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INTRAVAGINAL DRUG DELIVERY

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INTRODUCTION

The vagina is an important area of the reproductive tract. The primary function of vagina is to receive and ensheath the penis during intercourse and thus afford the seminal fluid protective entrance through the external os of the cervix. A secondary function is fulfilled during parturition since the vagina is the lowermost part of the birth canal. A third function is that of an excretory duct for menstrual discharge. From the view point of a clinician, a fourth function is the opportunity this structure provides for examination of the internal genitalia. Thus the main functions of vagina are generally related to conception. We now know the anatomy and physiology of vagina in detail. The research efforts of various investigators have provided us with substantial knowledge regarding the microflora, hormones and secretions of vagina. Though we know that in general the pH of vagina is four to five, it is still not very clear by which mechanism this pH is maintained. Issues that must be considered in the development of pharmaceutical products for use in the vagina include the maintenance of an appropriate pH, drug release from the vaginal dosage form and patient acceptance. One should remember that vagina is not just a physiological organ. Therefore this review deals with not only anatomy and physiology of the vagina but also with psychological and social factors that play a

vital role in the use of vaginal products for a woman. It also describes the various vaginal products available and in vitro and in vivo tests for these products. This review has been divided into the following main sections :

1. Vagina
a) Anatomy
b) Physiology
2. Psychological and Sociological influences on the use of vaginal products
3. Dosage forms used for intravaginal applications
4. Tests performed on these dosage forms
a) In vitro
b) In vivo

1] VAGINA

1.1 Anatomy of the vagina

" In its entire length the vagina is located between the rectum and the urinary bladder - urethra. It is a strong canal of muscle approximately 7.5 cm long that extends from the uterus to the vestibule of the external genitalia, where it opens to the exterior. Along the entire length of the vagina, a comparatively thick layer of connective tissue is located between the anterior vaginal wall and the intestinal canal respectively. Towards its lower end, the vagina pierces the urogenital diaphragm and is surrounded by the two bulbocavernosus muscles and bodies, which act as a sphincter (sphincter vaginae). In the virginal state, an incomplete fold of highly vascular tissue and mucous membrane, the hymen, partially closes the external orifice(1) ".

The vaginal wall consists of three layers : the epithelial layer, the muscular coat, and the tunica adventitia. " The epithelium is a noncornified, stratified squamous epithelium, subject to the changes of aging. With hormonal activity the vaginal epithelium increases in thickness and gains resistance. Under special load or exposure, the epithelium may become cornified in certain places. Although the cyclical changes of the vaginal epithelium are less pronounced than those of the endometrium, differential cytology of the vaginal epithelium can be used to indentify the stages of the cycle. The

epithelium is highest in the proliferative stage and reaches the highest glycogen content during ovulation. During the secretory phase, the thickness of the epithelium again decreases due to the shedding of cells. The muscular coat of the vagina consists of smooth muscles and elastic fibers. The muscular fibers can withstand stretching without bursting. Tunica adventitia is a part of the visceral pelvic fascia and consists of loose connective tissue. The posterior vaginal fornix has no tunica adventitia. Rather, the peritoneum, with an extension of one to two cm, coats the vagina (2)".

" The main blood supply to the vagina is through the vaginal branch of the uterine artery. After forming the coronary or circular artery of the cervix, it passes medially, behind the ureter, to send five main branches onto the anterior wall to the midline. These branches anastomose with the azygos artery and continue downward to supply the anterior vaginal wall and the lower two thirds of the urethra. The uterine artery eventually anastomoses to the urethral branch of the clitoral artery. The posterior vaginal wall is supplied by branches of the middle and inferior hemorrhoidal arteries, traversing toward the midline to join the azygos artery from the coronary artery of the cervix. These branches then anastomose on the perineum to the superficial and deep transverse perineal arteries. The veins follow the course of the arteries (1)".

" The lymphatics are numerous mucosal plexuses, anastomosing with the deeper muscular plexuses. Fine meshed networks of lymph capillaries are lacated in the lamina propria mucosae and in the tunica muscularis of the vagina. The lymph vessels of the tunica adventitia have valves, thereby enabling a passive regulation of the direction of the flow. The superior group of the lymphatics join those of the cervix and may follow the uterine artery to terminate in the external iliac nodes or form anastomoses with uterine plexus. The middle group of lymphatics which drain the greater part of the vagina appear to follow the vaginal arteries to the hypogastric channels. In addition, there are lymph nodes in the rectovaginal septum that are primarily responsible for drainage of the rectum and part of the posterior vaginal wall. The inferior group of lymphatics form frequent anastomoses between the right and left sides and

either course upward to anastomose with the middle group or enter the vulva and drain to the inguinal nodes (1)".

" The sensory and autonomous nerves of the vagina originate mostly in the plexus uterovaginalis, which is located in the most inferior part of the parametrium, the ligamentum cardinale. The paraganglionic sympathetic nerves originate in the inferior pectoral segments and the superior lumbar segments. The preganglionic parasympathetic fibers originate in the second, third, and fourth sacral segments. Clinical examination reveals that pain sensitivity and sensitivity to touch of the vagina with the exception of the area around the ostium vaginae, are very low in most women. Sensory corpuscular terminal organs are never or rarely found in the epithelial layer of the vagina (2)".

1.2 PHYSIOLOGY OF VAGINA

1.2.1. pH

It has been known since 1877 that the vaginal discharge is acidic and since 1892 that this acidity is due to the presence of gram-positive organisms, the Doderlein bacilli. The acidity is directly correlated with the amount of lactic acid present, although it has been suggested that perhaps other acids may be causative in certain cases. The exact origin of vaginal lactic acid is unknown but most evidence suggests that it represents a breakdown product of glycogen. Glycogen is deposited in the cells of the vaginal epithelium under the influence of estrogen although the administration of progesterone in castrates will accomplish the same effect. This is probably due to conversion of progesterone to estrogen. Diminution in the amount of estrogen results in the disappearance of cellular glycogen. Conversely, when estrogen levels are high, vaginal glycogen is abundant. Cellular glycogen may be converted directly to lactic acid by the action of Doderlein's bacilli or it may be fermented to simpler carbohydrates by vaginal enzymes and then reduced by bacteria to lactic acid. Other possibilities are that glycogen is converted to lactic acid by enzymes alone or that bacteria other than Doderlein's are capable of fermenting carbohydrates. Dodrelein's bacillus is probably identical with lactobacillus acidophilus, a facultative anaerobic, nonmotile, gram- positive rod (4).

1.2.1.1. Changes in pH with life cycle

The vagina of newborn has a pH of about 5.7, the elevation presumably due to the presence of alkaline amniotic fluid. Doderlein's bacilli appear about the fourth day and the pH falls to about 4.8. Beginning on the eighth day there is then rise to neutrality, and neutral values persist until the onset of puberty. Following onset of the menarche the pH varies between four and five depending on the stage of the menstrual cycle. Lowest values have been found at ovulation and premenstrually. This parallels the curves of estrogen excretion for the normal cycle. A pH of four or less is found during pregnancy, whereas in the postmenopausal women neutral or alkaline values may be seen. There is also a pH gradient, depending on the area of the vagina sampled. Thus, the lowest values are found near the anterior fornix, intermediate ones in the midvagina and highest ones near the vestibule (4).

1.2.1.2. Relationship between pH and vaginal infections

The clinical importance of this maintained acidity is emphasized by the fact that most pathogenic bacteria disappear when the pH is kept between 4.1 and 4.9. Several reports have been published concerning the relationship between vaginal yeasts, other microflora and their effects on pH. Peeters and his coworkers found a higher pH in patients with clinical signs or symptoms of candidal vaginitis than in controls but not all patients had the diagnosis confirmed by culture (5). Cohen (6) demonstrated lower pH in the posterior fornix in women with clinical vaginitis than in controls. Due to these conflicting reports, Drake and his co-workers (7) decided to study the changes in pH values in relation to the menstrual cycle and yeast infection. Drake and his co workers found no relationship between vaginal pH and vaginal morbidity due to yeast infection. Thus the protective effect of vaginal acidity does not appear to be confined to a critical range above or below which there is increased susceptibility to vaginal infection. They confirmed the relationship between the numbers of lactobacilli and vaginal acidity.

1.2.1.3. Relationship between pH and sexual arousal

Masters (8) was the first one to assess the influence of sexual arousal to orgasm on the acidity of the vaginal surface in women. He

reported that in five regularly menstruating women, small increases in pH were seen at some sites immediately after orgasm induced by clitoral self-stimulation. In others the pH either remained unaltered or even decreased. Wagner and Levin (9), in a pilot study of five patients, confirmed that increases in vaginal surface pH occured after self stimulation to orgasm in some women. Fox et al. (10), however, using a pH telemetry pill inserted into the vagina of one female subject, did not obtain any change in pH during normal coitus to orgasm.

Due to these conflicting reports Wagner and Levin (11), reinvestigated the effects of sexual arousal induced by clitoral self-stimulation on the vaginal surface pH in a group of normal women. They showed that there was an overall significant mean increase in the vaginal pH induced by sexual arousal. They did not find any relationship between the duration of stimulation and the mean change in vaginal pH. They found evidence of increases in vaginal surface pH in two out of five subjects. During sexual arousal to orgasm, the usually low Na^+ and Cl^- concentrations of basal vaginal fluid are increased significantly, while high basal urea levels fall to those of plasma. They found out that sexual arousal often induces changes in the surface pH of one part of the subject's vagina but has little effect elsewhere. Though vaginal acidity is necessary to avoid the infections, it has been proposed as a cause of infertility. Douching with sodium bicarbonate has yielded improved postcoital tests and has increased the pregnancy rate. While in some women extensive precoital sexual arousal may reduce the acidity of their vaginas and thus aid fertility, the data by Wagner and Levin support in general the conclusion of Masters that " vaginal lubrication produced by auto-manipulative techniques usually has little influence upon the vaginal acidity."

