

Chapter 1

Biological Preliminaries

Facts are the air of science. Without them a man of science can never rise.

I. Pavlov

1.1 The Uterus

The nonpregnant human uterus is a hollow, thick-walled, organ situated deeply in the pelvic cavity. It measures on average 7.5 cm in length, 5 cm in breadth, at its upper part, and nearly 2.5–4 cm in thickness (Fig. 1.1). Anatomically the organ is divided into: (1) the fundus, (2) the body, (3) the uterotubal angles, and (4) the cervix. A region between the body and the cervix is called the isthmus. The cervix of the uterus is connected to the vagina. It is conical or cylindrical in shape, with the truncated apex.

The uterus is supported by eight ligaments: anterior, posterior, and dual lateral, uterosacral, and round ligaments. The anterior and posterior ligaments consist of the vesicouterine and the rectovaginal folds of the peritoneum. They contain a considerable amount of fibrous tissue and nonstriated muscular fibers. At one end, they are attached to the sacrum and constitute the uterosacral ligaments. The two broad ligaments pass from the sides of the uterus to the lateral walls of the pelvis. The round ligaments are two flattened bands situated between the layers of the broad ligament in front of and below the uterine tubes. They consist principally of muscular tissue, prolonged from the uterus, and of some fibrous tissue. The ligaments contain blood and lymph vessels, and nerves. Additionally, there are fibrous tissue bands on either side of the cervix uteri – the ligamentum transversalis coli. They are attached to the side of the cervix uteri, to the lateral walls of the pelvis and to a part of the vagina.

The arterial supply to the uterus is mainly from the hypogastric artery. The arteries are remarkable for their tortuous course and frequent anastomoses within the wall of the organ. The venous return corresponds to the course of the arteries

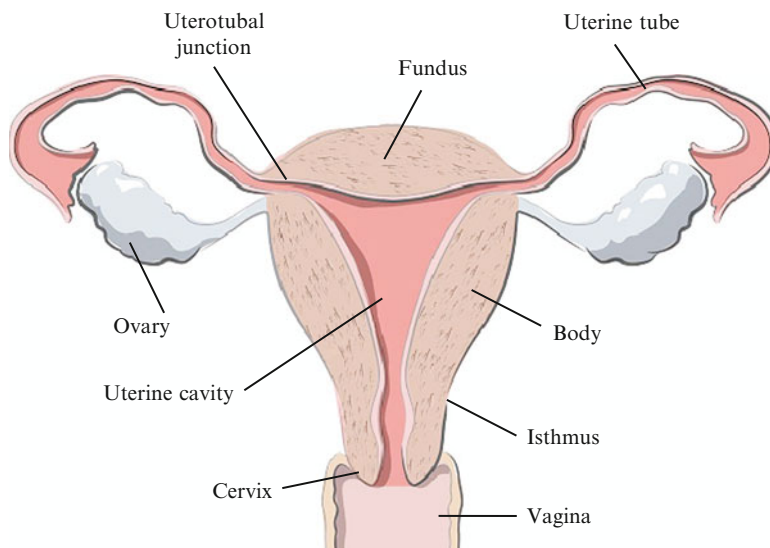


Fig. 1.1 Anatomy of the nonpregnant human uterus

and drains in the uterine plexi. In the pregnant uterus the arteries carry the blood to, and the veins convey it away from the intervillous space of the placenta.

The nerves are derived from the hypogastric and ovarian plexi, and from the third and fourth sacral nerves. It suffices to note that there is afferent and no efferent innervation to the uterus.

The actual position of the body of the uterus in the adult is liable to considerable variation. It depends chiefly on the condition of the nearby organs – the bladder and rectum. When the bladder is empty, the uterus is bent on itself at the junction of the body and cervix and lies upon the bladder. As the bladder fills, it becomes more erect, until with a fully distended bladder, the fundus of the uterus may face the sacrum. Movements of the cervix though are very restricted.

The cavity of the nonpregnant womb resembles a mere flattened slit. It is triangular in shape, with the base being formed by the internal surface of the fundus and the apex – by the internal orifice of the cervix. The uterine tubes connected on either side of the fundus allow the ova to enter the uterine cavity. If an ovum is fertilized, it imbeds itself in the uterine wall and is normally retained there until prenatal development is completed.

1.2 Functional Unit

The human uterus is a multi-component system with optimal spatiotemporal arrangements among morphological elements. It is composed of three histologically distinct layers (from inside out): the endometrium, the myometrium, and the

perimetrium. The endometrium of the womb is lined with a surface epithelium and has three types of cells: secretory, ciliated, and basal. The main function of the endometrium is to provide implantation of a fertilized ovum and to support the growth of a fetus. The outermost perimetrium is composed of a thin layer of connective tissue – collagen and elastin fibers.

