#).)

arch. Thickening in the obturator fascia is called the arcus tendineus fascia pelvis, extending from the pubis anteriorly to the ischial spine ([Ziouziou et al., 2013](#)). Alcock's canal syndrome or pudendal nerve entrapment ([Labat et al., 2008](#)) is a condition caused by compression of the pudendal nerve in the canal, resulting in neuralgia in the area of distribution of the pudendal nerve (vulva, vagina, clitoris) ([Oelhafen et al., 2013](#)).

THE VASCULAR SYSTEM

External genitalia

The arterial supply of the vulva is derived from the external and internal pudendal arteries. The internal pudendal artery is a branch of the anterior division of the internal iliac artery and the veins drain into the internal iliac vein ([Netter, 2010](#)). The inferior rectal artery supplies the anal canal; the perineal artery supplies the superficial perineal muscles; the posterior

labial branch provides an artery to the bulbs of the vestibule, dorsal and deep arteries of the clitoris. The superficial and deep external pudendal arteries are branches of the femoral artery and supply the labia majora with branches of the pudendal artery ([Beech and Adams, 2009](#)).

The internal pudendal arteries are the key resistance vessels controlling the peripheral circulatory component of sexual response in both males and females. Structurally the pudendal artery has a smaller lumen diameter, wall thickness, and much lower wall-to-lumen ratio compared to that of the male. The lumen of this artery also tapers as it travels distally and becomes the clitoral artery. Based on its smaller wall thickness, as expected, the female pudendal artery does not contract to the same magnitude attained by the male pudendal artery. However, the sensitivity to adrenergic-mediated contraction is not different between men and women ([Hannan et al., 2012](#)).

Many of the differences between the male and female pudendal arteries can be explained by the hemodynamic demands of their genital organs. The volume of blood and inflow pressures required to fill the penis are much greater than the demands of the female genitalia when sexual purposes are considered. Furthermore, various clinical studies have confirmed the difference in volume of blood as well as the pressures achieved by the genital organs during orgasm in both sexes. In fact, the volume of blood required to fill the clitoral tissue during sexual response is one-tenth that required to fill the penis (10 mL vs 100 mL) (Kaufman et al., 1993; Maravilla and Yang, 2008). Furthermore, the intracavernosal pressure within the penis reaches suprasystolic values during orgasm/ejaculation, whereas the vaginal, clitoral, and labial pressures only increase approximately 30–40 mmHg at peak sexual response (Kandeel et al., 2001; Sommer et al., 2001). Thus the male pudendal artery needs to be able to withstand greater inflow of blood at higher pressure and these requirements are reflected in the increased wall-to-lumen ratio of the pudendal artery.

The pudendal artery in the female rat is very similar anatomically to that in women. In women, the origin of the internal pudendal artery is also located on the internal iliac artery, but appears to arise much further down after the obturator, vesicular, and inferior gluteal branches (Yamaki et al., 1998; Beech and Adams, 2009). In both species, the internal pudendal artery gives off branches supplying the labia and distal vaginal wall and terminates as the common clitoral artery with branches forming the clitoral cavernous and dorsal clitoral arteries (O'Connell and De Lancey, 2005; Fatu et al., 2006). There is also evidence in both men and women of accessory pudendal arteries which arise off the inferior vesical, obturator, and external pudendal arteries and supply the genital tissues (Benoit et al., 1999).

The internal pudendal artery has markedly heightened susceptibility to vascular damage compared to other vessels in the body. Evidence suggests that the female may also be susceptible to vascular pathologies contributing to sexual dysfunction. Indeed, vaginal/clitoral engorgement is a central nervous system-driven event, leading to increases in blood flow to the genital organs – an event that precedes arousal (Traish et al., 2010). This increased blood flow to the vagina, clitoris, and labia is responsible for vasocongestion, engorgement, and lubrication in the sexual arousal response.

Internal genitalia

The internal genitalia are supplied by the internal pudendal artery and the uterine artery.

The vagina receives blood from the descending branch of the uterine artery, vaginal artery, and internal pudendal artery. The veins form the vaginal venous plexus into the internal iliac veins (Standring, 2008).