1.2.2. Vaginal Microflora

Each external area of the body or an area with an opening to the exterior, has a unique flora of microorganisms. The normal flora can be defined as microorganisms which inhibit and replicate in an area and do no harm and may even serve a beneficial role. The human vagina is an area exemplifying the microbiological dynamics

of a normal flora. The physiological condition of the vagina changes dramatically at different ages and this causes major changes in the microorganisms which reside there. The conditions of the vagina affecting the microbial population are age regulated and can be divided into four periods.

1.2.2.1. Neonatal period

At birth, the newborn contains no microorganisms in the vagina under normal conditions. However , even at the time of birth, the neonate is being exposed to an environment of thousands of bacteria, particularly in a vaginal delivery. Immediately, the infant begins to be colonized with these organisms which within hours will have established a normal flora. The bacteria replicate by binary fission and most have the ability to double their numbers every fifteen to twenty minutes. When one considers that certainly more than one bacterium enters the vagina either during or shortly after birth, it clarifies why vaginal vault can have the number of bacteria that are found there within hours after birth. This quantitative aspect is easily understood if we note that bacteria replicate by binary fission. However, one must realise that the microbial genetic information determines which organisms will best adapt to this vaginal environment. This is reflected by the shift in microbial population as the physiological condition of the vagina changes. The neonate has a high level of estrogen transplacentally and from the syncytial cells of the placenta. The hormonal level is sufficient to cause anatomical and physiological changes in the newborn's vagina so that the vaginal lining has the characteristics of a woman in the menarchal stage of life. This pseudomature neonatal vagina maintains physiological conditions similar to the mother for two to three weeks. Therefore, the microorganisms present in the newborn are similar to those found in the mother as long as the estrogen continues to cause the vaginal effect in the newborn. When the maternally derived estrogens are metabolized and excreted, the adult like vaginal epithelium exfoliates to a much thinner form of several layers of stratified epithelium cells. There is also a marked drop in glycogen content. It is the hormonal control of glycogen content that is believed to be the major factor controlling the

microbial population (12). Studies of the pathogens of group B streptococcal infection of the neonate have suggested that colonization of the genital tract of the mother at the time of delivery plays a significant role in infection of the neonate by this organism. Since bacterial adherence to tissue surfaces appears to be important step in colonization, Zawaneh and his co workers (13) undertook studies to examine the bacterial and the host factors that influence the adherence of the group B streptococcus to vaginal epithelial cells. During the course of preliminary studies of factors that influence the adherence of group B streptococci to vaginal epithelial cells of pregnant women, recurrent fluctuations were noted. This observation provided the first suggestion for a cyclic variation in the adherence of group B streptococci to vaginal epithelial cells. A cyclic pattern of adherence was demonstrated by these studies. A gradual rise in adherence was observed during the first half of the menstrual cycle. It was followed by a sharp decline to low levels of adherence that persisted through the second half of the cycle. The data provided support for the role of the hormonal influence on the adherence of group B streptococci to the vaginal epithelium.

1.2.2.2. Premenarchal period

As the maternally derived estrogen is reduced, there is a corresponding decrease in the vaginal glycogen content. The acidophilic organisms no longer have a selective advantage. The constant exposure to a wide variety of microorganisms gives other bacteria a chance to become part of the normal flora and soon they predominate because of selective environmental pressures. During the premenarchal period, usually a variety of different microorganisms are present without one predominating. Gram positive cocci and bacilli (other than lactobacilli) and gram negative bacilli predominate. However, the total colony count indicates that lower number of bacteria are present during this period (Kotcher, 1967). On the other hand, Weinstein et al. found acidophilic organisms in the eighteen percent of children. We now recognize that the normal flora of almost all vaginae contain anaerobic bacteria. The predominant bacteria in normal premenarchal women are referred to as Doderlein's bacilli (12).

1.2.2.3. Menarchal period

With the development of pubescence, there is an increase in estrogen and the vaginal mucosa begins to thicken with glycogen rich cells forming multi-layered, stratified, squamous epithelium. The organisms that can utilize glycogen or products resulting from the hydrolysis of this polysaccharide will have a selective advantage for colonization and growth. The fermentable substrates favor acidophilic organisms since a more acid environment will develop. The microorganisms in the vagina of women without vaginitis and with normal menstrual cycles are a heterogeneous group. It is not a homogeneous population of organisms representing one organism as studies utilizing only smear examination would indicate. The organisms which occur in the greatest or the least numbers in any one given woman will not necessarily occur in the greatest or the least numbers in other women of the same age.

Sanitary methods and contraceptive techniques generally have some effect on the vaginal microbial flora. The incidence of the yeast, Candida albicans, is slightly elevated in women using oral contraceptives. The estrogen supplementation in women taking oral contraceptives may promote conditions favorable for yeast multiplication in the vagina (12). Although the incidence and significance of actinomycetes in the general population have not been established, a study by Curtis and Pine (14) suggests that certain of these organisms may exist in essentially asymptomatic individuals with or without IUDs. Using the combined criteria of morphology and direct fluorescent antibody staining with species specific conjugates, they found one species of Arachmia and two of Actinomyces in an unexpectedly high percentage of the series of patients. Although this data do not necessarily reflect the true incidence of these organisms in either the general population or IUD wearers, they do reveal that these bacteria may be vaginal inhabitants of virtually asymptomatic women, not just in those with intrauterine or intravaginal devices but also in those with no devices. The clinical significance of Actinomyces israelli, Actinomyces naeslundii and Arachnia propionica in the human vagina is not apparent from this study, even when colony population seemed very high. The symptoms, if any experienced by the women studied were mild and remained so. None

of the women developed signs of acute pelvic inflammatory disease, even with continued use of IUDs, the known presence of actinomycetes, and lack of treatment with antibiotics. Elhag K. M. et al (15) found out that copper had a detrimental effect on gram positive anaerobes with the exception of Actinomyces spp., which were apparently favored by its presence. The isolation of actinomyces increased with the duration of IUCD in situ. The insertion of an IUCD breaches the protective barrier of cervical mucus and the IUCD tail creates a transmission link between the sterile uterine cavity and the bacteria rich vagina. Kleiman D. et al (16) found out that Chlamydia trachomatis growth can be inhibited in cultured human endometrial cells by copper ions at concentrations of copper known to be released by the copper IUDs. Preincubation of endometrial cells with copper and infection with medium without copper ions appeared to be necessary for inhibition to take place. The inhibition of Chlamydial growth can be due to the interference of copper with the function of Chlamydial specific proteins. Another possibility is that copper does not inhibit Chlamydial replication by direct effect on the agent, but by altering the concentration, thus inhibiting the Chlamydial development.

Robin Percival-Smith and coworkers (17) have confirmed the prevalence of vaginal colonization with E. coli and have observed a strong association of vaginal carriage of E. coli with previous history of urinary tract infection. They found out that vaginal carriage of E. coli is significantly higher among women using a diaphragm or cervical cap for contraception, compared to the rates among women using other contraceptive methods or no contraception. This difference remained significant even when other confounding factors such as phase of menstrual cycle, presence of genital complaints, previous history of urinary tract infection or prior use of antibiotics were kept constant.

Most published studies describing the human vaginal bacterial flora do not describe changes occuring during menstruation. Barlett et al (18) did use modern methods for anaerobic study and measured changes in the bacterial flora in two groups of young healthy volunteers. The combined data from the two groups indicated a 100 fold decrease in the mean number of aerobes during the last week of

menstrual cycle, compared with numbers during the first week of menstrual flow. The number of anaerobes remained relatively constant throughout the cycle, although there was considerable variation in the individual species recovered. A number of studies have investigated whether the microflora of women using tampons is different from those using other sanitary methods. Morris and Morris (19) found that the microflora of women using tampons was not significantly different from that of women using other forms of catamenial protection. Smith et al (20) found a significant association between menstruation and the frequency of isolation of Staphylococcus aureus. No differences were seen in the rate of colonization with this organism in users of tampons compared with the rate in users of menstrual pads.

Onderdonk and co workers (21) undertook studies to address the following questions : 1) do quantitative and qualitative bacterial analyses of tampons differ from data obtained by using a vaginal swab for sampling, and 2) does the presence of a tampon alter the vaginal microflora compared with the microflora in women using external catamenial pads ? It was seen that the total aerobic counts on day two of menstrual flow were generally lower than those for the intermenstrual sample obtained on day 21. Although the low aerobic count on day two of menstrual flow may be explained by a washout effect, the low counts on day 21 suggest an inhibitory effect due to the use of tampon for a short period. An unexpected finding that the total anaerobic populations show only modest changes during the menstrual cycle regardless of sample type and catamenial product was seen. Despite the relatively aerobic environment created by tampon insertion on day 21, the obligately anaerobic counts both on the tampon and within the vaginal vault tended to be consistent, with no apparent decline in numbers associated with the tampon use. The protective effect of a mucosal surface may explain the persistence of these microbes at the vaginal vault surface. However, the survival of these organisms within or on the tampon suggests that the local environment is less inhibitory than expected. A comparison of the tampon microflora with that of the vaginal vault suggests that tampons per se do not serve as a focus for microbial multiplication within the vaginal vault. If tampons were a focus for

microbial multiplication, the total counts of both aerobic and obligately anaerobic microorganisms were consistently lower in tampons than in samples obtained by the vaginal swab technique. During the menstrual flow, the genus Lactobacillus was replaced by a variety of other gram positive organisms including facultative and anaerobic cocci of various genera. Regardless of time or sample type, the vaginal and tampon microfloras were gram positive. Although the members of the genus Bacteroids were present with regularity, they were present in only a small part of the total microflora. When present in any volunteer, gram negative rods such as Bacteroides melaninogenicus or E. coli tended to persist for several cycles. Other organisms were sporadic in occurrence, suggesting either that they were present at detectable levels only rarely or that their presence represented a random attempt at colonization with little ability to persist as an integral part of vaginal microflora.

