Chapter Twelve

Vaginal and Intrauterine Drug Delivery

ANATOMY AND PHYSIOLOGY

The word vagina means sheath and it is a fibromuscular tube between 6 and 10 cm long in a adult female extending from the cervix (outer end) of the uterus (Figure 12.1). The vagina lies obliquely upward and backward behind the bladder and urethra and in front of the rectum and anal canal. The axis of the vagina forms an angle of over 90° with that of the uterus, but this can vary considerably depending on the fullness of the bladder and rectum, and during pregnancy. The cervix of the uterus extends for a short distance into the vagina. It is normally pressed against its posterior wall creating recesses in the vagina at the back, on each side, and at the front of the cervix. These are known as the anterior and posterior fornices located to the front and back of the cervix. The posterior fornix is the largest of the fornices and the lateral fornices found to the sides. The upper part of the posterior wall of the vagina is covered by peritoneum which is folded back onto the rectum to form the rectouterine pouch. The lower part of the posterior vaginal wall is separated from the anal canal by tissue known as the perineal body.

In female mammals the function of the vagina is to receive the male reproductive cells, or sperm, and is part of the birth canal. In humans, it also functions as an excretory canal for the products of menstruation.

The uterus or womb is a hollow, inverted pear-shaped fibro-muscular organ. Its shape and weight varies enormously depending on menstrual cycle and previous pregnancies. In a young female, with no previous pregnancies, the uterus is approximately 8 cm long, 5 cm wide and 2.5 cm thick and weighs approximately 30–40 g but it enlarges to four to five times this size in pregnancy.

The narrower, lower end is called the cervix; this projects into the vagina. The cervix is made of fibrous connective tissue and is of a firmer consistency than the body of the uterus. The two uterine tubes enter the uterus at opposite sides, near its top. The part of the uterus above the entrances of the tubes is called the fundus; that below is termed the body.

Between birth and puberty, the uterus gradually descends into the true pelvis from the abdomen. After puberty, the uterus is located behind the symphysis pubis and bladder and in front of the rectum. The uterus is supported and held in position by the other pelvic

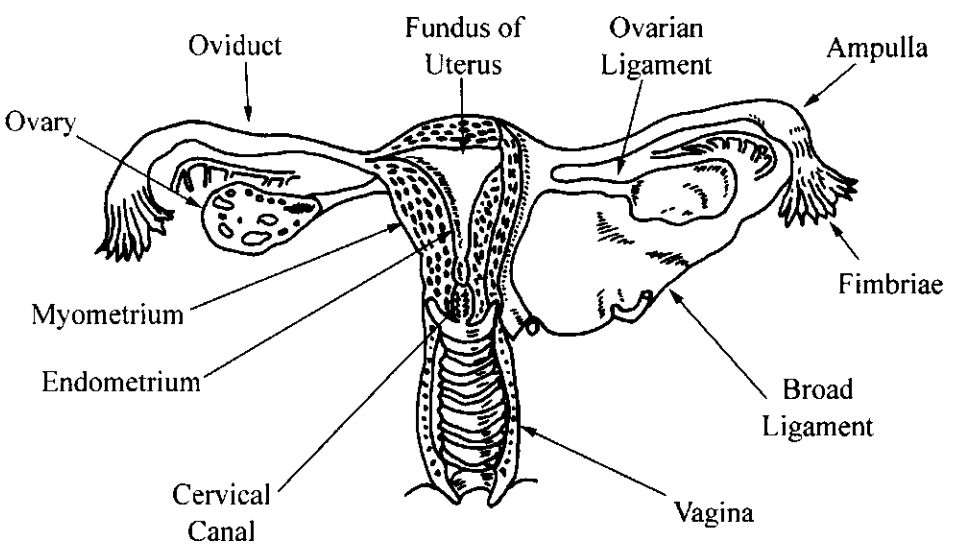

Figure 12.1 The female reproductive system

organs, the muscular floor or diaphragm of the pelvis, certain fibrous ligaments, and by folds of peritoneum. Among the supporting ligaments are two double-layered broad ligaments, each of which contains a uterine tube along its upper free border and a round ligament. Two ligaments at each side of the cervix are also important in maintaining the position of the uterus.