The vascular system of the uterus is based on the uterine artery from the internal iliac or hypogastric artery and on the ovarian artery from the abdominal aorta. These vessels give origin to an important anastomotic trunk with a typical circular disposition. The uterine artery derives from the anterior division of the hypogastric and runs medial to the levator ani muscle; about 2 cm from the cervix it crosses above and in front of the ureter. Reaching the side of the uterus it ascends in a tortuous manner between the two layers of the broad ligament to the junction of the fallopian tube and uterus. It ends joining with the ovarian artery. The uterine veins correspond with the arteries and end in the uterine plexuses.

The arteries of the ovaries and uterine tubes are the ovarian arteries from the abdominal aorta. Each ovarian artery anastomoses in the mesosalpinx, with the uterine artery giving some branches to the fallopian tube and to the ovary. The veins emerge from the hilum in the form of a plexus, the pampiniform plexus (Netter, 2010).

Veins from the ovary have a different ending: the right ovarian vein drains into the vena cava, with an acute incident angle that facilitates blood flow into the bigger leading vein. The left ovarian vein drains into the renal vein, with an orthogonal incidence which reduces the draining flow (Standring, 2008). This mechanic flowing difference is credited as the leading cause of pelvic varices on the left side. It can contribute to chronic pelvic pain, mostly when it is more localized on the left side of the pelvis.

THE LYMPHATIC SYSTEM

The lymphatic vessels of the perineum and of the external genitalia follow the course of the external pudendal vessels, and end in the superficial inguinal and subinguinal glands. Those from the ovary ascend with the ovarian artery to the lateral and preaortic glands. The lymphatic vessels of the uterus consist of two sets, superficial in the peritoneum and deep inside the organ. The vessels of the cervix go into the external iliac glands, to the hypogastric glands, and to the common iliac glands. The vessels of the body of the uterus run in the broad ligament principally and with the ovarian vessels ascend to the lateral and preaortic glands (Standring, 2008).

The innervation of genitals and pelvic floor system

The pudendal nerve arises from the sacral plexus; it is formed by the second, third, and fourth sacral nerve

roots. It passes between the piriformis and coccygeus muscles and leaves the pelvis through the lower part of the greater sciatic foramen. It then crosses the spine of the ischium, being situated between the sacrospinous and sacrotuberous ligament (Robert et al., 1998), and re-enters the pelvis through the lesser sciatic foramen. It goes along the lateral wall of the ischiorectal fossa with the internal pudendal vessels (the pudendal artery lies on its medial side), contained in a duplication of the obturator fascia called Alcock's canal (Shafik et al., 2004) and divides at the level of the perineum into three terminal branches: the dorsal nerve of the clitoris, the perineal nerve, and the inferior rectal nerve, providing the sensory branches to the skin of the perineal area, labia majora, and clitoris (Mahakkanukrauh et al., 2005; Tagliafico et al., 2013). It also innervates the external anal sphincter (inferior rectal nerve) and deep muscles of the urogenital triangle (perineal nerve).

The perineal nerve is situated below the internal pudendal artery and divides into a posterior labial branch and a muscular branch. The dorsal nerve of the clitoris is the deepest division of the pudendal nerve. Considering the relatively small size of the clitoris, even including the crura and bulbs, in comparison to the penis, the size of the dorsal nerve of the clitoris is proportional to its extraordinary sensory capacity, although it is small in absolute terms. The dorsal nerve supplies the clitoris (Peng and Antolak, 2009). The pudendal nerve is the most important human nerve in terms of pleasure perception. At the same time, it is also critical in sexual pain disorders, namely introital dyspareunia and vaginismus.

The lumbar plexus is formed by the loops of communication between the anterior division of the first three and the greater part of the fourth lumbar nerves; it is situated in the posterior part of the psoas major, in front of the transverse processes of the lumbar vertebrae. It divides into many branches, giving origin to the ilioinguinal nerve and genitofemoral nerve, which are important for innervation of the pelvis. The ilioinguinal nerve arises from the first lumbar nerve, giving branches to the obliquus internus muscle and to the skin covering the mons pubis and labia majora. The genitofemoral nerve arises from the first and second lumbar nerves and divides into the external spermatic nerve (which accompanies the round ligament of the uterus and becomes lost on it) and into the lumboinguinal nerve (which supplies the skin of the anterior surface of the upper part of the thigh) (Standing, 2008).