Garland and coworkers (22) undertook a study to test the hypothesis that, certain organisms of the normal vaginal flora may possess cellulolytic enzymes and are capable of degrading constituents of some tampons, releasing hydrolysis products that might be available as substrates for strains of S. aureus. They found that none of the osolates from the organs of healthy volunteers had cellulase activity. They isolated the species of endoglucanase positive organisms which are uncommon in normal vaginal flora. Their study could not support the hypothesis that significant cellulolytic activity occurs in the presence of tampons within vagina. They could not find the evidence for the degradation of tampons during their use. Thus it is shown that, if cellulolytic bacteria exist in the vaginal flora, they must be present in small numbers and are most unlikely to have any detectable effect on cellulosic products placed within the vagina for the usual periods of time in which such products are used.

Larsen and Galask (23) have shown that the density of the vaginal flora appears to fluctuate with the rising level of estrogen which in turn influences the glycogen store of vaginal epithelial cells and pH of vaginal secretions. Heather and coworkers (24) found that bacterial vaginosis was the permanent factor in the pathogenesis of postpartum endometritis. Bacterial vaginosis is the most common

vaginal infection, although it is infrequently diagnosed and rarely treated during pregnancy. The concentration of the vaginal microorganisms is greatly increased in bacterial vaginosis. The mean concentration of vaginal microorganisms in women with normal vaginal flora is approximately 10^5 / mL of vaginal fluid, compared with 10^7 or 10^8 / mL of vaginal fluid in women with bacterial vaginosis. Some microorganisms present in bacterial vaginosis seem to be particularly virulent, at least more virulent than Lactobacillus spp. and other vaginal microorganisms found in high quantities among women with normal gram stains. Thus, the high prevalence , the increased concentration, and the presence of particularly virulent microorganisms are probably all operative in the pathogenesis of postpartum endometritis caused by bacterial vaginosis. It was seen that the women with antepartum bacterial vaginosis were significantly more likely to have G. vaginalis, Peptostreptococcus spp. and Bacteroides spp. isolated from endometrial cultures than were the women with normal flora by Gram stain criteria.

Pregnancy may affect the vaginal microbial flora. During pregnancy the glycogen content increases so that conditions become even more favorable for acidophilic organisms. In addition, the glycogen content is higher in the last weeks of pregnancy and the incidence of acidophilic bacteria is correspondingly higher (12).

1.2.2.4. Postmenarchal period

During menopause, the vaginal histological and physiological changes result in a vaginal environment similar to the prepuberty vagina. The acidophilic organisms no longer predominate since there is no selective pressure in favor of these organisms. The variety of bacteria may increase during this period but the quantity is reduced and is similar to the premenarchal period (12).

1.2.3. Vaginal Fluid

The male and female genital epithelia and accessory glands produce numerous secretions. Their involvement in reproductive mechanisms is complex. In the nonmenstruating women vaginal fluid is a mixture of fluids from a number of sources. Its major components are cervical fluid, exfoliated epithelial cells from the

vaginal wall, vaginal fluid per se, with small amounts of the secretion from Bartholin's glands. Some secretions from higher up the tract may reach the vagina via uterine fluid, oviductal fluid, follicular fluid at ovulation and perhaps even peritoneal fluid, but obviously the further the source of the fluid from the vagina the less likely it is to reach that organ without being modified by the other epithelia. Finally small amounts of urine may enter and contaminate the vagina (25).

1.2.3.1. Basal Unstimulated Volume

No glandular elements have ever been identified in the normal human vagina, which is stratified squamous epithelium. Despite this lack of glands, the epithelium is usually covered with a surface film of moisture like a mucus membrane. Early estimates of the volume of this fluid were little more than guesses. Values of 0.5 to 1 ml were quoted by Voge. The weight of the fluid obtained by Stone and Gamble, 1959 was 0.76 $\pm$ 0.04 gm. It was stated that weight increased significantly thirteen to sixteen days before menstruation due to the increases in cervical secretion around ovulation time (25). Changes in the physical properties and chemical constituents of the cervical mucus have been intensively studied during the course of the menstrual cycle. Glucose and glucosamine levels increase at midcycle, while sialic acid, alkaline phosphatase and soluble protein decrease at this time. Lactic acid, urea and acetic acid undergo the most definitive changes in concentration which appear to coincide, at least in part, with changes in the estrogen/ progesterone levels. The proliferative phase concentration increases in the vaginal lactic acid, urea and acetic acid are a reflection of the initial biochemical events in the vaginal mucosa caused by small rises in circulating estrogens. Since vaginal secretion consists of a transudate from the vaginal mucosa, the presence of a large number of serum type proteins in vaginal fluid is to be expected. Many serum proteins including the immunoglobulins are normally present in the cervical mucus and may become mixed with the vaginal secretion. It is likely that, the bulk of these proteins are diffused from serum through the mucosa into the vagina. There is also a distinct possibility that some proteins, particularly the immunoglobulins may be synthesized locally by the

vaginal mucosa. In fact biosynthesis of IgG and IgA in the vaginal tissues of the rabbit has been reported. These immunoglobulins may play a significant role in the protection of the vagina against infective organisms (26). Vaginal secretions can be formed in the absence of any other part of female internal genitalia or ovaries, ovarian hormones increase the amount formed. Vaginal fluid contains carbohydrates from the epithelial glycogen, amino acids, aliphatic acids and proteins. It is debatable whether these should be regarded as being secreted by vagina, as many of them may be released by disintegration of the constantly exfoliated epithelial cells. In the case of acids, it is generally accepted that, the predominant microorganisms of the healthy human vagina - the Doderlein's bacillus- ferments carbohydrate to aliphatic acids, primarily acetic and lactic acid. It was found by Levin and Wagner (25) that the mean urea concentration of the basal vaginal fluid was nearly twice that of the plasma. The concentrations of K^+, Na^+, and Cl^- in the basal vaginal fluid were very different from those of plasma. The K^+ was some 6.6 times greater while the Na^+ and Cl^- were approximately only 46% and 61% of the plasma levels.

1.2.3.2. Vaginal Lubrication during sexual arousal

Studies have revealed that the vagina responds to effective sexual excitement by an increase in the production of fluid on its surface within ten to thirty seconds of the commencement of the sexual stimuli. This phenomenon named vaginal lubrication appears like a sweating reaction. Sexual arousal causes a rapid increase of blood flow in the vaginal area. This secretion changes the ionic composition of the vaginal fluid and provides the principal source of vaginal lubrication for coitus. While Masters and Johnson never objectively quantified the amounts of vaginal fluid formed during erotic stimulation, they have stated that the greatest production is during the initial excitatory phase. The amount appears to be influenced by the type and duration of the stimulus employed (25). While Preti G. et al (27) have stated that these changes appear to be quantitative in nature. There do not appear to be any consistent qualitative changes in the small volatile organic compounds during stimulation. It appears that the concentration of organic compounds

present during a normal base like period of six hours are altered during stimulation. Sexual activity might cause the intravaginal concentration of organic compounds in the transudate to increase. Since glycerol is known to be both a membrane stabilizer and to activate certain enzymatic systems, the marked rise in glycerol concentration during sexual arousal may be significant in early reproductive events. Unlike other compounds, acetic acid decreases during the stimulation interval. Many of the odoriferous constituents of vaginal secretions such as C_2-C_5 aliphatic acids, hydroxybutanone, dimethylsulfone, cresol, 2- piperidone and indole result from the metabolism of the vaginal microflora. These intravaginally produced compounds may decrease in concentration during arousal due to dilution by the plasma derived transudate. The accumulation of transudate within the vaginal barrel may cause an increased flow of secretion out of the vagina. Except for the effect of pH on spermatozoa, little is known concerning the effects that small organic compounds in the vaginal secretions have upon the motility and respiration as well as fertilizing capabilities of these gametes .

2] PSYCHOLOGY AND SOCIOLOGY IN USE OF VAGINAL PRODUCTS

In earlier days, the knowledge about the rectum was applied to vaginal products without realizing the differences between the vagina and the rectum. Initially little was known about the anatomy and physiology of the vagina. Though they lie next to each other in body, their anatomy and physiology is significantly. Now the picture is changing and the vagina is considered as an organ different from the rectum. Women being the only users of vaginal products, it is very important to determine their opinion and acceptability of vaginal products before developing any new vaginal product.

Clinical studies have revealed a great variation in the effectiveness of vaginal contraceptive methods. Compliance is generally considered a key factor. However, our knowledge of the determinants of compliance in the use of vaginal products is still limited. For instance, what use- related problems, complications and discomforts would lead to irregular use of a vaginal product ? How do different cultural settings affect the incidences of these problems, complications, complaints and events?

Several researchers have tried to answer these questions for the vaginal contraceptives. Among the factors associated with the selection, adoption and continued use of a contraceptive is the acceptability of the method. Marshall (28) discusses the qualities which makes an object, person, event or idea attractive, satisfactory, pleasing or welcome and argues that it is the subjective evaluation of these qualities or attributes which determines acceptance. Polgar and Marshall (29) have identified attributes hypothesized to influence the acceptability of contraceptive methods. Among these attributes are : effectiveness, safety, other minor side effects, client convenience in obtaining and using, familiarity to client and gender of user. Since the decision to use a particular contraceptive method occurs within a matrix of normative and social pressures, the influence of other significant events must also be examined in order to understand the contraceptive behavior.

A number of investigators have emphasized the influence of partners, friends, relatives and contraceptive providers on the initiation or continuation of the contraceptive use. Findings from a longitudinal study of married couples indicated that couples were influenced to use their current method most frequently by physicians. Conversely, the media, relatives and friends had little influence on the use of specific contraceptive methods.