The most prominent layer – the myometrium – is divided into three poorly delineated self-embedded layers (strata): the strata supravasculare, vasculare, and subvasculare. The morphostructural functional unit of the muscle tissue of the uterus is the uterine smooth muscle cell – myocyte. It has a characteristic spindle-like shape which is determined by the cytoplasmic cytoskeleton (Yu and Bernal 1998; Small and Gimona 1998). The latter is formed by intracellular thin actin, ~6 nm, intermediate, ~10 nm, and microtubular filaments, ~20–25 nm, in diameter. Arranged into a lattice, with multiple insertions of cytoplasmic dense bodies, and attached to the cell membrane at the sites of plasmalemmal dense plaques they guarantee the integrity, strength, and high degree of deformability of the myometrium.

Plasmalemmal dense plaques contain focal adhesion complexes which comprised multifunctional proteins, i.e., integrins, syndecans, paxillin, vincullin, tallin, and a family of kinases, i.e., focal adhesion, extracellular signaling, and c-Src kinases (Gerthoffer and Gunst 2001; MacIntyre et al. 2008; Li et al. 2003). They make direct structural and functional contacts between the intracellular cytoskeleton and the extracellular matrix (ECM), and act as mechanosensors in tyrosine kinase signaling pathways (Gabella 1984; Burridge and Chrzanowska-Wodnicka 1996; MacPhee and Lye 2000; Williams et al. 2005).

Individual myocytes are integrated into bundles, $\approx 300 \pm 100 \mu\text{m}$, surrounded by fine fibrillar matrix interspersed with microvasculature. Multiple pore structures between myometrial cells allow cell-to-cell communication via diffusible intracellular components – gap junctions. Immunofluorescent studies showed that they are formed predominantly by the connexin-43 protein with varying degrees of connexins 40 and 45 (Sakai et al. 1992; Tabb et al. 1992; Kilarski et al. 2001). Gap junctions provide the structural basis for electrical and metabolic communications, support synchronization and long range integration in myocytes. These ensure the property of myogenic syncytia necessary for the coordinated, phasic contractions of labor. Immunohistochemical labeling studies has demonstrated that the expression of connexin-43 is not even in the pregnant uterus. There is a significant increase in the protein content in the fundus compared to the lower segment of the organ. This fact has been suggested to be pivotal in electrogenic coupling asymmetry and conductance anisotropy (Blanks et al. 2007). Bundles of myocytes are further organized into fasciculi, $\approx 1\text{--}2 \text{ mm}$ in diameter, which are interconnected into a three-dimensional network. The network is submerged into ECM that provides a supporting stroma to myocytes (Young and Hession 1999; Blanks et al. 2007).

Myometrial cells acutely adjust their structure and function by reorganizing the cytoskeleton and altering signaling pathways (Salomonis et al. 2005). Thus, hypertrophic changes in pregnant uterus are associated with remodeling of ECM from

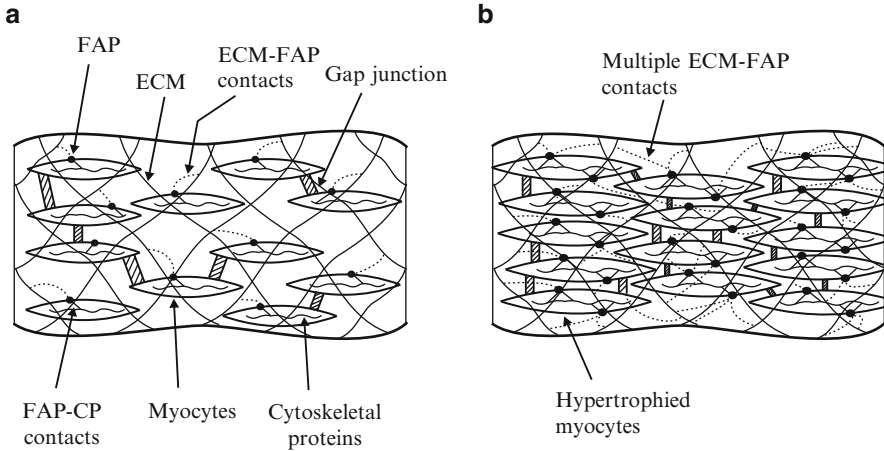


Fig. 1.2 Structure of myometrium in a nonpregnant (a) and pregnant (b) uteri

a fibrillar to sponge-like architecture (Gunja-Smith and Woessner 1985; Leppert and Yu 1991; Metaxa-Mariatou et al. 2002). Activation of integrin and fibronectin proteins promotes the development of new cell-matrix contacts and formation of the mesh-like fine fibrillar matrix on the cell surface and their cytoplasmic domains attach to cytoskeletal proteins (CP) (Williams et al. 2005; Robinson et al. 2004; Woodward et al. 2001; Shynlova et al. 2007) (Fig. 1.2). Such changes ensure myometrial homogeneity and affirm even stress-strain distribution in the tissue.