THE PHYSIOLOGIC AGING OF WOMEN'S GENITALIA

The female genital tract undergoes anatomic and functional changes from birth to menopause and beyond, due

to the levels and roles of estrogen, progesterone, and androgen (testosterone, dehydroepiandrosterone, and androstenedione) production (Venkatesh and Cu-Uvin, 2014). After the menopause, the loss of sexual hormones accelerates the process of aging, with two prominent characteristics:

1. A low-grade inflammation, genital and systemic, leading to a new word “inflammaging” – a process that constitutes the common denominator of cancer, neurodegenerative and cardiovascular diseases, among others (Michaud et al., 2013; Fulop et al., 2014).
2. A progressive involution of all the genital structures, unless a well-tailored hormone replacement therapy (HRT) is considered and prescribed.

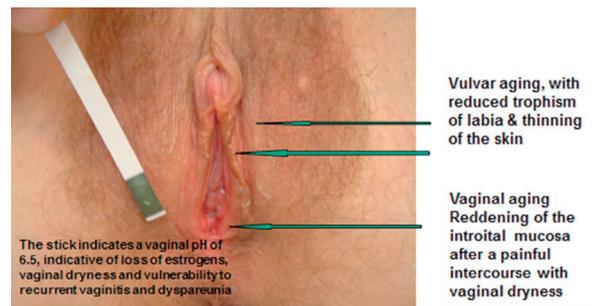
Specifically, menopause is defined as the permanent cessation of ovarian follicular activity (Mishra and Kuh, 2011). It is a natural bodily process which has a different clinical expression for each woman. The cessation of estrogen production causes a variety of symptoms and signs (hot flashes, night sweats, breast tenderness, vaginal dryness and atrophy, loss of sexual drive, osteoarthritis with joint pain, osteoporosis, heart disease, and mood changes) (Hoffman et al., 2012).

Typical aging changes include the following.

Vulvar aging

Prominent features include: reduced epithelial and mucosal trophism, progressive reduction in the volume of labia majora and minora (Fig. 4.5), reduced fibroblastic activity, up to 30%, with reduced production of collagen, elastin, and mucopolisaccharides, reduced sweat and sebaceous gland production, both qualitative and quantitative, with parallel reduction in genital pheromones (Farage and Maibach, 2006).

This change, together with the modification of the vaginal ecosystem, secretion, and lubrication, is responsible for the loss of the genital “scent of a woman,” critically important as a pleasant trigger for oral sex and for



A.Graziottin, 2006

Fig. 4.5. Progressive vulvovaginal aging after the menopause.

erection. Many partners report this specific change as a major impairment in the couple's intimacy liturgy only to the listening and caring gynecologist! Other changes include a progressive involution of the corpora cavernosa, that loses on average 50% volume by the menopause (Tarcan et al., 1999). When the process is particularly accelerated, as may happen in thin, hypoestrogenic postmenopausal women, it may contribute to the clinical complaint that "my clitoris is dead" (Hunter et al., 2008) in terms of loss of congestion and pleasurable sensations up to orgasm during genital foreplay, reported by 20% of postmenopausal women.

Other changes include the involution of peripheral nerves, of skin immune system activity and in hair distribution, color, and density (Tan et al., 2012). Hair whitening may be perceived as an aging-related sexual "insult," particularly by women who undergo a premature menopause and have to face these genital changes in spite of their relative youth, unless appropriate HRT (and hair coloring) is prescribed, when feasible and not contraindicated. Senile atrophy, kraurosis vulvae, leukoplakia, and lichenification are the epiphenomena, the visible tip of the iceberg of a full-thickness aging, involving all the tissue components, as mentioned above. They indicate how the progressive skin, submucosal, vascular, connective, nervous and immune involution may affect vulvar appearance and function (Kingsberg et al., 2013).

Introital dyspareunia up to frank impossibility to accept intercourse because of the extreme narrowing of the vestibular area is the most frequently reported sexual consequence in advanced aging (Krychman, 2011). Vulvar lichen sclerosis, a probable autoimmune disease with accelerated vulvar aging, and a prominent symptom of night itching, may further contribute to the sexual complaint of clitoral hyporesponsiveness, orgasmic difficulties, and introital dyspareunia, complained of during and after menopausal transition (Fig. 4.6).

On a positive note, topical treatment with a 2% testosterone propionate powder in Vaseline jelly may dramatically delay and partially reverse vulvar aging and its sexual consequences, more so if timely initiated – the sooner the better (Graziottin and Murina, 2011).