Beckman L. J. et al (30) investigated the use of the contraceptive sponge in United States . The purpose of their investigation was to explore the importance of sponge attributes, social influences on the adoption and discontinued use of the vaginal sponge. Their sample consisted of 792 women. Both current and former sponge users reported that the characteristics of the contraceptive sponge affected their decision to try a new method. The positive attributes of the sponge as well as the perception of the sponge in comparison to a previous method were regarded as important. It is noteworthy that the attribute which received the highest importance rating was " effective." Since this sample is a highly educated group of women who would be expected to be knowledgeable about contraception, and since other reversible contraceptives are known to be more effective than the sponge, this finding is surprising. The data suggests that women may adopt and

continue to use the sponge in part because of the relative undesirability of previous methods they have experienced.

The results of this study suggests that sexual partners are not perceived as influencial in the decision to use the contraceptive sponge. Not only did the women rate partner influence as a factor of little importance in their decision to try the sponge, but also less than four percent of the sample reported that their partners influenced them to use the device. Similarly, friends, parents and relatives appeared to have little influence on the decision making process. Nearly one fourth of the sample cited physicians as influencial in their decision to use the sponge. Seventy-nine percent of the sample reported that they have tried the sponge partly because of the media. Selection procedures for this sample limited participants to women who looked at one type of media magazine, which may have skewed the sample towards the women likely to be influenced by the media. Over one fourth of the women reported that a particular event had occured before they initially tried the sponge. The majority of these events involved a change of relationship status such as divorce, separation etc.

Some women initiate sponge use during a transitional phase of their life. Women in transition may have sporadic and infrequent sexual encounters and therefore may be unwilling to take birth control pills or invest in the prescription contraceptives. When women were asked about the reasons why they stopped using the sponge, the highest rated structured items were " concern about effectiveness " and " preferred another method." A major reason why the pill, diaphragm or sterilization were preferred over the sponge is that they were perceived as more effective. The next most important reasons for stopping sponge use concerned irritation, discomfort or vaginal infection. These results agree with previous findings and suggest that the cost or the difficulty of removal or insertion are not significant determinants of discontinuation of sponge use for this largely middle class sample.

Various studies have been conducted worldwide to study the use patterns of contraceptives. Some important inferences can be drawn from the results of these studies regarding the cultural and social differences that affect the use patterns of these products. Chi

I- cheng et al (31) conducted an international, multicenter randomized clinical trial. The trial was conducted in Yugoslavia, Taiwan and Bangladesh. They used the contraceptive sponge and foaming tablets for their study. Clinical acceptability of products was examined in terms of the problems encountered by the women in use of the products. This includes the insertion, retention and removal problems and other complications and complaints reported by the subjects. Use patterns included incidences of and reported reasons for irregular use and / or discontinuation of use of the method. This study addresses the need for randomized clinical studies of vaginal contraceptive methods in different cultural settings. As expected, the sponge was associated with a significantly higher frequency of the insertion and retention problems. The tablet, on the other hand, was associated with a higher incidence of burning, stinging and heat sensation. This sensation, however, appeared to be generally well tolerated. Very few acceptors (less than four percent) discontinued use of a tablet for this reason. More sponge users reported irregular use than tablet users. " Too troublesome " was the primary reason given for the irregular use. This complaint did not decrease as the length of the use was increased. For either method, discontinuations due to the personal reasons were predominant. For the two Asian centers, problems related to the use of product like messiness, inconvenience and insertion or retention or removal problems and for the Bangladesh center alone, partner's objection appeared more likely to lead to the discontinuation for the sponge users. For the two Yugoslav centers, the failure rates were comparable between the two method groups. In the Taiwan center, the failure rate was lower for the sponge users than for the tablet users, but the difference was not statistically significant. The total failure rates for sponge and tablet users were lower in the two Yugoslav centers than in the Taiwan center. This might be due to the fact that, a considerable proportion of all users in the Belgrade center had an experience with a vaginal method and that more that 40 % of both user groups in the Maribor center had contraindications to the other contraceptive methods.

Perhaps the most important finding of the Chi study is the remarkable center specific pattern in the acceptability and the use

patterns of these vaginal contraceptive methods. While sponge was generally well received and successfully used in the two Yugoslav centers, user compliance, continuation rates and use effectiveness were lower in the Taiwan center. There was only nominal acceptability of the sponge use in the Bangladesh center. The discontinuations were mainly due mostly to a general dissatisfaction with the method, often by the husband. Women using tablets in the Bangladesh center generally fared well in the terms of acceptability, use patterns and use effectiveness.

It is evident that the results from one center can not be expected to apply to the centers in different cultural settings. In some centers, like the Bangladesh center , considerable effort would be needed to persuade women to use the sponge effectively. Youssef Hafez and co workers (32) have compared the efficacy, acceptability and short term safety of the foaming tablet and aerosol foam in a sample of 349 women from Egypt. For both the contraceptive products, compliance was high, relatively few product related and medical complaints were reported. The absence of frequent discontinuations for any specific reason suggests that there were few identifiable unacceptable features of either product.

The absence of partner complaints in a society where the husband is often the primary decision maker, bodes well for both spermicidal products. Over 60 % of the women who completed the study period chose to continue to use a vaginal contraceptive following the study. This coupled with the observation that most of the women had never used a vaginal contraceptive method upon admission to the study leads credence to the overall acceptability of the products. User motivation was apparently very high, as evidenced by the reported high product compliance and desire to have no additional children. Previous studies have shown that high user motivation significantly improves the efficacy of vaginal contraceptives. A review of patient characteristics at admission suggests that the women in this study are a typical of many women who choose to use vaginal contraceptive methods.

Vaginal contraceptives are often used by women with higher educational levels (women in this study had a mean education of less than five years) and by women desiring to have but space

additional children. In addition, vaginal contraceptive acceptors have often successfully used those products previously, but over 75 % of these study participants had no prior experience with female barrier methods. That both vaginal contraceptive products investigated in this study were as acceptable and effective as they were is therefore remarkable. The observation that this sample of Egyptian women is a typical of many vaginal contraceptive users is not meant to imply that such methods are inappropriate for Egypt; rather these results confirm that the user motivation can play a key role in the successful use of these methods.

Chompootaweep S. (33) conducted a study on two types of foaming vaginal tablets in Thai women. The primary reason for participating in this study was vaginal tablets recommended by family, friends or other health staff and other methods were contraindicated. Concerning the regularity of the use and the reasons for irregular use of both the tablets, it was found that nearly all of the women reported using their tablet at every intercourse. The most common reasons given for irregular use were patient neglect and male discomfort. The results of this study indicate that with the regular and proper use, both the tablets are a comparable and safe means of birth control. Although few related or medical complaints were reported by both groups of tablet users, the high incidence of user failures indicates that the tablets may not be suitable for Thai women.

All these studies have shown that not only the women but the other factors such as partners, families, physicians, media play a vital role in women's choice of the vaginal products. Several studies have been conducted to find out about the acceptability and efficacy of contraceptive vaginal products. Not many studies are conducted to find out about the other products like products used for the treatment of vaginal infections. Recently a survey was conducted to find out women's preferences about use of intravaginal products. The sample consisted of 185 women from the University of Rhode Island and other Rhode Island residents. It was found that women are ready to use the intravaginal products if they are given proper and complete information about these products. Women preferred the solid intravaginal dosage forms because they perceived them as

being easier to use. Many women find creams to be messy and thus prefer to use the tablets or the suppositories (34).

3] DOSAGE FORMS USED FOR INTRAVAGINAL APPLICATION

While developing vaginal preparations, several factors besides their antimicrobial and contraceptive activity should be taken into consideration. The vaginal pH is normally acidic. This acidic pH is essential for the maintenance of the squamous cell characteristics of the vaginal epithelium. It is therefore necessary that the administered agents alter the vaginal flora and affect the pH of the vaginal fluid as little as possible. This is sometimes difficult to accomplish particularly in the treatment of bacterial infections but should be always considered as a possible harmful side effect. Suitable buffering systems are therefore an essential part of all the vaginal preparations. The pharmacological and physiological properties of the vaginal preparations should also include the following : 1) the absence of tissue irritation; 2) easy application; 3) an even distribution of the drug throughout the vagina; 4) the retention of the drug in the vagina so that it is not removed when the woman is in the upright position; 5) the absence of an offensive odor; 6) no stains on clothes or skin; 7) compatible with other medications; 8) a lack of irritation to the penis during intercourse (35). Vaginal preparations are used for two purposes, namely, the contraception and the treatment of infections. Thus amoebicides, sulfonamides, antibiotics and disinfectants are frequently prescribed, sometimes combined with local anesthetics and astringents. Estrogens are also given to restore the vaginal mucosa. In contraception, spermicidal compounds have been used. Even prostaglandins are used now as abortefacient agents.

Among all the various dosage forms currently utilized for contraception or the treatment of infections, there have been surprisingly few published studies comparing in vitro to in vivo efficacy and acceptability.

4] VARIOUS TESTS CONDUCTED ON INTRAVAGINAL PRODUCTS

4.1. IN VITRO STUDIES

Lactobacilli have long been thought to protect against vaginal

infection by producing lactic acid, thereby maintaining a pH of 4 to 4.5. Lactobacilli have been shown to inhibit the growth of the other vaginal microorganisms by decreasing the pH or by producing hydrogen peroxide or other inhibitory metabolites. Treatment of vaginitis with Lactobacillus replacement therapy was described in the United States in 1933 by Mohler and Brown. Some women still use various Lactobacillus products to restore their normal vaginal flora. Hughes V. L. et al (36) investigated the concentration and viability of Lactobacillus species in non- prescription products to determine whether the Lactobacillus species present were as advertised. They tested the dairy products and commercially available powders and capsules. Lactobacillus species was found in only four out of sixteen commercially prepared non prescription products. These products were not optimal for recolonization of the vagina.

Although yogurt products contain hydrogen peroxide producing lactobacilli and are free of the other contaminants, a study by Wood et al (37) revealed that the Lactobacillus strains from the yogurt did not adhere as well to the vaginal epithelium. They undertook a study to detect any differences in adherence which may exist among the various species of lactobacilli recovered from vaginal cultures. They found out that there was a relationship between the vaginal epithelial cells and the lactobacilli of vaginal origin. No difference in adherence was found among various species of the lactobacilli recovered from the vaginal cultures.

