Uterine physiology

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Abstract

The role of the uterus is to nurture the fetus until parturition. Functionally it consists of a lower cervix (which acts at different times as a passageway, a barrier and a reservoir) and an upper body in which the fetus develops.

Keywords Endometrium; myometrium; nitric oxide; oestrogen; progesterone; prostaglandins; sympathetic and parasympathetic nervous system; uterus

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Learning objectives

After reading this article, you should know the:

- general anatomy of the uterus, including its layers, histology and nerve supply
- contractile properties of the myometrial muscle cells and hormonal regulation of these
- changes in the anatomy and physiology that occur during the course of pregnancy
- changes in the cervix just prior to parturition
- changes in hormonal status and myometrial function associated with parturition, it being noted that humans and animal models might differ in some details
- role of drugs in altering uterine contractility, and their role in promoting or delaying childbirth

Anatomy

The superior part of the uterus is called the fundus; on either side of this, the uterus communicates with the fallopian tubes at the cornua (Figure 1). It is connected to and supported at its lower end by a number of ligaments connected to the bladder, the rectum and the walls of the pelvis. Some of these are peritoneal folds, others consist of unstriped muscle and fibrous tissue. The two broad ligaments pass from the margins of the uterus to the lateral wall of the pelvis. In 80% of women, the uterus tilts up towards the abdominal wall, in 20% it is retroverted, tilting back into the pelvis.

The uterus has three layers (serosa, myometrium and endometrium). The serosa is formed by peritoneum. The muscular coat or myometrium is the middle layer and is composed of smooth muscle with areolar tissue, blood and lymph vessels and nerves. It is arranged in three distinct layers and the muscle fibres hypertrophy in pregnancy. The muscle of the uterus is not an anatomical syncytium like the heart, but in late pregnancy it forms a functional syncytium by the electrical coupling of the branching bundles of cells at gap junctions which greatly increase in number towards term. The formation of gap junctions is stimulated by the rise in the oestrogen/progesterone ratio (see later). The cervix is a more collagenous structure with a muscle content of only 10–15%. This gives it the capacity to undergo profound tissue remodelling during pregnancy and labour and to return to its former state after parturition. The endometrium or inner layer of the uterus is lined by columnar epithelium. It contains many tube-like glands that open into the uterine cavity and secrete mucus.

The uterus is supplied by the uterine branch of the internal iliac artery; it anastomoses with the ovarian artery (a branch of the aorta) and inferiorly with vessels of the upper vagina. The arteries supplying the uterus are remarkable for their tortuous course within the substance of the organ. The lymphatic drainage from the body of the uterus goes to the pelvic nodes, but lymph from the upper part drains to the para-aortic nodes. Occasionally, infection or malignancy may spread to the inguinal nodes.

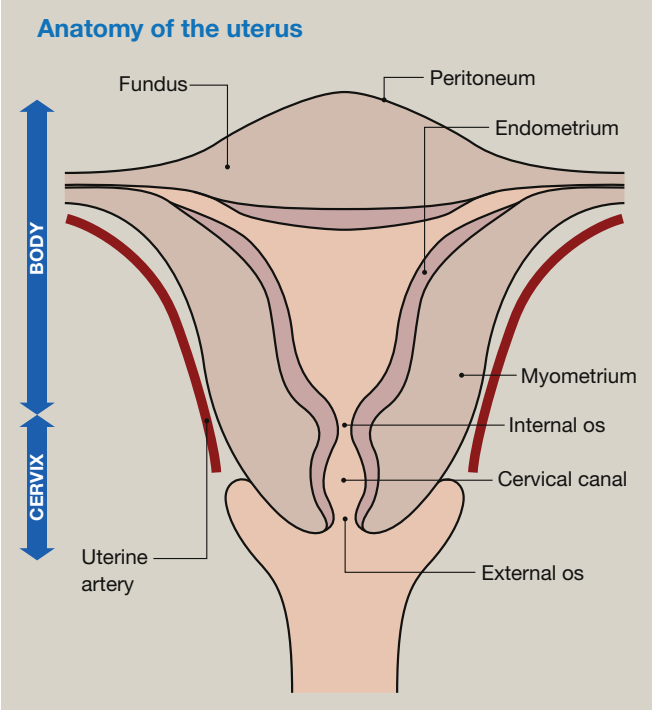

Figure 1

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Nerve supply

The nerve supply to the uterus is via autonomic pathways (Figure 2): the body is supplied predominantly by sympathetic fibres from T10–L1, the cervix by parasympathetic pathways from the sacral outflow S2–S4. The sympathetic nerves pass via the superior hypogastric plexus; this is formed from the union of branches from the aortic plexus and the third and fourth splanchnic nerves and lies in front of the abdominal aorta. It gives off branches to the ovarian plexus and then divides below into the right and left hypogastric nerves. These lie in the extraperitoneal connective tissue before passing into the pelvis where they are joined by parasympathetic fibres from the pelvic splanchnic nerves and a few fibres from the sacral sympathetic ganglia to form the inferior hypogastric plexus that lies on the front of the sacrum. Branches from this plexus are distributed to the pelvic viscera either directly or accompanying the branches of the internal iliac artery.