Ovarian aging

The ovaries undergo aging by a continuous decrease in number of follicles, diminished quality of oocytes, and ovarian hormonal deficiency until the menopause, which is the final step in this aging process (Li et al., 2012). Sexual mechanisms are involved and oxidative stress is considered one of the most important, leading to follicular atresia and reduction of quantity and quality of oocytes (Agarwal et al., 2012). The number of follicles in the



Fig. 4.6. Introital postmenopausal dyspareunia with vulvar dystrophy. Carla, 54 years; three children. Main consulting symptoms: hypoactive sexual desire disorder, itching, vulvo-vaginal dryness, and introital dyspareunia. Associated symptoms: delayed orgasm, with diminished intensity, mild stress incontinence, leakage during thrusting. (Reproduced from Graziottin and Murina, 2011.)

ovary has a direct relation with the hormonal levels of estrogen, progesterone, and gonadotropin (Agarwal et al., 2012). During menopause, there is a rise in follicle-stimulating hormone and luteinizing hormone levels with a decrease in the amount of estrogen (Doshi and Agarwal, 2013). Estrogen is synthesized by granulosa cells of the ovary in three forms: estradiol (the most common and potent form which is predominant during the fertile age of the woman), estriol, and estrone (the weaker form, which is prevalent during the postmenopausal phase, derived from the conversion of androstenedione in adipose tissue and liver) (Cooke and Naaz, 2004). In addition, estrogens are synthesized in smaller amounts by other tissue, adrenal glands, fat cells, hepatocytes, and even from muscles, which during physical exercise metabolize dehydroepiandrosterone to estradiol and testosterone. The reduction of estrogen levels increased the oxidative stress in the body depending on the proper chemical structure of the hormone correlating with breaks in genetic material (Lei et al., 2010).

Vaginal aging and atrophy

It has been estimated that 25–50% of postmenopausal women experience vulvovaginal atrophy, with symptoms of burning on urination, vaginal discharge, itching or burning sensation, vaginal dryness, and painful sexual intercourse (MacBride et al., 2010; Tan et al., 2012). The reduction of estrogens removes the trophic stimulus

from the vaginal tissue: the vaginal epithelium becomes thin, vaginal secretions and vascularization decrease, the submucosal layers lose mucopolisaccharides and elastic fibers, and the vagina becomes shorter, narrower, and less elastic, with an increase in the pH level (Freeman, 2010) and in the content of inflammatory cytokines (interleukin-1 (IL-1) and IL-8). The hormonal changes influence the vaginal microbiome, with a continued decrease in lactobacilli, the prominent acid production bacteria typical of the healthy vaginal ecosystem in the fertile age. The consequent change in resident flora contributes to the increased vulnerability to *Escherichia coli* infections, leading to recurrent vaginitis and urinary tract infections (Lamont et al., 2011; Broatman et al., 2014). Pathogenic biofilms produced by and containing *E. coli* and other pathogenic microorganisms of colonic origin contribute to recurrent cystitis and vaginitis in the postmenopausal years.

Uterine and tubal aging

With age, and in the absence of HRT, the uterus and tubes undergo progressive involutive changes. The muscle component is reduced, an increased collagen production is documented, and the endometrium becomes subtle and thin (Bitti et al., 2014). Myomata, previously present in the fertile age, undergo a reduction in size and, sometimes, there are local involutive inflammatory processes with calcifications (Grings et al., 2012).

Vascular aging

Aging is associated with structural and functional changes in the vasculature, including endothelial dysfunction, arterial stiffening and remodeling, impaired angiogenesis, and defective vascular repair with an increased incidence of atherosclerosis (Novella et al., 2012). Cardiovascular risk increases in women after the menopause: it has been correlated with loss of the protective effects of estrogens on vascular endothelium (Stice et al., 2009). Estrogen promotes endothelial nitric oxide production and modulates prostacyclin and thromboxane A₂ release (vasodilator substances) and decreases the production and effects of vasoconstrictors such as endothelin and angiotensin II (Orshal and Khalil, 2004; Khalil, 2013). Early initiation of estrogen replacement produces more favorable results than if started later (Prentice et al., 2009). Specifically, progressive vascular involution of the vaginal vessel is first responsible for the progressive vaginal dryness complained of by an increased percentage of postmenopausal women (Guthrie et al., 2004; Dennerstein et al., 2007).