The triangular cavity of the uterus is remarkably flat and small in comparison with the size of the organ, except during pregnancy. The function of the uterus is to protect and nourish the embryo and foetus. At term, its thick muscular walls contract powerfully to expel the infant through the vagina.

Mucosa

The vagina has a mucous membrane comprised of stratified squamous epithelium. This has longitudinal ridges, known as the columns of the vagina, in the midline of both the anterior and posterior walls. Folds or rugae extend from them to each side. The furrows between the rugae are more marked on the posterior wall and become especially pronounced before birth of a child.

The vaginal epithelium consists of 5 layers, basal, parabasal, intermediate, transitional and superficial, however the changes between layers are gradual (Figure 12.2). Attachment of the cells is primarily by desmosomes with some tight junctions.

Attached to the mucous membrane is an outer smooth muscle coat consisting of an outer longitudinal layer and a less developed inner circular layer (Figure 12.3). The lower part of the vagina is surrounded by the bulbospongiosus muscle, a striped muscle attached to the perineal body. Covering the muscle tissue is a sheath of connective tissue which consists of blood vessels, lymphatic ducts, and nerve fibres. This layer joins those of the urinary bladder, rectum, and other pelvic structures.

The cervical canal is lined with columnar mucous secreting epithelium which are thrown into a series of V-shaped folds. Its wall, comprised mainly of dense fibrous connective tissue, only has a small amount of smooth muscle.

The uterus is composed of three layers of tissue. On the outside is a serous coat of peritoneum which partially covers the organ, exudes a fluid like blood minus its cells and the clotting factor fibrinogen. In front it covers only the body of the cervix; behind it covers