Several studies have indicated a clear relationship between the adherence and colonization. Thus it would seem unlikely based on in vitro studies that colonization of the vaginal epithelium by the lactobacilli found in yogurt would occur, but rather these bacteria would be lost once their application by douching ceased. Many other factors are involved in the colonization including the hormonal levels, other flora present in the vagina, vaginal pH and antibiotic therapy. The presence of G. vaginalis, which adheres to the vaginal epithelial cells strongly, interferes with the adherence of lactobacilli.

As we know, the main function of the vagina is considered to be conception and thus various studies are done to find out more about the vaginal contraceptives. Some in vitro studies have been

done to study this aspect of the vagina. Previously, little was known about the permeability of the vaginal epithelium. To study the transport properties of this epithelium, Hajjar J. J. et al (38) examined the unidirectional transmural fluxes of a neutral solute, alanine. The studies were done on isolated rabbit vagina. These experiments have suggested that there is a mechanism in the epithelium capable of transferring alanine from the blood to the luminal side of the membrane. This transfer occurs in the absence of a concentration difference between the two sides of the membrane and can not be the result of an electrical gradient across the membrane. This mechanism may be dependent on the female sex hormones.

In the earlier days of development of the vaginal contraceptives, research was done to find out about the effect of vaginal lubricants on the sperm motility. Goldenberg R. L. et al (39) evaluated a number of vaginal lubricants for their effect on the sperm motility. They found out that the initial concentration, morphology and motility did not seem to influence the lubricant sperm interaction during the incubation period. Incubation with saline alone had no effect on the motility. Several commercial vegetable oils were tested and while each limited the motility to some extent, none inhibited the motility totally. Glycerin and petroleum jelly had only a slight effect on the motility. Although vaginal lubricants have not been shown to cause an infertility problem, their use may contribute to one. If an infertility problem exists, these agents should be avoided if at all possible. Loewit K. (40) tested several substances in search of a suitable vehicle acting as a carrier of spermicide and as a physical barrier to the sperm migration at the same time. Of the compounds studied, hydroxypropylmethyl celluloses (HPMCs) showed inherent sperm immobilizing activity. This effect did not seem to depend on osmolarity nor was it influenced by the changes of pH and viscosity measured during the study.

Boyers S. P. et al (41) examined the effects of Lubrin- a patented lubricating insert of glycerin and polyethylene glycols- on the sperm motility in vitro. It was seen that Lubrin impaired both the mean sperm velocity and the percent motility in a dose and time

dependent manner. Even after a brief Lubrin exposure, the motile, migrated sperm deteriorated rapidly, making it unlikely that sperm migrating to the upper reproductive tract might escape Lubrin's action. In addition, the concentrations of Lubrin tested were ten to hundred fold lower than those that sperm might be calculated to encounter when a two ml Lubrin insert melts and mixes with the vaginal secretions and semen during intercourse.

When it comes to tests on the actual vaginal products, tests like the hardness testing, release rate etc. are conducted. Halstead G. W. (42) focussed on in vitro drug release testing of the carboprost methyl controlled release vaginal device. The effects of temperature, pH and apparatus design were investigated. Accelerated drug release testing was found not to be feasible due to an apparent change in the release mechanism observed at 60^0C. At temperatures between 30 and 50^0C, Arrhenius behavior was observed with an activation energy of eighteen Kcal/ mol. Drug release for the device was found to be insensitive to the pH changes. Parrott E. L. (43) has presented formulations for a foaming spermicidal vaginal tablet and a suppository. Some pharmaceutical characteristics such as weight variation, disintegration test, dissolution etc. peculiar to both dosage forms were measured. He has suggested a simple method for the evaluation of the quantity and collapse resistance of the foam. For most vaginal contraceptives, it is directed that the insertion occur at least ten minutes prior to the intercourse. Thus, it is logical to evaluate a product in terms of the quantity of the foam produced and its collapse resistance at that time. When an experimental and a commercial suppository was compared to an experimental tablet formulation, the tablet produced approximately a ten fold greater volume of foam which collapsed less readily than the foam from the suppositories. The disintegration test for peroral tablets is always described in various Pharmacopeias, but a test for vaginal tablets is not prescribed in either the Japanese Pharmacopoeia or the United States Pharmacopoeia. The British Pharmacopoeia (BP) does state a disintegration test for vaginal tablets. Yamaguchi M. et al (44) have suggested a modified BP method, a watch glass method for the disintegration of the vaginal tablets.

In last few years, public awareness has been created about the role of tampons in toxic shock syndrome. Robbins R. N. and coworkers (45) have reported the effect of commercially available tampons on Toxic Shock Syndrome Toxin- 1 (TSST- 1) production in a disk membrane agar (DMA) method with incubation at 37^0C for nineteen hours under 50 % CO_2 in air. The amount of toxin produced increased with all tampons when blood was added to the Blood Heart Infusion agar medium. Decreasing amounts of TSST- 1 were recovered from the agar layer as the tampon size increased. Tampons are made of a core consisting of either a single fiber or a blend of fibers and may contain deodorants or fragrances, absorbents and surfactants. Some tampons include a wrap which may have a binder as well as a surfactant. The tampon composition, both fiber and additives, does affect the cell growth and the toxin production. Cell growth on the membrane and the TSST- 1 in the agar layer were unaffected for most of the part by the tampon composition. Agar layer toxin represents that portion of the total toxin which may be available for absorption by the tampon user in contrast to that which is absorbed by the tampon and hence is relatively unavailable. The functions of the tampons may be to support the vaginal infection by supplying a fibrous surface for the heavy colonization and to provide a sufficiently aerobic environment for the toxin production. Lee Wong A. C. et al (46) conducted a study for two purposes, namely 1) to better stimulate the vaginal environment during menstruation by limiting the available air to that present in the tampon, buffering the culture medium and adding CO_2 and blood to the medium, 2) to better assess the reproducibility of the method by running five replicates of each sample on five separate days for each of two different S. aureus strains. 27 different sizes and types of tampons were included in this study.

It was seen that in general, with the exception of one brand, tampons either inhibited or had no effect on TSST-1 production. It is important to note that in vitro and animal models have not yet been able to explain the etiology of or to fully replicate this disease. It is acknowledged that in vivo microbe- host factors such as the host immune status and the effects of growth conditions can at best only be approximated in an in vitro model. It was anticipated that the

effects of weight, air content and absorbency on TSST- 1 levels might be discernible, particularly among those brands which maintained a constant fiber composition for all the sizes. The data did not indicate any relationship between the amount of TSST- 1 produced and any of the variables mentioned above, except for one brand.

The amount of air present was of particular interest since Todd et al (47) , Kass et al (48) and Schlievert and Blomster (49) showed that more TSST- 1 was produced under the aerobic than the anaerobic conditions. Since the available air was limited to that which is contained within a tampon, it allowed the focus to be placed on the role of the air volume within the tampon in the production of TSST- 1. The production of TSST- 1 did not increase as the air volumes increased. Less TSST- 1 was produced in the brand with a deodorant than in the nondeodorant tampons. These results implied an inhibitory effect of the deodorant.

Other contraceptive devices have also been shown to produce Toxic Shock Syndrome (TSS). One such study was conducted by Stumpf P. G. et al (50) to determine the effect of the vaginal contraceptive sponge (VCS) on the growth of TSS- S. aureus in vitro. A study was designed to test the hypothesis that VCS which contain Nonoxynol- 9 (N- 9) would not enhance the growth of TSS- S. aureus over the time period recommended for the VCS use namely between six and twenty-four hours. At all time points tested there was no evidence of enhanced bacterial growth in media containing VCS or N- 9. Instead, the colony counts from the control media were higher than from the media containing the VCS for up to twenty hours of incubation. The VCS was associated with the greater inhibition of TSS- S. aureus than N- 9 alone. Thus it can be concluded that VCS which contains N- 9 does not enhance the growth of bacteria known to be associated with the clinical TS.

4.2. IN VIVO STUDIES

Though a few tests are done in vitro on the vaginal products, the main emphasis is always on in vivo tests. In the literature there is substantial data available on the clinical trials of vaginal products in women. Here again the emphasis is more on contraceptive products than any other products. Now a days, more attention is paid

to treating of the infections. We will deal this vast topic by describing various dosage forms individually. These will be subdivided in to topics according to their use.

4.2.1. Suppositories

4.2.1.1 For termination of early pregnancies

Brenner P. F. et al (51) investigated the use of vaginal suppositories containing prostaglandin analogues to evaluate the clinical and laboratory parameters related to the efficacy of these products for pregnancy termination.

Sixty-one out of one hundred patients had a successful termination of pregnancy. Thirty-five subjects required a surgical procedure to terminate their pregnancies and four were lost to follow up. Other investigations have reported success rates of more than 90% using prostaglandin analogues abortifacient in early pregnancies, where as the overall success rate of Bresnner et al was 61%. This could be due to the different definitions of what constitutes a successful abortifacient. Those who reported earlier define the success as the initiation of uterine bleeding where as Brenner et al considered the vaginal suppositories as the success only if the patient required no surgical intervention to terminate her pregnancy. These investigations have reached the conclusion that the success of prostaglandin vaginal suppositories in terminating pregnancies of fourty-nine days gestation or less can not be totally predicted using clinical parameters such as maternal age, gestational age and parity. Success of this therapy can usually be predicted by the passage of the tissue from the vagina and by comparing the serum beta-hCG concentrations 7 ± 2 days after treatment with the pretreatment values. A beta-hCG level 7 ± 2 days posttreatment which is less than fifteen percent of the pretreatment level indicates success. A beta-hCG level 7 ± 2 days posttreatment which exceeds the pretreatment level indicates abortifacient failures. A beta-hCG level 7 ± 2 days post treatment which is less than the pretreatement value but greater than fifteen percent of the pretreatement level requires further hormonal monitoring to determine the outcome.