Pelvic floor aging, sarcopenia, and bone mass loss

Pelvic floor aging involves all the connective structures with a prominent involution in the levator ani muscle. Sarcopenia is age-related loss of muscle mass and function, caused by multifactorial mechanisms (impaired regenerative capacity, attenuated ability to respond to stress, elevated reactive oxygen species production, and low-grade systemic inflammation) (Lightfoot et al., 2014).

Sarcopenia at the level of the pelvic floor muscles is of special importance in the aging woman as it may contribute to the prolapse of genital organs, to urinary incontinence, and even anal incontinence in women who suffered from subclinical anal lesions during delivery.

The decrease of estrogens leads to a bone mass loss which predisposes to osteoporotic fractures (Ahn and Song, 2009) in association with vitamin D insufficiency (Lips et al., 2006; e Silva et al., 2014). Loss of vitamin D may further accelerate the sarcopenia process. This may further contribute to back pain (Silva et al., 2006; Lightfoot et al., 2014).

THE PHYSIOLOGY OF WOMEN'S SEXUAL FUNCTION

The anatomy of the genital organs is a prerequisite for sexual function in both genders. Physiology encompasses all the functions and changes of the systems – nervous, muscular, vascular, mucocutaneous, metabolic, endocrine, immune – that are essential to lead to a complete sexual response (Graziottin and Giraldi, 2006). Physicians should master the basics of the anatomy and physiology of sexual function to be able to diagnose and treat women's sexual dysfunction (Graziottin, 2007a, b). Sexual function includes desire/interest, central and peripheral arousal with genital congestion and vaginal lubrication, orgasm, resolution, and satisfaction. Recent debate supported a common reading of sexual desire/interest and central arousal in women (Greenberg and Jerrold, 2010).

Sexual desire/interest and central arousal may be activated by both internal and external stimuli (Fig. 4.7). Internal stimuli include erotic and non-erotic dreams, fantasies, memories, love, attachment/intimacy needs, and physical drive. External stimuli include all the sensory signals: olfactory (including pheromones), tactile, gustatory, auditory, and visual. In women the first three are prominent and are also referred to as “cenesthetic signals.” Whatever the stimulus, as soon as it is perceived/read as “sexual,” it will massively activate a complex neuronal functional response in many different brain

areas (see Chapter 2), a process known as psychoplasticity. This is the functional correlation of the huge neuroplasticity biologically activated by the sexual stimulus, that is constantly modulated during the fertile age by the presence of and changes in sexual hormone levels (see Chapter 10). After the menopause, massive central, peripheral/somatic, and genital changes are induced in women’s sexual response by the loss of sexual hormones (Table 4.1).

Once the sexual stimulus is perceived, four major brain systems are activated at the same time (Stoléru et al., 2012):

1. the autonomic system, mediating the neurovascular, cardiovascular, respiratory, mucocutaneous, olfactory, salivary, and genital response, preparing the whole body for sexual intercourse
2. the emotional/affective/limbic system, which sets the emotional color/atmosphere of this specific feeling of desire and arousal, which may be enhancing, when a positive, reciprocal response is perceived in the desired partner, or inhibiting, when a negative response is anticipated/perceived and/or when

3. the cognitive system, which evaluates the wish for and risks of behaving sexually
4. the motor system, usually neglected in classic descriptions; in contrast, it is an absolutely vital part of sexual behavior in both genders. It is involved in two main areas: (a) motor behavior is a vital part of courting, foreplay, hugging, kissing, and caressing, i.e., in the music of loving and sexual bodies; and (b) it is also a critical component of orgasm, by definition a sensory/motor reflex. It seems that decreased blood flow in the left lateral orbitofrontal cortex signifies behavioral disinhibition during orgasm in women, and that deactivation of the temporal lobe is directly related to high sexual arousal. In addition, the deep cerebellar nuclei may be involved in orgasm-specific muscle contractions, while the involvement of the ventral midbrain and right caudate nucleus suggests a role for dopamine in female sexual arousal and orgasm (Georgiadis et al., 2006). It is of special relevance for