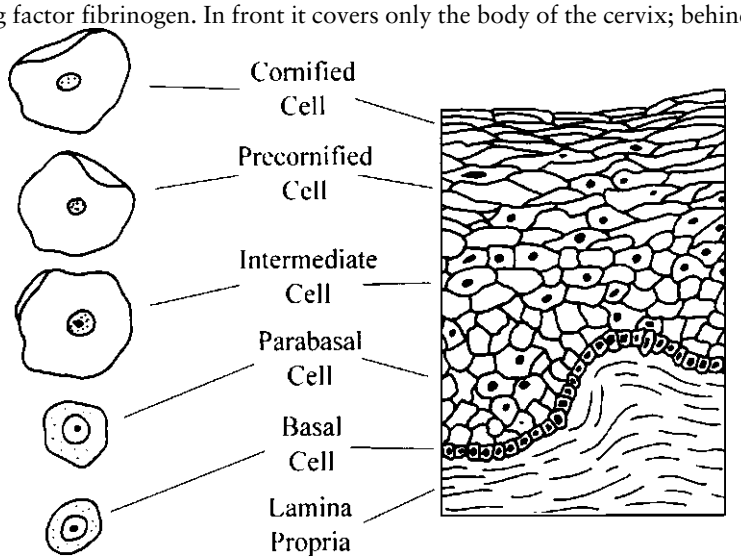

Figure 12.2 Cross section through the vaginal mucosa

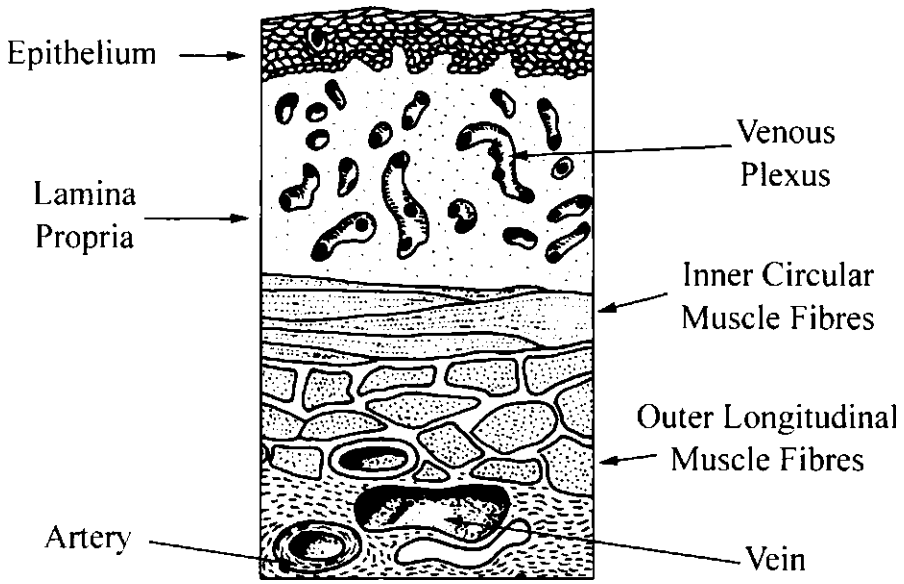

Figure 12.3 Cross section through the vaginal wall

the body and the part of the cervix that is above the vagina and is prolonged onto the posterior vaginal wall; from there it is folded back to the rectum. The middle layer of tissue, the myometrium, is muscular and makes up the majority of the organ. It is very firm and consists of densely packed, unstriped, smooth muscle fibres with blood vessels, lymphatics, and nerves. The muscle is arranged in three layers of fibres running in different directions. The outermost fibres are arranged longitudinally. Those of the middle layer, which is the thickest, run in all directions without any orderly arrangement. The innermost fibres are longitudinal and circular in their arrangement.

The innermost layer of tissue in the uterus is the mucous membrane, or endometrium. It lines the uterine cavity as far as the internal os, where it becomes continuous with the lining of the cervical canal. The endometrium contains numerous uterine glands that open into the uterine cavity and that are embedded in the cellular framework or stroma of the endometrium. Numerous blood vessels and lymphatic spaces are also present. The appearance of the endometrium varies considerably at the different stages in reproductive life. It begins to reach full development at puberty and thereafter exhibits dramatic changes during each menstrual cycle. It undergoes further changes before, during, and after pregnancy; during the menopause; and in old age. These changes are for the most part hormonally induced and controlled by the activity of the ovaries. The endometrium is divided into three layers, the stratum compactum, the stratum spongiosum, and the stratum basale, which are functionally distinct, but blend together. The stratum compactum is nearest to the uterine cavity and contains the lining cells and the necks of the uterine glands; its stroma is relatively dense. Superficial blood vessels lie beneath the lining cells. The stratum spongiosum is the large middle layer and it contains the main portions of uterine glands and accompanying blood vessels; the stromal cells are more loosely arranged and larger than in the stratum compactum. The stratum basale lies against the uterine muscle; it contains blood vessels and the bases of the uterine glands. Its stroma remains relatively unaltered during the menstrual cycle.

Blood and nerve supply

The blood supply to the vagina is derived from several adjacent vessels, a vaginal artery extends from the internal iliac artery, uterine, middle rectal, and internal pudendal arteries. As the vagina is not structurally related to the gastrointestinal system, the drainage avoids the liver and hence is not subject to first pass metabolism. The blood vessels are located close to the basal epithelial layer, but pores are present in the endothelial cells lining the capillaries through which an interchange of blood and vaginal fluid constiuents can occur. The channels in the basal, parabasal and intermediate levels change width depending upon hormonal levels, expanding to their maximum width during ovulatory and luteal phases. Molecules as large as albumin and immunoglobulins are able to pass from the blood to the lumen.

The nerve supply to the lower part of the vagina is from the pudendal nerve and from the inferior hypogastric and uterovaginal plexuses.

The uterus is supplied with blood by the two uterine arteries, which are branches of the internal iliac arteries, and by ovarian arteries, which connect with the ends of the uterine arteries and send branches to supply the uterus. The nerves to the uterus include the sympathetic nerve fibres, which produce contraction of uterine muscle and constriction of vessels, and parasympathetic (sacral) fibres, which inhibit muscle activity and cause dilation of blood vessels.