Bygdeman M. et al (52) studied the efficacy of a single dose administration of a vaginal suppository for the interruption of second

trimester pregnancy. They used various types of vaginal suppositories. The first type contained 2mg of methyl ester of 15-methyl PGF_2 in 2.2 gm of a standard Swedish pharmaceutical base. The other types of vaginal suppositories contained 2.5 and 3 mg of methyl ester of 15-methyl PGF_2 in 2.2 gm of Witepsol E-76 and 3.5 mg in 2.5 gm of Witepsol E-76. The abortion time was defined as the period between the insertion of a suppository and expulsion of the fetus or the whole conceptus into the vagina. If the patient had not aborted within 24 hours following the administration, the trial was regarded as a failure. If the placenta was not expelled spontaneously the trial was regarded as an incomplete abortion.

The results indicate that some of the new prostaglandin analogues are more suitable than the primary compounds if the efficacy and the frequency of side effects are considered. It was suggested that a longer acting vaginal suppository would be even more satisfactory. The design of such a suppository was based on the experience collected with the repeated vaginal administration of 15-methyl PGF_2 methyl ester. The results from these studies indicated that the desire and effective plasma level of 15-methyl PGF_2 free acid and methyl ester is 500-1000 pg/ml maintained for upto 24 hours. The amount of the compound and the base and the physical characteristics of the base turned out to be of importance for the rate and duration of the absorption of the drug. If the amount of the original base was increased from 1.1 to 2.2 gms a significant prolongation of the release was achieved. The plasma concentration remained at a higher level upto six hours with the 2.2 gm suppository compared to three to four hours following the administration of a 1.1 gm suppository. A further prolongation of the release could be achieved by using a similar base Witepsol E-76 with a slightly higher melting point. This study showed success rate of 92%. The frequency of gastrointestinal side effects (vomiting and diarrhoea) was acceptable and comparable to that following repeated vaginal administration of 15-methyl PGF_2 methyl ester. The results have shown a high success rate with an acceptable frequency of minor side effects. This suggests that the administration of one vaginal suppository containing 3 to 3.5 mg 15-methyl PGF_2 methyl ester offers a primary therapeutic alternative in patients in the second trimester.

Martin R. W. et al (53) studied the use of prostaglandin E (PGE) vaginal suppository in third trimester fetal demise. The discovery of the oxytocic properties of prostaglandins and the subsequent use of the drug by Karim et al for induction of labor has provided a superior method for the treatment of intrauterine fetal demise. Prostaglandins have been administered by many routes but vaginal prostaglandin E suppository seems to be very effective and is associated with fewer adverse effects than the intraamniotic or the extraamniotic administration.

Southern et al (54) have shown that PGE vaginal suppositories have an efficacy of 97% in the induction of labor in the second and third trimester fetal demise. The data by Martin et al also demonstrated that the PGE suppositories are highly effective. They demonstrated that a small amount of PGE is adequate. Martin et al felt that laminaria insertion prior to prostaglandin induction decreases the chance of the cervical laceration and the uterine rupture. No infectious complications were demonstrated in this study. Thus PGE vaginal suppositories appear to be a safe and effective alternative to expectant management of intrauterine fetal demise in the third trimester. Because of reports of uterine rupture PGE must be used cautiously.

Anderson L. F. et al (55) have compared the efficacy, tolerance and side effects of gemeprost (16,16-dimethyl-trans- -PGE_1 methyl ester) one mg vaginal pessaries given at three hour intervals up to five times and a single intraamniotic administration of 40 mg PGF for termination of second trimester pregnancy. 152 women were divided into two groups. One was treated with a single one mg gemeprost vaginal pessary where as the other was given a single dose of 40 mg PGF instilled into the amniotic cavity after aspiration of 30 to 40 ml amniotic fluid . Eighty-one percent patients in the gemeprost group and 64% in the PGF group aborted within 24 hours from the first administration of prostaglandin. The mean number of pessaries used in the gemeprost group was 4.2 . The mean abortion time in the successful cases was 14.3 hours for gemeprost and 14.8 hours PGF. The higher mean age in the gemeprost group is not judged to have any major impact on the results. There was no true difference in the total incidence of gastrointestinal side effects between the two

groups. Thus this study has shown than gemeprost one mg vaginal pessaries given at three hour intervals upto five time were more effective. Both treatments were well tolerated and had a comparative frequency of side effects. Gemeprost vaginal pessaries have an additional advantage of an easy and safe non invasive administration.

Check J. H. et al (56) designed a study to see if the use of a profilactic progesterone vaginal suppository (PVS) reduced the risk of spontaneous abortions in women with a history of at least one spontaneous abortion. A hundred patients were enlisted in this study. A prerequisite for inclusion in the study was that they had never been treated previously in any pregnancy with progesterone. PVS was initiated after ovum release and four days from the demonstration of a mature follical at a dosage of 25 mg twice daily. Ten percent subjects had a first trimester spontaneous abortion during this pregnancy despite PVS therapy. The highest percentage of abortions (33%) occured in the group of women with three or more previous abortions. The incidence of spontaneous abortions in the normal population is estimated at approximately fourteen percent. The risk of spontaneous abortion in the women with previous abortions has been estimated at 33%. This study revealed an incidence of spontaneous abortion in these previous aborters who were treated with PVS to be lower than expected from the general population.

Spilman et al (57) have reported the analysis of a study of menses induction using vaginal suppository containing a three mg of 15(s)-15-methyl PGF methyl ester. They studied 80 patients who were treated with a single long acting vaginal suppository placed high in to the vagina. The success was considered as evidence of the sustained uterine bleeding characteristic of menses induction, a negative pregnancy test at fourteen days after the treatment. The plasma concentration of 15-methyl PGF demonstrated the distinct differences among three clinically defined groups of patients. The successful induction of menses was associated with a more rapid rise in the blood levels of 15-methyl PGF , a higher peak level of the drug and a sustained elevation of the drug in the blood. This study has shown that the temporal profile of drug affects the efficacy of

this treatment for menses induction. It can be predicted that menses would be successfully induced in 100% of the patients in whom the four hour blood concentration of 15-methyl PGF was atleast 528 pg/ml. This suggests the need for a delivery system that would be expected to release the prostaglandin faster than does the slow melt E-76 vaginal suppository.

4.2.1.2. For labor induction

Intravenous infusion of oxytocin for induction of labor both with and without the primary amniotomy has been used for many years. It has been an efficient and safe method in cases of a favorable cervical state. A major disadvantage is that the intravenous infusion reduces the mobility of the patients. Prostaglandin administration locally for the induction of labor has given encouraging results and is an easy and noninvasive technique. Thus Legarth J. et al (58) studied these two different methods for induction of labor in 100 women with singleton pregnancies, cephalic presentation and a ripe cervix were. The patients were divided into two groups, namely a suppository group and an oxytocin group. In the suppository group, a suppository containing 2.5 mg PGE in a wax base was placed in the posterior vaginal fornix. In the oxytocin group, the intravenous infusion was started with four mIU/minute. This dose was increased by four mIU every twenty minutes until satisfactory uterine activity was achieved or the oxytocin dose was 32 mIU/minute. If the women did not deliver within 48 hours , the induction was considered unsuccessful. The women delivered vaginally were asked to evaluate the induction.

The evaluation strongly favoured administration of suppository. When comparing prostaglandin applied as an intracervical gel with the vaginal suppository used in this study, the suppository proved to be more efficient and easier to administer. Kennedy et al (59) in their randomized study of 100 women with a Bishop score of five or more compared amniotomy and intravenous oxytocin with a vaginal tablet containing three mg PGE. They found that the prostaglandin group had a longer induction delivery interval but a shorter amniotomy delivery interval than the oxytocin group. The prostaglandin treated group was more satisfied and had less

pain and less bleeding. In the oxytocin group, there was a mean induction delivery time of only 5.7 hours. This together with the much greater analgesia requirement in the oxytocin group compared with the prostaglandin group, indicates that the semiautomatic oxytocin infusion rate had been rather high. This might explain the difference between their results and the results of this study. Another explanation might be that amniotomy in this study was performed in similar circumstances in both the groups. Another explanation might be that the suppository was more efficient than the vaginal tablet with its lactic base.

Legarth J. et al (60) also conducted a study to compare the safety and efficacy of vaginal and intracervical application of PGE for induction of labor with an unripe cervix. The study included 120 women. In the suppository group , a suppository containing 2.5 mg PGE in a base of five gm of Witepsol S55 was placed in the posterior vaginal fornix. In the cervical gel group five ml cervical gel containing one mg PGE in a base of five gm HPMC was applied within the cervical canal. It was seen that the vaginal suppository with 2.5 mg PGE was superior to the intracervical gel in the induction of labor. The median interval from the start of the induction to the labor was 5.2 hours in the suppository group and more than twice as much in the cervical gel group. The higher success rate after 48 hours could indicate the suppository treatment to be superior to the cervical gel treatment. It was seen that the suppository and the cervical gel methods had same effect on the Bishop score in women not in labor but the time interval from start to delivery was significantly less in the suppository group. It is seen that the suppository is a more suitable method for the vaginal application of prostaglandin than the gel. The authors found that most women consider it agreeable to avoid intravenous infusion.