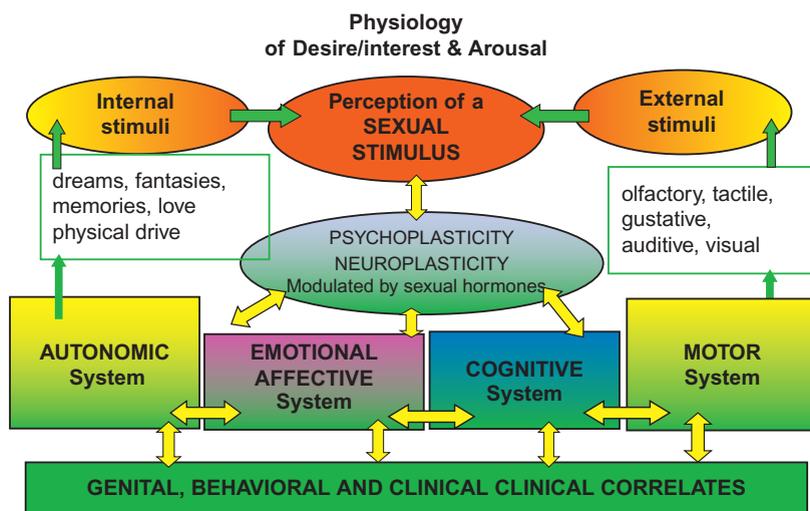


Fig. 4.7. Physiology of sexual desire/interest and central arousal. (Reproduced from Graziottin and Giraldi, 2006.)

Table 4.1

Mean steroid levels in women: values converted to pg/mL

Steroid	Reproductive age	Natural menopause	Iatrogenic menopause
Estradiol	100–150	10–15	10
Testosterone	400	290	110
Androstenedione	1900	1000	700
Dehydroepiandrosterone	5000	2000	1800
Dehydroepiandrosterone sulfate	3 000 000	1 000 000	1 000 000

Reproduced from Lobo (1999).

neurologists, as motor system pathology may affect women’s (and men’s) sexuality in a complex, and yet not completely understood, way. For example, in multiple sclerosis, cerebellar components of orgasm in women are selectively affected (Gruenwald et al., 2007).

MODELS OF WOMEN’S SEXUAL FUNCTION

Different models of women’s sexual function have been proposed over the years. The main change is from a linear reading of the sexual response (Fig. 4.8) (Masters and Johnson, 1966), without desire as a major starting point, to including desire (Fig. 4.9) (Kaplan and Horwith, 1983), to a more sophisticated model (Basson, 2000) more focused on emotional/affective reading, appreciating the role of intimacy needs in women. In this model (Fig. 4.10) four major contributors modulate the final perception of desire. This model is endorsed mostly by women in long-lasting relationships when intimacy needs may activate a responsive desire to the partner’s sexual cues. Basson’s key contributors of sexual desire/interest include biologic, psychologic, sociocultural, and relationship factors.

Graziottin’s circular model focuses on the biologic component of women’s sexual response to help physicians in their basic reading of key functional and dysfunctional biologic contributors (Fig. 4.11) (Graziottin, 2000). It should be considered as a detailed reading of the biologic contributors in Basson’s integrated biopsychosocial model. Here the focus will be on the genital physiology contributing to the genital sexual response in women.

During sexual stimulation, the female sexual arousal response is triggered by sensory stimulation, synchronous with central nervous activation, resulting in increased blood flow to the genitals (Berman et al.,

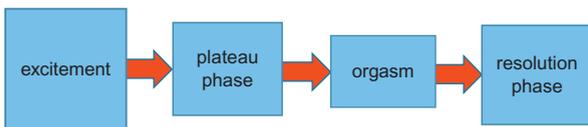


Fig. 4.8. Masters and Johnson’s sexual model – a linear model with one phase occurring before the next in the same order.



Fig. 4.9. Kaplan’s triphasic model – a linear model with implementation of the sexual desire phase.

Understanding female sexuality: A model

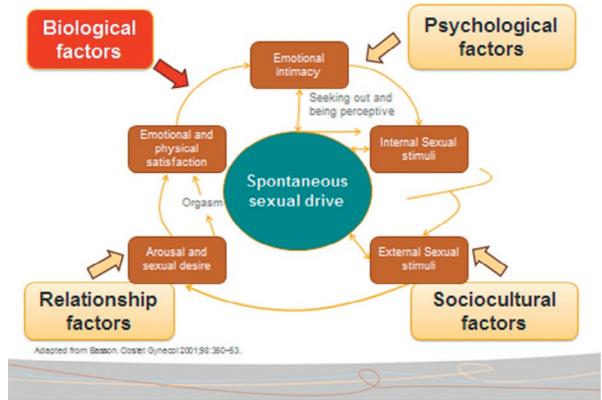


Fig. 4.10. Basson’s sexual model. (Adapted from Basson, 2001.)