Uterine and vaginal fluid

The vagina does not possess any glands except Bartholin's and Skene's glands, but these are not believed to contribute significantly to the vaginal fluid. The fluid consists mainly of cervical secretions and transudation from the blood vessels with desquamated vaginal cells and leucocytes. The fluid will also contain secretions from the endometrium and fallopian rubes. The amount and composition of fluid will vary with the menstrual cycle, but women of reproductive age produce about 1 $g.h^{-1}$, but post-menopausal women produce only about half this much.

Cervical secretions originate both in the uterine cavity and the cervix and they flow constantly towards the vagina. During ovulation, the secretions are watery to facilitate the movement of spermatozoa. In response to increased levels of progesterone during the luteal phase of the menstrual cycle, or during pregnancy, the secretions become more viscous to prevent the passage of microorganisms and sperm into the body of the uterus.

pH

The Lactobacillus acidophilus present within the vagina produce lactic acid from glycogen to maintain the pH at between 4.9 and 3.5 which has a bacteriostatic action. The anterior fornix has the lowest pH, which gradually rises towards the vestibule.

At birth, there is passive transfer of maternal hormones and Lactobacilli which are present for the first 4 weeks of life. Consequently vaginal pH is low and after the concentration of hormones has receded, the pH rises to 7 where it remains until puberty. This high pH is associated with an increased risk of infection[1].

In post-puberty women, the pH can be raised during menstruation, but also it can increase after periods of frequent acts of coitus because both vaginal transudate and ejaculate are alkaline. Acidity can also be decreased by alkaline secretion of the cervical glands. During pregnancy the mean vaginal pH isapproximately 4.2.[2].

Cervical bacterial flora in sexually active healthy women using oral contraceptives or intrauterine contraceptive devices is rich in anaerobes, however, barrier contraception with a condom prevents this anaerobic shift and maintains a lactobacilli-dominated flora in the cervix[3].

Enzymatic activity

The outer cell layers of the vagina contain ß-glucuronidase, acid phosphatase, with smaller amounts of a-naphthylesterase, DPNH diaphorase, phosphoamidase and succinic dehydrogenase. Basal cell layers contain ß-glucuronidase, succinic dehydrogenase, DPNH diaphorase, small amounts of acid phosphatase and a-naphthylesterase.

Alkaline phosphatase, lactate dehydrogenase, aminopeptidase and esterase activity are all markedly elevated in the follicular phase of the menstrual cycle, but fall immediately prior to ovulation[4]. Their activity begins to rise again one day after ovulation.

Mucus

Mucus is secreted by endocervical glands and its production is oestrogen dependent. It is minimal immediately after menstruation, but during the pre-ovulation stage, the raised oestrogen increases mucus production. The mucus also becomes more transparent, viscous and elastic reaching a maximum just before ovulation which lasts approximately 2 days post-ovulation.

Menstruation

The menstrual cycle lasts approximately 28 days and it can be divided into 4 phases: the follicular, ovulatory, luteal and menstrual phases. The phases equate to repair, proliferation, secretion and menstruation. Repair begins even before menstruation has completely ceased. During the follicular or proliferative phase, the oestradiol levels increase, resulting in the uterine epithelium increasing in thickness from 20 layers or 0.2 mm to over 40 layers during the ovulatory phase (Figure 12.4). The major feature of the proliferative phase is the increase in ciliated and microvillus cells. The ciliogenesis begins on day 7–8 of the cycle. The stroma becomes becomes vascular and oedematous and a large number of cells including lymphocytes and macrophages derived from bone marrow are present in the endometrium. Secretion takes place from days 16–28. In this phase the oestrogen levels drop and the levels of progesterone incrase and hence the effects become dominant. The drop in oestrogen can