4.2.1.3. For local treatment of vaginal infections

The increasing prevalence of gonorrhoea is widely acknowledged and is of increasing concern to the health professionals. The factors of additional concern are the development of resistance to the available antibiotics and the failure of current methods to reduce the rising incidence of infections. Of the different

methods of prophylaxis vaginal preparations have received the most attention. Systemic and mechanical prophylaxis while theoretically highly effective have several disadvantages. The prophylactic use of the systemic antibiotics may cause sensitization of with adverse reactions and also an increase in the number of resistant organisms. Research has turned to the evaluation of local methods which can be used by the female. Of specific interest is chemoprophylaxis using commercially available products such as vaginal contraceptives. Cole C. H. et al (61) have evaluated the potential of a chemoprophylactic vaginal contraceptive in reducing the incidence of gonorrhoea in women. They tried to find answers to the questions namely a) to what extent women infected with gonorrhoea could be encouraged to use a pessary before sexual intercourse, b) whether or not chemoprophylaxis would reduce the reinfection rate in the women. It was seen that during the controlled period the reinfection rate was higher than after chemoprophylaxis was introduced. It was shown that venereal disease education should be directed to those below the median educational level (eleventh grade) of study patients. This analysis indicates that the clinic staff should interview patients who have a greater number of sexual contacts than average , more intensively during subsequent interviews. It was seen that the women could be motivated to use a pessary ; 65% women claimed that they some times used a pessary before sexual intercourse. The older patients used them more often than the younger ones. This study has shown that vaginal prophylaxis has a place in the control of gonorrhoea.

Vaginal candidiosis is the most common genital infection in women and a large number of women develop recurrent disease. It is not known why only some women get recurrent attacks. One of the theories proposed is that recurrent vaginal candidiosis may be associated with the disordered carbohydrate metabolism. No single cause has yet been defined. Davidson and Mould (62) showed that intermittent prophylactic treatment with clotrimazole pessaries and cream kept symptoms to an acceptable level in women with recurrent vaginal candidiosis. But prophylaxis did not prevent the return of yeasts to the vagina. An alternative approach has been to use ketoconazole , an orally active antifungal agent. Balson M. J. and

Tobin J. M. (63) studied 183 women with recurrent vaginal candidiosis who received prophylactic courses of miconazole pessaries. The study was designed to assist the suitability of the regular use of miconazole pessaries. During the maintenance treatment symptomatic vaginal candidiosis did not occur but relapse was common after the prophylaxis stopped.

Thus, regular use of miconazole pessaries can reduce the recurrence rate but the prolonged prophylactic courses may not have any long lasting benefits after the treatment stops. Apart from some cases of minor irritation the only side effects reported by the patients were two cases of allergic reactions. In view of the dramatic reduction in recurrences achieved by prophylaxis the reported level of side effects is acceptable and not regarded as a cause for concern. This study has shown that symptomatic vaginal candidiosis does not occur during the regular long term prophylaxis with one or two miconazole pessaries a week. Women are pleased and relieved at their lack of symptoms that previously caused much distress in their personal and sexual lives. Long term maintenance treatment with miconazole pessaries appears to be highly effective in reducing the incidence of recurrent vaginal candidiosis. It is also acceptable to patients.

Butoconazole is a new antifungal imidazole that has been proven effective in the treatment of vulvovaginal candidiosis. Adamson G.D. et al (64) studied the safety and the efficacy of butoconazole vaginal insert in a large number of patients. This development is important since some patients consider the solid type vaginal preparations more acceptable than the vaginal creams. Patients received either 100 mg butoconazole vaginal suppository or two 100 mg clotrimazole vaginal tablets for three consecutive nights . The efficacy of the drugs was judged by complete absence of the signs and symptoms of vulvovaginal candidiosis and by the culture proven absence of Candida albicans in the vaginal secretions. This study demonstrated that butoconazole vaginal suppositories given for three days is effective and acceptable therapy for the vaginal candidiosis.

Salem H. T. et al (65) conducted a trial to evaluate and compare the oral and local regimens of treatment of vaginal candidiosis.

Eighty patients were divided into two groups. One received oral treatment in the form of ketoconazole tablets. The other received local treatment in the form of nystatin vaginal suppositories. There was significant improvement in all the clinical manifestations after one week of the treatment. Both drugs were very effective in relieving pruritus vulvae, vaginal discharge, vaginitis and vulvitis. This study has shown that the patients who received ketoconazole orally had marginally higher clinical and mycological cure rates and less recurrence rate than those who received a nystatin vaginally. The demonstration of Candida albicans in 35% of the rectal swabs justifies the use of oral ketoconazole.

Sobel J.D. et al (66) conducted a double blind study using monthly single administration of clotrimazole in women with recurrent vulvovaginal candidiosis. 80% of the women given placebo developed the symptomatic recurrences within six months of the initial course of clotrimazole and even fewer were culture negative. The patient population, the severity index and the natural history of the placebo treated patients were remarkably similar to those in the previous studies. The use of monthly prophylactic clotrimazole 500 mg suppository reduced the attack rate in the study patients by approximately one third. This study indicates that the maintenance prophylactic regimens with the antimycotic agents do provide some protective effect from the relentless, clinically disabling frequent recurrences of Candida albicans infections.

4.2. 2. Creams and Gels

4.2.2.1. For local treatment of vaginal infections by creams

Sulfonamide containing vaginal creams have been a popular treatment for nonspecific vaginitis since the original description of the syndrome. Piot Peter et al (67) conducted a study to carry out a controlled, double blind comparison of oral tinidazole, a vaginal triple sulfonamide cream and a vaginal acidified cream base for the treatment of nonspecific vaginitis. They conducted the tests on 85 women. At one and three weeks after the start of the treatment, all patients except one who had been given tinidazole were free of signs

and symptoms of the nonspecific vaginitis as compared to 59% (at one week) and 43% (at three week) of women who had been given the oral placebo. This trial suggests that tinidazole 500 mg twice daily for five days is effective in the treatment of nonspecific vaginitis and that both vaginal triple sulfonamide cream and acidified cream base for seven days are effective in only half of the cases. Although the use of vaginal sulfonamide cream has been advocated for the treatment of the nonspecific vaginitis, the low efficacy of topical sulfonamide cream was confirmed in this double blind trial. In fact, this trial suggests that sulfonamide cream may not be more effective than the cream base itself. The effect, if any, of the cream may be due to the low pH of the compound in as much as sulfonamides are basically inactive in vitro against G. vaginalis and are poorly active against anaerobes. A decrease in the vaginal pH with the use of a buffered cream with a pH of 3.9 provided some temporary relief of the symptoms in half of the patients during the treatment but had an unacceptable overall failure rate.

Andersch B. et al (68) conducted a study to compare the effect of a locally applied lactate gel with that of the systemically administered metronidazole on the symptoms and the clinical and microbiological findings in bacterial vaginosis. The patients were randomly allocated to one of the two treatment regimens : 1) oral metronidazole, 500 mg twice daily for seven days 2) five ml lactate gel inserted into vagina once daily every evening for seven days. The main active component of the lactate gel was acidum lacticum. The lactate gel was buffered to pH 3.5. The recent studies have shown a low efficacy of vaginal sulfonamide cream for the treatment of bacterial vaginosis. But lactate gel had a clinical effect equal to the oral metronidazole. With respect to short term results, both treatments were effective since all women were symptom free and none had a positive amine test on day eight. This study has shown that bacterial vaginosis is a frequently occuring infection and generally looked upon as a mild non inflammatory condition. Lactate gel seems to be a suitable treatment for this disease.

Thomason J. L. (69) conducted studies in Europe and United States to define the efficacy and safety of terconazole in both the

cream and the suppository form in the treatment of vulvovaginal candidiosis. In the United States, in the short term evaluation, the microbiologic cure rate with 0.4 % terconazole cream was equivalent to or significantly higher than the rate with two percent miconazole nitrate cream. When terconazole suppositories, miconazole nitrate suppositories and placebo were compared, there was no significant difference between the continued cure rates of the active agents or between the rates of terconazole suppositories and placebo. When studies were conducted on the European patients, it was seen that the terconazole cream was more effective than clotrimazole cream in terms of higher microbiologic cure rates. Terconazole cream was also found to be more effective than clotrimazole cream in the terms of the lower relapse rates.

4.2.2.2. For cervical priming and induction of labor by gel

Local application of prostaglandin E (PGE) in viscous gel has been reported to be an effective means of priming the cervix and / or inducing labor in the patients at term gestation with an unripe cervix. The vaginal route has gained much attention since it implies an easy and noninvasive technique. It also offers the possibility for self administration. However, because of relatively higher doses of PGE than used systemically, PGE gel may result in the side effects such as gastrointestinal discomfort and uterine hypercontractility. Intracervical administration is more complicated but requires a much smaller dose of PGE. Thus Ekman G. et al (70) compared these two routes of application of PGE gel in patients at term gestation with an unfavorable cervix. Sixty pregnant women were studied. They received at random, either 0.5 mg of PGE in two ml of gel intracervically or four mg of PGE in three ml of gel intravaginally. It was seen that, in patients with a relatively ripened cervix there were small differences in the efficacy between the two routes of application. However, in patients with highly unfavorable cervix, the intracervical application was significantly more effective than the intravaginal route. No obvious adverse side effects were registered after the intracervical application of five mg of PGE in gel. After intravaginal application of the gel many patients complained about

the gastrointestinal discomfort and also about the intense uterine contractions. The reason for the more pronounced side effects after intravaginal application is most certainly a prompt absorption of the prostaglandin compound into the systemic circulation as pointed out previously by Gordon Wright and Elder (71). Most probably, the related side effects could be diminished if the intravaginal dose of PGE was reduced. But this would reduce the effectiveness of the treatment too.

4.2.2.3. Absorption of drugs from the vagina

Methods employed for vaginal examinations during labor vary among different practitioners and facilities. There is a general agreement that sterile technique for such examinations is desirable. Antiseptics are employed frequently. Currently utilized agents include solutions such as benzalkonium chloride or detergents that contain povidone iodine or hexachlorophene. There is no evidence to indicate that the use of such agents reduces infectious morbidity for either the mother or infant. Moreover, the use of hexachlorophene containing materials poses a theoretical hazard to the fetus if the vaginal absorption and the placental transfer or absorption through the fetal scalp occurs. To quantify such absorption, Strickland D. M. and co workers (72), assayed hexachlorophene in the maternal serum and mixed cord of the women whose lubricant for the vaginal examinations during labor was a detergent that contained hexachlorophene. They used a vaginal soap. This study has shown that hexachlorophene can be identified in maternal and cord serum in an appreciable number of women whose vaginal examinations during labor were lubricated with such a soap. Labor that was longer than four hours correlated significantly with the presence of detectable levels of hexachlorophene in maternal serum. The limited scope of this study precluded an evaluation of the possible neonatal morbidity resulting from the vaginal absorption and the placental transfer of hexachlorophene. Nevertheless, in the absence of a unique benefit from hexachlorophene soap, the proved absorption and theoretical hazards of hexachlorophene to the neonate warrant that such lubricants not be utilized for the vaginal examinations during labor.

