1 EMBRYOLOGY OF THE LOWER FEMALE GENITAL TRACT

CERVIX AND VAGINA

The differential diagnosis of a number of benign and malignant lesions of the lower female genital tract is facilitated by an understanding of the embryology of these organs. In the past, our understanding of the embryology of the human cervix and vagina was based on experimental work in animals whose embryologic development differed from that of the human. These studies have been summarized by Forsberg (7), O'Rahilly (10), and Mossman (9). Subsequent studies in which human fetal genital tracts were implanted into athymic (nude) mice by Cunha and Robboy (4,11,13) have greatly advanced our understanding of the embryology of the human vagina. The discussion of the development of the cervix and vagina that follows is a brief account of what remains a complex and incompletely understood subject (12).

The anlage of the uterine corpus and cervix and the upper vagina is termed the uterovaginal canal. This structure develops from the fusion of the mesoderm-derived, paired müllerian ducts at about day 54 postconception. The canal is initially a straight tube lined by müllerian columnar epithelium, which joins the endoderm-derived urogenital sinus. The point at which the two meet is referred to as the müllerian tubercle (fig. 1-1). This site is destined to be the location of the vaginal orifice at the hymenal ring.

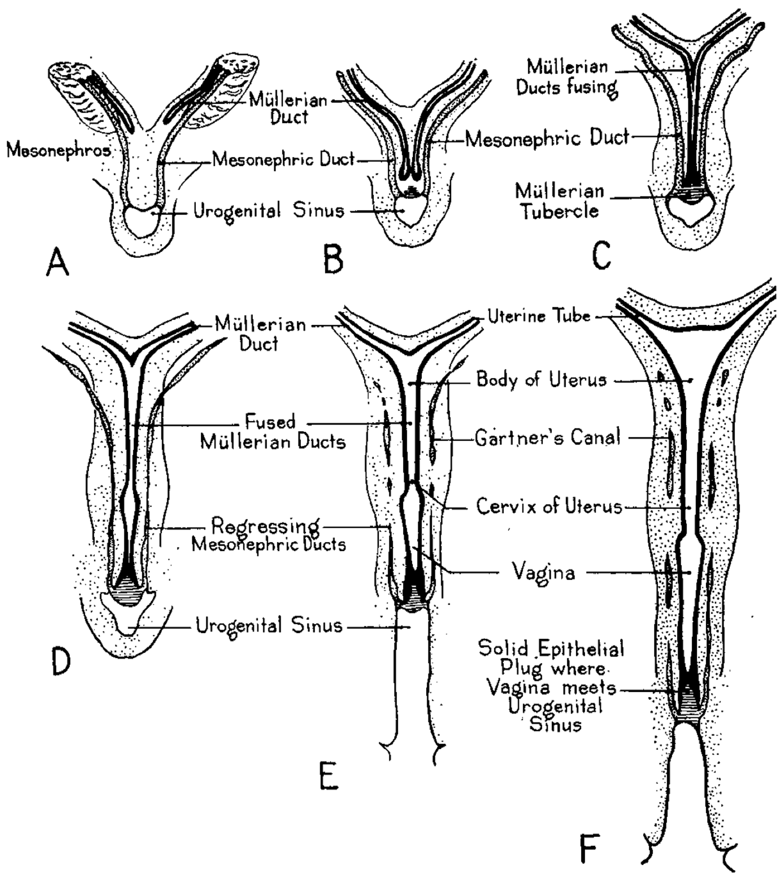

Figure 1-1

FUSION OF THE MÜLLERIAN DUCTS TO FORM THE UTERUS AND VAGINA

The close relationship of the epithelium of the müllerian ducts to the urogenital sinus explains, in part, the difficulty in determining which epithelium gives rise to that of the vagina. (Fig. 363 from Pattern BM. Human embryology. Philadelphia: Blakiston; 1953:580. Redrawn from Koff AK. Contrib Embryol 1933;24.)