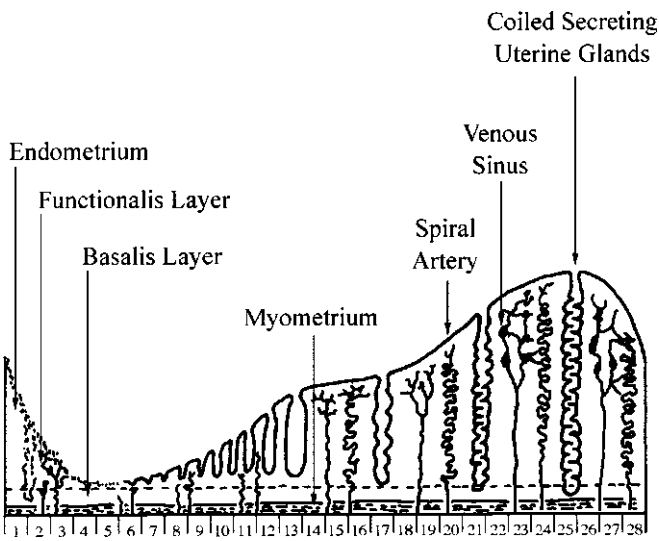

Figure 12.4 Effect of the menstrual cycle on the uterine epithelium

lead to the thickening of the endometrium being reduced and intermenstrual bleeding occurring. The endometrial glands produce a thick glycogen-rich mucoid secretion. There is an increase in vascularisation and the uterus is ready to receive an embryo. If implantation does not occur, the corpus luteum begins to degenerate, progesterone levels drop which causes the endometrium to breakdown. The coiled arterioles of the superficial layers of the outer endometrium contract thus depriving the superficial layers of oxygen, resulting in menstruation. Menstruation can last for anything up to about a week.

Menopause

The menopause is associated with a gradual change in the vagina which can take up to 5 to 8 years to stabilise. The length and the diameter decrease with age and the pH can rise to between 6 and 8 increasing the risk of infection. Elasticity and blood supply decrease with age and the upper vagina may atrophy. The epithelium becomes thinner which is an important consideration in intravaginal drug delivery since this would lead to an increased permeability. Vaginal secretions and hence lubrication decrease and become more watery. The levels of several enzymes increase, such as ß-glucuronidase, acid phosphatase and non-specific esterases, in postmenopausal women.

Disorders of the vagina

These include bacterial infections eg leukorrhea, vaginitis, ulcerated sores, prolapse in which the internal portions of the vagina protrude out of the vaginal orifice, and occasionally cancerous tumours. Rectocele is caused when the muscles and connective tissues supporting the rectum and back wall of the vagina are weakened, usually due to repeated childbirth or aging, and the rectum sags until it bulges into the back wall of the vagina. A rectocele often occurs together with enterocele, which is a bulge of the small intestine into the vagina. Women with small rectoceles or enteroceles may not feel much distress; a larger and more serious rectocele can cause discomfort and a sagging sensation in the pelvic area and difficulty in emptying the lower bowel. Both conditions can be corrected by surgery in which the small intestine and rectum are pushed back into place and held there by reconstructed pelvic muscles.

DRUG ABSORPTION THROUGH THE VAGINA/UTERUS

A wide range of drugs have been studied for vaginal absoprtion. These include steroid hormones such as progesterone and oestrogen, prostaglandins, iodides and salicylates[5], peanut proteins, bacterial antigens and poly vinyl alcohol (m. w. 25,000 Daltons)[6]. Insulin, hydrocyanic acid, iodides, strychnine, pilocarpine, atropine, quinine and oxyquinolone are rapidly absorbed from cat and dog vaginas[5]. Quinine and phenol red are absorbed slowly and methylene blue only in very small quantities.

A recently reported observation is that drugs administered intravaginally accumulate in uterine tissue. This has been reported for danazol, terbutaline and progesterone[7–9]. These findings have lead to the hypothesis that there is a direct transport mechanism from vagina to uterus or a "uterine-first pass effect"[9].

DRUG DELIVERY

Vaginal

Traditionally, vaginally drug delivery was only used for contraceptive agents and also for treatment of local infections. Recently its potential for delivering peptides has been explored since it is vascular, permeable to many drugs[5] and drugs absorbed via this route avoid first-pass metabolism.