The contractile apparatus of myocytes consists of thin-actin and thick-myosin filaments, a family of special proteins and kinases, e.g., light chain myosin, tropomyosin, calmodulin, *h*-caldesmon, calponin, myosin light chain kinase, and myosin phosphatase. Actin filaments are single helical coils of actin associated with tropomyosin and caldesmon. Myosin filaments are made out of two coil rod-like structure heavy chains with a globular head domain. A principal determinant of the dynamics of contractions is free cytosolic calcium (Ca_i^{2+}) that triggers the cyclic actin-myosin complex formation. Two types of contractions – tonic and phasic – are produced by the myometrium. Thus, in the late phase of labor and immediately after delivery the myometrium produces tonic contractions. During delivery, though, it undergoes intensive phasic contractions.

1.3 Electrophysiological Properties

Myometrial contractions are driven by waves of electrical activity. The electrical repertoire of myocytes depends on balanced function of plasma-lemmal ion channels. Composed of discrete transmembrane proteins, they allow for the selective transfer of ions across the cell membrane. L- and T-type Ca^{2+} , Ca^{2+} -activated

K^+ , voltage-dependent K^+ and Na^+ , and Cl^- channels reflect the multiplicity and complexity of mechanisms involved in the regulation of uterine excitability and contractility. The presence of L-type Ca^{2+} channels in the human uterus has been confirmed by electrophysiological, pharmacological, and molecular studies (Young et al. 1993; Parkington and Coleman 2001; Chien et al. 1996; Collins et al. 1996; Mershon et al. 1994). They are formed of five distinct subunits: α_1 , α_2 , β , δ , and γ . The α_1 -subunit contains the channel pore, voltage sensor and drug binding sites, while α_2 , β , δ and γ -subunits modulate the channel's activity. L-type channels possess characteristics of long-lasting, high-voltage activated channels. They ensure the main influx of extracellular calcium ions, Ca_0^{2+} , during depolarization.

Three subfamilies of T-type Ca^{2+} channels, which differ in α -subunits, have been identified by cloning technique in human myocytes. They have distinct activation/deactivation kinetics: they are activated at low voltage and remain open for a short period of time (Young and Zhang 2005; Monteil et al. 2000; Lee et al. 1999). Experimental data suggest that T-type channels are responsible for the generation of spikes and pacemaker activity, and play a key role in regulation of the frequency of phasic contractions (Lee et al. 2009a, b).

Potassium channels constitute a superfamily of five channels: the large Ca^{2+} -activated K^+ (BK_{Ca}), intermediate (IK_{Ca}), small conductance (SK_{Ca}), voltage-gated (K_v), and ATP-sensitive (K_{ATP}) potassium channels. The channels are associated with caveolin-1, lipid rafts, and scaffolding proteins. They are located in invaginations of the cell membrane – caveolae (Brainard et al. 2005). The BK_{Ca} channel is made of six transmembrane proteins. The two distinct α - and β -subunits regulate channel's sensitivity to Ca^{2+} . They remain uncoupled at low $[Ca_i^{2+}]$ and switch to a calcium sensor mode with the rise in intracellular calcium. It has been proposed that the up-regulation of BK_{Ca} channels during pregnancy is the major factor that sustains quiescence and relaxation of the uterus (Korovkina et al. 2006).

Two types of K_v channels are identified in human myocytes: delayed rectifying and rapidly inactivating. They are formed by a single unit of six transmembrane proteins and the pore-hairpin loop (Jan and Jan 1994). Electrophysiological studies confirmed that channels are responsible for repolarization and slow wave generation in myometrium.

Data on kinetics and dynamics of K_{ATP} and SK_{Ca} channels are limited. There is no compelling experimental evidence to support their existence in the human myometrium. Even if they are present, their density is expected to be relatively low. Their overall effect is the maintenance of the resting membrane potential at a constant level and inhibition of phasic uterine contractions. Modulation and function of these channels during pregnancy has not been fully studied.

The expression of the two voltage-gated Na^+ channels has been reported in the human uterus (Young and Hendon-Smith 1991). Their role in gestation and labor is still a matter of debate. It has been proposed that the current facilitates and augments the propagation of the wave of excitation and synchronizes contractions.

The distinct role of Cl^- channels is unclear due to the uncertainty of their molecular identity (Adaikan and Adebisi 2005; Hartzell et al. 2005). Calcium-activated chloride currents have been recorded on the isolated uterine smooth

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