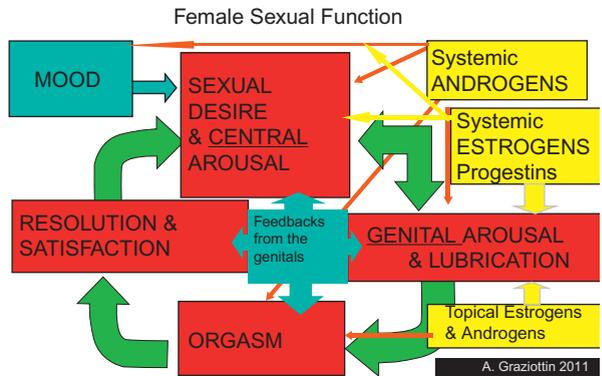


Fig. 4.11. Graziottin’s model stresses: (1) the interdependence between desire/interest and central arousal, genital arousal, with cavernosal congestion and vaginal lubrication, orgasm, resolution, and satisfaction, leading to either positive or negative feedback, according to the quality and intensity of the sexual experience; (2) in contrast to previous models, the importance of genital feedback: (a) the quality of cavernosal/vulvar and urethral congestion and vaginal lubrication and the sensations/feelings the woman is having from it (pleasure, indifference (“I feel nothing”), pain and/or burning feelings at penetration); (b) the impact of the man’s genital sexual response on the woman’s genital arousal (quality of erection, hardness, and duration). These biologically based genital factors may further enhance or inhibit the woman’s genital and mental response, through either positive or negative feedback; (3) the model also stresses the role of mood as a central desire/interest modulator encompassing: (a) the biologic mood levels (serotonine/dopamine-correlated); (b) the impact of sexual hormone patterns and fluctuations on mood itself; (c) the impact of the specific sexual experience (whether rewarding, neutral, or negative) on mood; (d) the inhibiting role of negative/painful genital feedbacks (often disregarded/neglected) in women; and (e) the impact of male genital factors (functional/lasting erections vs erectile deficit or premature ejaculation).

1999; Deliganis et al., 2002; Maravilla et al., 2003; Girdali and Levin, 2006; Cuzin, 2012). During sexual arousal, the cavernosal bodies of the labia/periuethra and clitoris become engorged with blood (increased by two to three times) (Suh et al., 2004). The concomitant activation and secretion of Bartholin's gland liquid contribute to the lubrication of the internal part of the labia minora and of the vestibular region; it is essential to prevent painful coitus (Riley and Riley, 1983).

The clitoris with the clitoral bulbs plays a central role in female sexual function. Under basal conditions, the blood vessels in the clitoris have a high tone (through sympathetic activity) and are mainly closed (Yilmaz et al., 2002), but show evidence of vasomotion (Levin, 2005), the random opening and closing depending on local tissue needs. The neural innervation is through VIPergic nerves releasing vasoactive intestinal peptide (VIP), which dilates the arterial supply and nitric oxide (NO), which promotes relaxation of the smooth muscle of the cavernous sinuses (Martin-Alguacil et al., 2008). In both genders testosterone is a "permitting" factor for NO-mediated vasodilatation; in women, estrogens are the permitting factor for VIP-mediated systemic vasodilatation and vaginal lubrication (Levin, 2005). During sexual arousal, the central reduction of sympathetic tone and the release of the two vasodilator neurotransmitters create an increase in blood flow to the clitoris, relaxing the trabecular smooth muscles, thus promoting clitoral vasocongestion along with increased width of the clitoris during arousal (Salonia et al., 2012).

Since there is no subalbugineal layer between its tunica and the erectile tissue, the clitoris only becomes swollen or tumescent and not rigid, even when fully filled (Toesca et al., 1996). This congestion is usually associated with pleasurable genital feelings of engorgement and lubrication: with positive feedback this contributes to improved mood, positive emotional feelings, and desire/interest/motivation for intercourse and penetration.