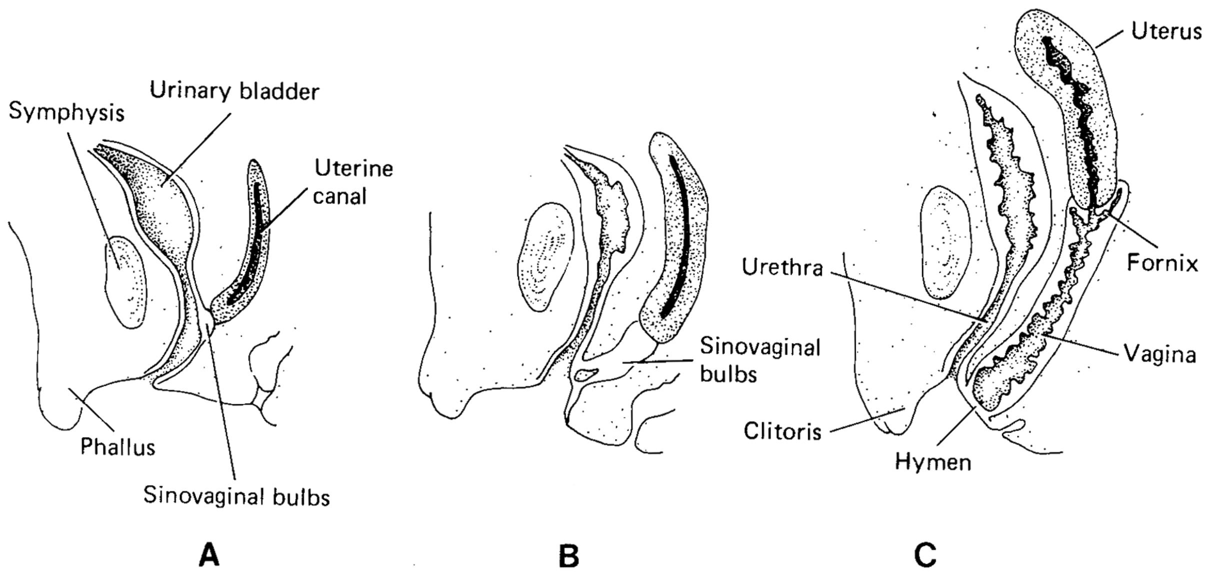

Figure 1-2

FORMATION OF THE UTERUS AND VAGINA

These sagittal sections show the formation of the uterus and vagina at various stages of development. (Fig. 15-24 from Sadler TW. Langman's medical embryology, 5th ed. Baltimore: William & Wilkins; 1985:267.)

At approximately day 66, the epithelium of the caudal uterovaginal canal begins to stratify, either as a result of cephalad migration of cells from the urogenital sinus (1,11) or by direct squamous transformation of the columnar cells lining the uterovaginal canal (6). Clinical evidence favoring the former interpretation is provided by women born with an imperforate, transverse vaginal septum (14). In these patients, the vagina lying above the septum is lined by columnar epithelium, whereas the vagina below the septum is lined by squamous epithelium. The stratification of cells in the region of the müllerian tubercle is the first evidence of the formation of the vaginal plate, a structure unique to humans. The stratified squamous epithelial cells of the vaginal plate proliferate, so that by day 77 the vagina is a nearly solid core of squamous epithelium (fig. 1-1). Endocervical glands and the vaginal fornices appear between 91 days (13th week) and the 15th week, thereby permitting the first definitive identification of the cervix (fig. 1-2). At this time, the vagina and cervix are highly sensitive to steroid hormones, and from about the 16th week of fetal life to birth the cervix responds to estrogenic stimulation by marked growth. Similarly, mucin secretion in endocervical glands begins in response to estrogenic stimulation during the 7th month of gestation and decreases rapidly during the first 2 postnatal weeks, remaining at a low steady state until menarche, when increased secretion begins again.

Experimental studies in rodents provide cogent evidence that the primitive epithelium lining the uterovaginal canal is programmed to differentiate into squamous, mucinous, and tuboendometrial-like epithelia by the underlying stroma. Murine neonatal vaginal epithelium grown on uterine stroma differentiates into columnar epithelium whereas uterine epithelium grown on vaginal stroma differentiates into squamous epithelium (2). The cytosolic proteins in the resultant epithelia reflect that of the induced rather than the original source (3).