A major problem with using the vagina as a route for systemic drug delivery is that as the epithelium is highly sensitive to oestradiol and its thickness changes throughout the menstrual cycle, so the extent and rate of drug absorption will also vary. This has been reported for vaginal absorption of steroids[10] and vidarabine has been shown to have a 5–100 times higher permeability coefficient during the early dioestrus stage than during the oestrus stage in guinea pigs[11]. Other problems are gender specificity, personal hygiene and the influence of sexual intercourse.

The thick cervical mucosa may aid bioadhesion of drug delivery systems, but it will also act as a diffusional barrier to the drug. The distribution and coverage of materials within the vagina varies considerably with the nature of the delivery system, disintegrating tablets spread the least, whilst solutions, suspensions and foams spread the best. The rupture time of soft jelly capsules containing nonoxynol-9 after its vaginal insertion found to rely on local pH and acidity and level of infection present. Capsules did not rupture when the vaginal pH was alkaline of if the vagina was dry[12].

Creams and gels

Creams and gels have been the usual methods for delivering contraceptives and drugs for topical delivery. These are generally considered to be messy to apply and uncomfortable when they leak into undergarments; in addition, dosages are imprecise.

An emulsion based system to deliver anti-fungals seems to have great advantages over many current suppository formulations. It is a "multi-phase" liquid, or semi-solid and it does not seep from the vagina. The system is designed to give controlled delivery for 3 or more hours.

Pessaries or tablets

Pessaries can be either tablets or suppositories designed for vaginal application. They are usually designed to either dissolve or melt and which utilize a variety of materials. Tablets are often modifications of suppositories used for rectal drug delivery.

Intravaginal inserts consisting of a polyester resin plug or sponge have been tried[13], but traumatic manipulation of the sponge, use during menstruation or the puerperium, and prolonged retention of the sponge may increase toxic shock syndrome risk[14]. The use of osmotic pumps has also been investigated[15].

Vaginal rings

Vaginal ring delivery systems are usually based upon silicone elastomers with an inert inner ring which is coated with another layer of elastomer containing drug. A third, outer rate controlling elastomer layer may be added to prevent an initial burst release which could be observed with newly applied rings.

The rings are approximately 6 cm in diameter with a circular cross-section diameter of 4–7 mm. They are positioned in the vagina around the cervix. For most contraceptive applications, the rings are left in place for 21 days then removed for 7 days to allow menstruation. The main challenge is to deliver enough drug to prevent conception, whilst not producing bleeding irregularities. Since their development in 1970, they have been used to deliver medoxyprogesterone acetate, chlormadinone acetate, norethindrone, norgestrel and levonorgestrel, among others. A low dose oestradiol vaginal ring has been found to be significantly more acceptable than creams for the treatment of urogenital atrophy[16]. Recently, a contraceptive ring has been developed containing oestrogen and progestin particles dispersed in aqueous polyethylene glycol throughout the ring. It successfully delivers both drugs, at a consistent ratio with approximately zero-order kinetics.

Bioadhesive delivery systems

Bioadhesive tablets and microparticles in particular hydrogels such as poly (acrylic acid) and celluloses are currently being utilised for sustained and controlled delivery[17]. The first bioadhesive tablets contained hydroxypropylcellulose and polyacrylic acid and were used to treat cancerous lesions with bleomycin.

A bioadhesive polycarbophil gel, a lightly cross-linked polyacrylic acid, used to retain moisture and lubricate the vagina has recently been introduced onto the market (Replens, Columbia Laboratories). Clinical assessment of local tissue pH, in postmenopausal women, shows the polycarbophil gel produces a reduction in pH from about 6 to 4 and maintains the acidic pH for about 3–4 days after the last dose. Hydration of the vaginal tissue occurs through an increase in vaginal blood flow as determined by a laser Doppler measurement. In patients with a history of breast cancer who experienced vaginal dryness, vaginal irritation, or dyspareunia, the polycarbophil gel produced a statistically significant reduction in mean vaginal pH and an improvement in vaginal moisture, mucosa secretions, and elasticity scores, as well as significant improvement in vaginal health measures[18].