The vagina also plays a very active role in sexual arousal with its change in microcirculation. During quiescence, vaginal capillaries are closed due to contraction of the precapillary sphincters; the surface pO_2 of the vagina wall is thus basally at a low, hypoxic level (Wagner and Levin, 1978). When the local area around one of these becomes hypoxic, the released metabolites (pCO_2 , lactic acid, K^+ , and adenosine triphosphate) cause precapillary sphincter relaxation and the supplied capillaries to open up, washing away the metabolites and refreshing the local area with oxygen and nutrients. This intermittency of the microcirculation is known as "vasomotion" (Levin and Wylie, 2008). The degree of vaginal vasomotion is a sensitive and useful index of genital arousal. Thus, during basal conditions, a high

vasomotor tone of the arterial supply through central sympathetic activation and a high level of vasomotion keep the blood flow to the vagina at minimal levels. With sexual stimulus, the central sympathetic tone is reduced and the arterial supply is enhanced through the action of released neuronal VIP and some NO via the sacral anterior nerve root (Wagner, 1979). In this way the recruitment of the capillaries becomes maximal, the vagina becomes fully vasocongested (along with the labia and clitoris), and vasomotion is absent.

Within the sexually aroused vagina, the capillaries of the microcirculation are filled with blood and the increased hydrostatic pressure inside them forces out a plasma transudate (ultrafiltrate) into the interstitial space around the blood vessels (Wagner, 1979; Levin, 2005; Levin and Wylie, 2008). Continued formation of this neurogenic transudate fills up the interstitial space and then passes through and between the cells of vaginal epithelium to leak on to the surface wall of the vagina as vaginal lubrication. The final fluid is a modified plasma filtrate because the cells of the vagina can transfer Na^+ ions vectorially from the lumen back into the blood and add K^+ ions by secretion and cell shedding (Wagner, 1979). The ionic concentrations are different from those in the plasma, having a higher K^+ and a lower Na^+ than plasma (Wagner and Levin, 1980). In contrast, the arousal lubrication fluid has a much higher Na^+ concentration than the basal fluid, approaching that of plasma (Wagner and Levin, 1978). On cessation of sexual arousal, the vaginal Na^+ together with osmotically drawn fluid is transferred back into the blood, thus resetting the vagina to the basal "just moist" condition.

The pelvic muscles are an intrinsic part of the orgasmic process (Levin, 1981). Orgasm is characterized by seven to eight rapid sequential contractions of the levator ani muscles and muscles of the superficial trigonus. Hypoactivity of the muscles (low tone), more frequent after vaginal delivery, leads to poor sexual function and lack of pleasure during coitus and orgasm. A healthy and tonic pelvic floor is significantly associated with better arousal and orgasm (Lowenstein et al., 2010). In contrast, hyperactivity (high tone) may be pathophysiologically linked to the sexual pain disorders called dyspareunia (coital pain) and vaginismus (Graziottin and Girdali, 2006).

The orgasm in the female is a variable, transient peak of sensation of intense pleasure, creating an altered state of consciousness, usually accompanied by involuntary, reflex rhythmic contractions of the pelvic striated circumvaginal musculature, often with concomitant uterine and anal contractions and myotonia that resolves the sexually induced vasocongestion, usually with an induction of well-being and contentment (Meston et al., 2004). It can be induced by different physical

trigger stimulations, genital (clitoral, periurethral, vaginal, anal), non-genital (breast, nipple, skin), and mental stimulation (erotic dreams, fantasies, sexual daydreams) (Levin, 2001). During orgasm the so-called phenomenon of female ejaculation has been demonstrated (Korda et al., 2010): this consists of the expulsion of a small quantity – no more than one or two teaspoons – of whitish fluid produced by the female prostate, previously called Skene’s paraurethral glands (Rubio-Casillas and Jannini, 2011), characterized by the presence of prostate-specific antigen and prostatic specific acid phosphatase (Zaviacic et al., 1988).

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Orgasm is associated with different changes: (1) somatic: the peak of oxytocin contributes to relaxation of the musculature, lowering blood pressure and heart beat, reducing the frequency of breathing, leading to an overall sense of physical relaxation; (2) emotional affective: oxytocin also mediates a sense of contentment, further accentuated by emotional feelings if the experience has been appreciated as highly rewarding; (3) endocrine: oxytocin released at orgasm increases estrogen and androgen receptors in the genital organs and pelvic floor, thus creating the endocrine basis for further enhancement of the physical response; and (4) finally oxytocin potentiates the couple’s bonding through the powerful reward system specifically activated by intercourse with one or more pleasurable orgasms.

CONCLUSION

Anatomy and physiology of women’s sexual function still deserve further studies as many aspects remain unclear or controversial. Knowledge and continuous updating are key for all healthcare providers who are willing to really increase their competence in diagnosing and effectively treating women’s sexual dysfunctions.

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