Studies of the developing human genital tract implanted into nude mice have shown that the cervix and uterine corpus are invested by two layers of primitive mesenchyme (2,3). The inner layer is destined to become the endocervical and endometrial stroma and the outer layer the myometrium. The inner layer invests the uterine corpus and cervix, gradually tapering and ending at the point where the cervix joins the vagina, and possibly extending into the vagina and vulva (5). The outer layer is continuous throughout the fallopian tube, myometrium, and wall of the vagina. It has been postulated that the inner layer induces differentiation of the tuboendometrial type glandular epithelium of the fallopian tube, uterine corpus, and deep glands in the cervix (4). According to this view, the squamous epithelium of the vagina that may be derived from the urogenital sinus is not subject to the inductive stimulus of the cervicovaginal mesenchyme.

The above concept of cervical and vaginal development is attractive because it offers an explanation for many of the genital tract abnormalities observed in women exposed to diethylstilbestrol (DES) and related drugs in utero. In the DES-exposed female fetus, the primary teratogenic effect of the drug may be directly on the stroma, which in turn induces abnormalities in the overlying epithelium. Indeed, in the nude mouse model it has been shown that in utero DES inhibits the usual segregation of the inner and outer layers of the mesenchyme that surround the cervicovaginal canal (13). A similar mechanism may be involved in the gross structural abnormalities of the cervix (hoods, ridges, cervical hypoplasia, and vaginal fornix hypoplasia) and the abnormal contours of the endometrial cavity (uterine constriction and T-shaped uterus) that have been observed in human females exposed to DES in utero (8). In addition, enlargement of the transformation zone, evident in most DES-exposed women, may be due to a failure in the normal segregation of the underlying mesenchyme into discrete layers. As a result, the innermost layer of mesenchyme extends out laterally and cephalad beneath the ectocervix and upper vagina. This mesenchyme induces the differentiation of mucinous epithelium, i.e., the glandular component of the transformation zone, which in turn extends over the ectocervix and upper vagina. In the latter location, this results in mucinous type adenosis. Failure of the upgrowth of urogenital sinus squamous epithelium results in retention of the original embryonic müllerian epithelium and contact with the mesenchyme of the vagina results in induction of tuboendometrial type glandular epithelium (adenosis) in the more caudal portion of the vagina (fig. 1-3) (11). Clear cell carcinoma in the DES-exposed woman is characteristically associated with tuboendometrial type adenosis rather than with mucinous adenosis.

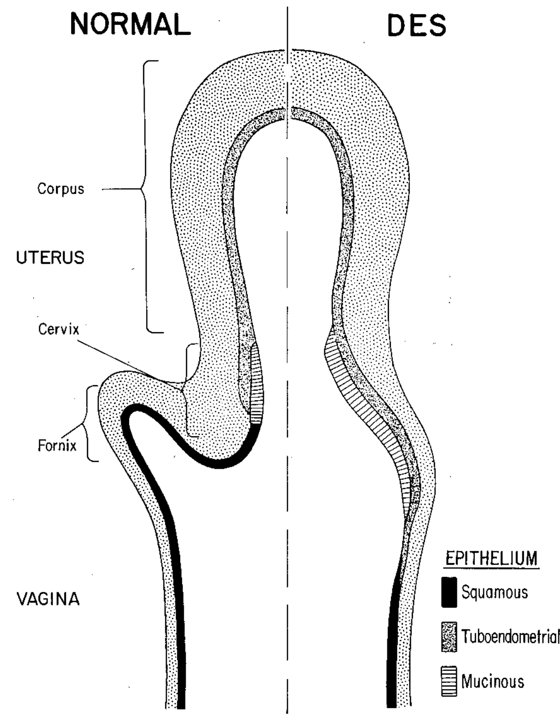

Figure 1-3

HYPOTHETICAL CONSEQUENCES OF PRENATAL DIETHYLSTILBESTROL EXPOSURE TO DEVELOPING VAGINA AND CERVIX

A normal genital tract is illustrated on the left. The genital tract in a patient exposed to diethylstilbestrol (DES) in utero is illustrated on the right. (Fig. 2 from Robboy SJ. A hypothetic mechanism of diethylstilbestrol (DES)-induced anomalies in exposed progeny. Hum Pathol 1983;14:832.)