The polycarbophil gel has been shown to remain on vaginal tissue for 3–4 days and hence has the potential to serve as a platform for drug delivery[19]. It appears to be an effective delivery system for the spermicidal/antiviral agent nonoxynol-9.

Intrauterine Devices

Intrauterine devices (IUDs) have been used for many years as a method of contraception. They are first described in 1909 by Richter[20] who used a ring made of silkworm gut. In 1930, Graefenberg also used silkworm gut but added an alloy of copper, nickel and zinc[21].

As a result of the long history of using IUDs, it is not surprising, therefore that intrauterine delivery has focused upon the use of medicated intrauterine devices. Newer IUDs have been constructed which contain copper or progesterone. Copper containing IUDs release some copper continuously whilst in situ. There was some concern about systemic absorption of copper with long term use, however this was not found to occur. The copper remains mainly in the uterine fluid which is thought to render it unabsorbable and only small quantities are found in the endometrium. Itching or allergic dermatitis, possibly due to absorption of copper into the circulation has been reported some months after insertion of the device. The concept of using conventional IUDs for the long-term delivery of contraceptive steroids is also being researched. The Progestasert IUD delivers progesterone at about 65 $\mu g.day^{-1}$ over 1 year. The drug reservoir contains 38 mg of progesterone dispersed in silicone oil surrounded by a release rate controlling mechanism composed of ethylene-vinyl acetate copolymer. The greatest advantage of this system is that it eliminates the need for oestrogen which is required in oral contraceptives. Progesterone's half-life is only a few minutes since the endometrium metabolizes progesterone rapidly and the local delivery allows reduction of the dose and reduction in side effects.

The uterine wall is permeable to negatively charged molecules, high molecular weight drugs and its permeability is not affected by the degree of ionization of the compound[22]. This observation has lead to speculation that the tight junctions in the uterine wall are more permeable than those in other tissues. The size of the tight junctions in the uterus is between 400 and 700 Å, which is about twice that in the intestine or nasal mucosa. Absorption is facilitated by the exceptionally rich blood and lymph supply to the uterus. One possible drawback is that the constant outward flow of cervical secretion can dilute and cause a loss of drug delivered into the uterus.

Intrauterine delivery of insulin, calcitonin and erythrpoietin has been investigated in rats, but no human data is yet available[22]. It has been suggested that this route may be useful for delivering drugs to treat conditions such as osteoporosis.

Introduction of a foreign body into the uterine cavity results in increased vascular permeability, oedema and stromal infiltration of leucocytes, including neutrophils, mononuclear cells and macrophages. The foreign-body reaction should not be confused with endometritis which is bacterial in origin. Complications which have arisen from IUD use include uterine perforation, abortion of unsuspected pregnancies, uterine cramp and bleeding, menorrhagia and pelvic infections.

CONCLUSION

Vaginal delivery has the advantage that self-insertion and removal of delivery devices is possible. This route does avoid first-pass metabolism, but the mucosa is not as permeable as the uterus to peptides and proteins and the variability in bioavailability is too high to be used clinically. In contrast, the uterus appears to be very permeable to a wide variety of substances, but insertion and removal of devices has to be performed by medically qualified personnel. Possible consequences of pregnancy occurring whilst the devices are in situ has to be studied thoroughly since the local concentration of the drug is likely to be high. Drugs absorbed from the uterus also avoid first-pass metabolism.