The uterine nerves come from the inferior hypogastric plexus, predominantly from the part that lies in the base of the broad ligament of the uterus and is known as the uterovaginal plexus. They pass directly to the uterus and upwards with the uterine artery in the broad ligament. They communicate with branches of the tubal nerve and nerves of the ovarian plexus. Branches of the uterine nerves ramify in the myometrium and endometrium, most of them accompanying blood vessels. Some nerves from the uterovaginal plexus pass to the uterine cervix. The ovarian plexus is formed from branches of the renal and aortic plexuses. It accompanies the ovarian artery and is distributed to the ovary and fallopian tube.

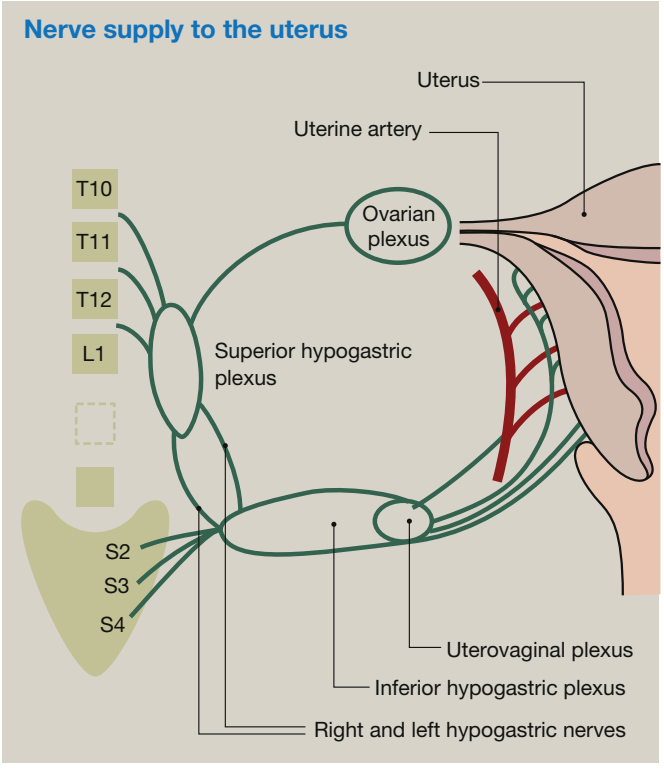

Figure 2

Motor function: While sympathetic activation normally produces uterine contraction and vasoconstriction, and parasympathetic activity produces uterine inhibition and vasodilatation, these actions, particularly in pregnancy and parturition, are complicated by the hormonal control of uterine function (see later).

Sensory function: Pain fibres from the body of the uterus pass centrally to T10–L1 in the sympathetic nerves via the superior hypogastric plexus and the lumbar splanchnic nerves. Afferent pain fibres from the cervix pass via the parasympathetic nerves S2–S4.

Physiology

Myometrial contractility

Growth and activity of the uterus are largely under hormonal control. In broad terms, oestrogen stimulates myometrial activity, the muscle becomes more active and excitable and action potentials in the individual fibres more frequent. An 'oestrogen primed' uterus is also more sensitive to oxytocin. Progesterone on the other hand depresses the excitability of the uterine musculature, decreasing spontaneous electrical activity and sensitivity to oxytocin. During the normal menstrual cycle, circulating oestrogens are at their highest immediately before ovulation, increasing the motility of the uterine tubes and thus potentially aiding conception. Progesterone is secreted by the ovary in the second half of the menstrual cycle and, by depressing uterine activity, potentially aids implantation. Uterine contractions during menstruation are stimulated by prostaglandin.

In pregnancy, the uterus increases from 30–60 g to 750–1000 g owing to hyperplasia and hypertrophy of the myometrium, largely under the influence of oestrogens. Muscle cell size increases from 50 to 500 μm, glycogen is laid down and there is an increase in adenosine triphosphate (ATP). Muscle contraction is induced by intracellular liberation of calcium from intracellular stores and from extracellular fluid. Spontaneous depolarizing pacemakers occur and if these exceed a critical threshold a sharp increase in intracellular calcium is seen and a contraction follows. Contractility can therefore be modulated by changing pacemaker potentials and the threshold for contraction. Prostaglandins enhance the liberation of intracellular calcium and oxytocin lowers the excitation threshold for contraction.