VULVA

The formation of the vulva becomes evident in the 4th embryonic week, when proliferation of the mesodermal stroma adjacent to the cloaca results in elevation of the overlying ectoderm. Ventrally, this results in the formation of the genital tubercle, which is destined to become the clitoris, while laterally, two parallel ridges, each composed of a medial and lateral fold, develop. The medial folds, or urogenital folds, develop into the labia minora. The lateral folds, or labioscrotal folds, develop into the labia majora.

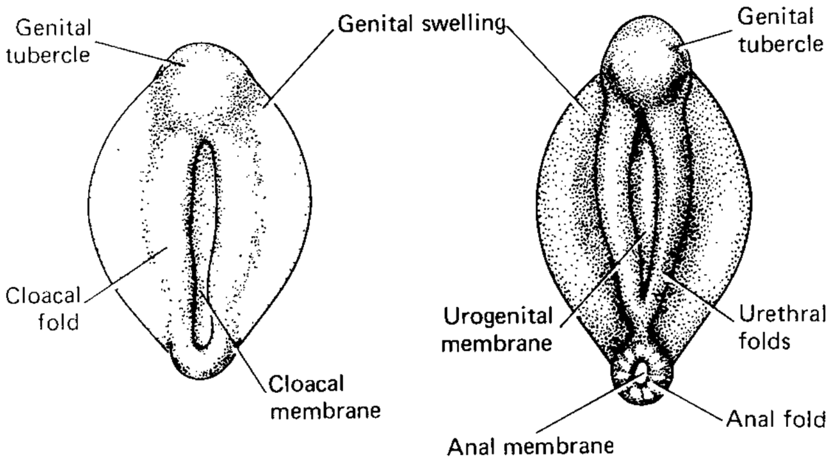

Figure 1-4

EMBRYOLOGY OF THE VULVA

The indifferent stage of the external genitalia is represented at approximately 4 weeks (left) and at approximately 6 weeks (right). (Fig. 15-26 from Sadler TW. Langman's medical embryology, 5th ed. Baltimore: William & Wilkins; 1985: 269.)

Table 1-1

FEMALE AND MALE HOMOLOGUES OF THE EXTERNAL GENITALIA OF THE HUMAN

Female	Male
Vulvar vestibule	Distal urethra
Skene glands	Prostate gland
Bartholin glands	Cowper glands (bulbourethral glands)
Minor vestibular glands	Glands of Littre
Clitoris	Corpus cavernosum of the penis
Labia minora	Corpus spongiosus of the penis
Labia majora	Scrotum

By the end of the 6th week of development the urorectal septum and the cloacal plate fuse to form the urogenital membrane anteriorly and the anal membrane posteriorly. Fusion of the lower portion of the labioscrotal folds anterior to the anal fold results in the formation of the perineum (fig. 1-4). Thus, the epithelia of the labia majora, the labia minora, and the clitoris are of ectodermal origin.

The bilateral labioscrotal folds fuse anterior to the genital tubercle to form the mons pubis. The junction of the distal vagina with the urogenital sinus results in the development of the vulvar vestibule, which is identifiable by the 16th week. Except for a small area immediately anterior to the urethra, which may be of ectodermal origin, the vestibule is of endodermal origin. The junction of the epithelium derived from endoderm and that derived from ectoderm is seen in the adult on the inner aspects of the labia majora and is marked by the presence of sebaceous glands underlying the epithelium derived from ectoderm evident on the medial aspects of the labia majora (see chapter 2). The Bartholin gland, the major gland of the vestibule, is of endodermal origin. Homologous structures of the male and female are compared in Table 1-1.

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