REFERENCES

1. Hanna NF, Taylor-Robinson D, Kalodiki-Karamanoli M, Harris JR, McFadyen IR. The relation between vaginal pH and the microbiological status in vaginitis. *Br. J. Obstetr. Gynaecol.* 1985; 92:1267–1271.
2. Gleeson RP, Elder AM, Turner MJ, Rutherford AJ, Elder MG. Vaginal pH in pregnancy in women delivered at and before term. *Br. J. Obstetr. Gynaecol.* 1989; 96:183–187.
3. Haukkamaa M, Stranden P, Jousimies Somer H, Siitonen A. Bacterial flora of the cervix in women using different methods of contraception. *Am. J. Obstetr. Gynaecol.* 1986; 154:520–524.
4. Blackwell RE. Detection of ovulation. *Fertil. and Steril.* 1984; 41:680–681.
5. Aref I, El-Sheikha Z, Hafez ESE. *Absorption of drugs and hormones in the vagina*. New York: North Holland Publishing Co., 1978.
6. Richardson JL, Ilium L. Routes of delivery: case studies. The vaginal route of peptide and protein drug delivery. *Adv. Drug Deliv. Rev.* 1992; 8:341–366.
7. Mizutani T, Nishiyama S, Amakawa I, Watanabe A, Nakamuro K, Terada N. Danazol concentrations in ovary, uterus, and serum and their effect on the hypothalamic-pituitary-ovarian axis during vaginal administration of a danazol suppository. *Fertil. and Steril.* 1995; 63:1184–1189.
8. Kullander S, Svanberg X. On resorption and the effects of vaginally administered terbutaline in women with premature labour. *Acta Obstet. Gynecol. Scand.* 1985; 64:613–616.
9. Bulletti C, De Ziegler D, Giacomucci E, Polli V, Rossi S, Alfieri S, Vaginal drug delivery: the first uterine pass effect. *Ann. N.Y. Acad. Sci.* 1997; 828:285–290.
10. Richardson JL, Ilium L. The vaginal route of peptide and protein drug delivery. *Adv. Drug Deliv Rev.* 1992; 8:341–366.
11. Durrani MJ, Kusai A, Ho NFH. Topical vaginal drug delivery in the guinea pig. I. Effect of estrous cycle on the vaginal membrane permeability of vidarabine. *Int. J. Pharmaceut.* 1985; 24:209–218.
12. Bassol S, Recio R, de la Cruz DL. Comparative trial between two soft jelly capsules containing Nonoxynol as spermicidal contraceptives. *Contraception* 1989; 39:409–418.
13. Ahmad M, Asch RH. Study of the intravaginal insert (IVI): Acceptability, side effects, and post-coital spermicidal activity. *Acta Europaea Fertilitatis* 1984; 15:369–376.
14. Faich G, Pearson K, Fleming D. Toxic shock syndrome and the vaginal contraceptive sponge. *J. Am. Med. Assoc.* 1986; 255:216–218.

15. Amkraut A, Eckenhoff JB, Nichols K. Osmotic delivery of peptides and macromolecules. *Adv. Drug Deliv. Rev.* 1989; 4:255–276.
16. Ayton RA, Darling GM, Murkies AL, Farrell EA, Weisberg E, Selinus I. A comparative study of safety and efficacy of continuous low dose oestradiol released from a vaginal ring compared with conjugated equine oestrogen vaginal cream in the treatment of postmenopausal urogenital atrophy. *Br. J. Obstetr. Gynaecol.* 1996; 103:351–358.
17. Knuth K, Amiji M, Robinson JR. Hydrogel delivery systems for vaginal and oral applications, formulation and biological considerations. *Adv. Drug Deliv. Rev.* 1993; 11:137–167.
18. Gelfand MM, Wendman E. Treating vaginal dryness in breast cancer patients: Results of applying a polycarbophil moisturizing gel. *J. Women's Health* 1994; 3:427–434.
19. Robinson JR, Bologna WJ. Vaginal and reproductive system treatments using a bioadhesive polymer. *J. Cont. Rel.* 1994; 28:87–94.
20. Richter R. Ein Mittel zur Verhutung der Konzeption (A means of preventing pregnancy). *Dtsch. Med. Wochenschr.* 1909; 35:1525–1527.
21. Graefenberg AE. An intrauterine contraceptive method. *In: The practice of contraception.* Proc. 7th Int. Birth control conference, Zurich, Switzerland, Sept 1930, Williams and Wilkins, Baltimore 1930:33–47.
22. Golomb G, Shaked I, Hoffman A. Intrauterine administration of peptide drugs for systemic effect. *Adv. Drug Deliv. Rev.* 1995; 17:179–190.