Cervical 'ripening'

In order for the fetus to be expelled the collagenous nature of the cervix changes or 'ripens'. There is a reduction in collagen and an increase in glycosaminoglycans (mucopolysaccharides). These are complex carbohydrates with a high amino sugar content. They have a high water content and occupy space, cushioning and lubricating. There is an influx of inflammatory cells and proinflammatory cytokines rise. The inducible form of nitric oxide synthase (iNOS) rises as does nitric oxide output. The pharmacological inhibition of iNOS prevents ripening. Prostaglandins also affect cervical ripening; both PGE_2 and $PGF_{2\alpha}$ increase the compliance of the cervix when given intravaginally or intracervically.

Parturition

During pregnancy prostaglandin synthesis is inhibited, but at parturition this inhibition is lifted and prostaglandins are

synthesized and released, principally by the endometrium, but also by the myometrium, cervix, placenta and fetal membranes. This occurs because of alterations in the stability of membrane binding phospholipase A2 and the consequent production of arachidonic acid. Oestrogens promote phospholipase A2 production and progesterone inhibits it. Thus a rise in the oestrogen:progesterone ratio results in an increase in prostaglandin synthesis and release. Oestrogen also increases the number of myometrial oxytocin receptors and oxytocin stimulates the release of prostaglandin directly. A rising oestrogen:progesterone ratio is also responsible for induction of iNOS activity. Release of oxytocin from the posterior pituitary is produced by tactile stimuli from the reproductive tract. In addition to myometrial contraction it contributes to cervical softening in interactions with oestrogen/progesterone, prostaglandins and possibly nitric oxide. This is known as the Ferguson reflex and is facilitated by a high oestrogen:progesterone ratio.

In animals, the pattern of change and the role of these various 'hormones' are well described. A decrease in progesterone is brought about by regression of the corpus luteum, which produces progesterone. Luteal regression is induced by $PGF_{2\alpha}$ produced by the placenta, which in turn is dependent on an increased output of glucocorticoids produced by the fetal adrenal cortex. Fetal corticosteroids also induce oestrogen release by the fetal adrenal cortex and these enhance the placental production of $PGF_{2\alpha}$. Thus the oestrogen:progesterone ratio is increased, the 'block' on the myometrium is removed and the myometrial contractions commence, reinforced by oxytocin release induced by the Ferguson reflex. In some animals the main site of progesterone production is the placenta.

The precise mechanisms surrounding the induction of parturition in the human are less certain. Maternal progesterone does not generally fall at parturition but the fetal adrenal gland stimulates placental oestrogen synthesis via secretion of androgen precursors from a specialized zone of the fetal adrenal cortex, which regresses soon after birth. They form the major substrates for oestrogen synthesis by the placenta. In humans the onset of labour does not appear to be critically dependent on any consistent alterations in oestrogen synthesis, though this does not rule out the possibility of alterations in binding or local tissue concentrations. Likewise elevations in circulating $PGF_{2\alpha}$ concentrations have not been consistently described in humans in advance of labour though they do rise in amniotic fluid and increase as labour progresses. Myometrial oxytocin receptors increase, even in the absence of changes in the oestrogen:progesterone ratio.

Pharmacology

A number of drugs affect uterine function, both directly and indirectly. Some are used in the management of labour (sympathomimetics, prostaglandins) and others have effects that are usually regarded as undesirable (inhalational anaesthetic agents). Prostaglandins are used to induce abortion and are administered intravaginally. α-Sympathomimetics (e.g. ergotamine, ergometrine) produce smooth muscle contraction. They cause the uterus to contract and are used in the control of uterine bleeding, both postpartum and following incomplete abortions. Syntocinon is a synthetic oxytocin. On the other hand, the β_2-sympthomimetics (terbutaline, salbutamol) produce smooth muscle relaxation and are used to delay the onset of labour. Inhalational anaesthetic agents depress smooth muscle contraction and given at concentrations in excess of 1 minimum alveolar concentration (MAC) can result in uterine haemorrhage. At less than 0.5 MAC they probably have little effect. The use of spinal epidural local anaesthetics and/or opiates, or opiates administered systemically can affect the progress of labour, but have no direct effect on the uterine musculature. ◆

FURTHER READING

Johnson MH. Essential Reproduction. 8th edn. Wiley-Blackwell, 2018.