Intravaginal application of estrogen containing creams has been widely used in the treatment of vaginal atrophy and related conditions due to an estrogen deficiency. Rigg L. A. (73) conducted a study to examine the quantitative absorption of estrogens after intravaginal application of estrogen containing creams. A vaginal cream containing 1.25 mg of conjugated estrogens was used for this study. Micronised 17 B-estradiol vaginal cream was also used. This study has demonstrated that conjugated estrogens as well as the 17 B estradiol admixed with a cream base, can be readily absorbed by the vaginal mucosa in estrogen deficient women. A prompt elevation of circulating estrogens was seen after a single intravaginal application. The time course and the incremental changes in estradiol and estrone were related to the dose and the type of estrogen cream used. The largest estradiol increments with the two mg dose of estradiol cream was accompanied by the greatest degree of gonadotropin suppression and the least with the conjugated estrogen cream. The cream vehicles appeared to retard the vaginal absorption of the micronized estradiol. It was clear that the biologic effect of the intravaginally administered estrogen cream was mediated principally through delivery to the target cells by the circulation. The assumed topical effect, if present, should be relatively small. Thus caution must be excercised when vaginal estrogen cream is used to manage estrogen deficiency in the presence of estrogen dependent neoplasms.

4.2.3. Sponge

4.2.3.1. Contraception

Recent concerns about the long term safety of the hormonal contraceptives and the lack of availability of the IUD have resulted in an increased interest in the vaginal contraception. The active ingredient in almost all the vaginal contraceptive formulations is nonoxynol- 9 (N- 9). While N- 9 is highly spermicidal in vitro, it is not an extremely effective contraceptive in vivo as indicated by animal studies.

Acrosin inhibitors have been investigated for some time as the potential vaginal contraceptives. Some of the most effective acrosin

inhibitors are the aryl 4- guanidinobenzoates (AGs). Quigg J. M. et al (74) studied Today sponge for the following purposes :- 1) N-9, the manufacturing process or the soluble components of the placebo polyurathane sponge adversely affected the properties of the AGs, 2) the AGs immobilized spermatazoa and if the antimotility activity of the AGs and N- 9 are additive, 3) adequate release of AGB could be obtained from the sponge in the absence or presence of N- 9. The studies have shown that the polyurathane sponge is a suitable vehicle for the vaginal delivery of AGs. Incorporation of the AGs in the sponge did not alter the chemical properties of these agents and their enzyme inhibitory activity was not altered by soluble materials released from the sponge. There may be a benefit to deliver a combination of AG and N- 9 for the contraceptive purposes. The two types of the compounds act additively in regard to their antimotility effect so that an enhanced spermicidal activity is obtained. The release rate of AGB is higher when N- 9 is also present in the sponge so that lower doses of AGB are required.

4.2.4. Tablets

4.2.4.1. Local treatment of vaginal infections

The present trend in the treatment of the yeast infections is the shortest possible therapy with the most effective dose of the active substance because in longer lasting therapy, many patients will stop treatment soon. Thus Loendersloot et al (75) compared a single dose therapy of one vaginal tablet with the six day treatment with the vaginal tablets. For a single dose they used a 500 mg clotrimazole tablet whereas for six day treatment they used 100 mg clotrimazole tablets. One week after the treatment , the results were slightly better with single dose therapy than with the six day therapy. Four weeks after the treatments the results were reverse. The difference in the results after one and four weeks might be due to a greater tendency toward relapses after the single dose therapy. Overall it can be seen that both the treatments give favorable results. In connection with the problem of patient compliance, treatment with a single dose of 500 mg clotrimazole should in general be preferred to the six day treatment.

Bushell and coworkers (76) assessed the effectiveness of intermittent prophylaxis with clotrimazole 500 mg vaginal tablets in managing the patients with the recurrent vaginal candidiosis. They found that the intermittent local prophylaxis with a single 500 mg dose of clotrimazole administered one week before menstruation led to fewer symptomatic recurrences than experienced with the placebo treatment. Overall 76% women were kept clear of the symptomatic vaginal candidiosis for twelve months by the prophylactic use of clotrimazole 500 mg vaginal tablets either once or twice a month. Although prophylaxis with clotrimazole was helpful in preventing recurrences of the symptoms and clinical signs, it did not affect mycological recurrence. Yeasts recurred at almost the same rate, irrespective of the prophylaxis regimen used.

Stein G. E. (77) conducted a study to compare the efficacy and acceptability of a single intravaginal application of 6.5 % ticonazole ointment with a three day regimen of clotrimazole vaginal tablets in the women with vulvovaginal candidiasis. 80 patients were divided into two groups. One group received ticonazole whereas the other received clotrimazole. The results of this study suggest that a single application of 6.5 % ticonazole ointment is as effective as a three day course of vaginal tablets. Although a number of patients experienced an untoward effect with ticonazole, none found the treatment unacceptable.

Kjaeidgaard Anders (78) conducted a clinical trial on 2000 European women. These trials were conducted to evaluate the clinical efficacy of terconazole in a Swedish suburban population with a high proportion of patients with the factors predisposing to therapeutic failure. A single dose as well as a three day therapy with terconazole vaginal tablets was compared with a three day therapy with 200 mg clotrimazole ovula. This study was conducted in a population with the high frequency of recurrence after the treatment with well established antimycotics such as nystatin and clotrimazole. No differences in the symptomatic relief and the initial cure rates were found between the three regimens. However, a significantly higher mycological cure rate at four weeks was demonstrated after a three day therapy with terconazole. This treatment was also highly efficient in the patients with a recurrent cadidiosis, while

unsatisfactory high mycological and symptomatic relapse rates were recorded in the high risk group after the treatment with 200 mg clotrimazole ovula or one 240 mg terconazole pessary. Single dose therapy with terconazole was clinically efficient in patients without predisposition to recurrence. Thus this treatment may represent a valuable therapeutic alternative for these patients, as the common problem with leakage of the pessary from the vagina is diminished by administration of the total dose in a single pessary. The overall results demonstrate that terconazole is a highly efficient and well tolerated antifungal agent when administered intravaginally at a total treatment dose of 240 mg. Treatment with terconazole was at least as effective as three day treatment with 200 mg clotrimazole vaginal tablets in terms of the initial relief and the mycological and symptomatic cure.

4.2.4.2. Contraception

The use of antiestrogen, antigonadotropin drugs in the treatment of endometriosis is well established. The most widely used antigonadotropin is danazol. Recently, gastrinone which is also a antiestrogen, antiprogesterone has been shown to produce the same results at much lower doses. While the effective therapeutic dosage of danazol is between 200 and 800 mg daily, gestrinone is effective with the dosages between 5 and 7.5 mg two or three times weekly. In order to overcome the difficulty of treating these patients by oral route and based on the knowledge of the vaginal administration of the contraceptive pills, Coutinho E. M. et al (79) decided to investigate the efficacy of gestrinone administered by the vaginal route in patients with endometriosis. It was expected that the absorption by the vaginal epithelium would result in the greater concentrations of the drug in pelvic area where it is needed, whereas avoidance of the first pass through liver would reduce the side effects associated with the impact of the steroid as a bolus on the liver cell. Comparison between the two routes, namely the vaginal and the oral, shows that the vaginal route may be used with equal success as the oral route in both the suppression of the symptoms and the pregnancy rate following discontinuation.

The significantly lower incidence of seborrhoea and acne confirms the expectation that the vaginal absorption allows better tolerance by the patients who already have acne and seborrhoea or who are more susceptible to developing these conditions under the long term treatment with an antiestrogen. Weight gain, which is a undesirable effect of most hormonal treatments, seems to be significantly reduced by vaginal administration. The higher drop out rate for the vaginal route users may reflect the lack of familiarity of the patients with this route of administration. The main reason for the discontinuation was inconvenience, strangeness of the technique or distrust in its effectiveness.

The vaginal route as an alternative delivery system for the oral contraceptive pills has been successfully tried. Souka A. R. et al (80) tested the effectiveness of a low dose oral contraceptive when administered vaginally on human ovulation. The study was conducted in Egypt. It was conducted on twenty women who were divided in two groups. One inserted two tablets vaginally daily while the other inserted one tablet daily. The tablets contained 1 mg norethisterone and 0.05 mg ethinyl estradiol. Suppression of ovulation was seen in the group using two tablets daily; it was not found in the other group. This failure may be due to the decreased absorptive capacity of the vaginal mucosa of the individuals under study. The incidence of side effects was more with the high dose regimen, indicating a relationship between the dose of the hormones administered vaginally and the occurrence of the side effects. Vaginal administration of the low dose pills was not associated with a greater incidence of breakthrough bleeding or spotting. Thus, it was concluded that ovulation was suppressed in a high percentage of cases using low dose combined pills vaginally, with minimal side effects and with good cycle control.

4.2.4.3. Induction of labor

The use of intravaginal tablets of prostaglandin E has been reported to be effective in inducing labor. The method is simple and the patients can ambulate until onset of an active labor in contrast to the standard method of intravenous oxytocin. Grunstein S. et al (81) conducted a randomized controlled trial to study labor induction by

prostaglandin E tablets, 110 women were selected for the study. It was seen that the scoring system reported can be useful for determining in each case the dose of vaginal prostaglandin E for the induction of labor. The uterine response to prostaglandin was not uniform and depends on the several factors. Thus the use of a standard dose for induction of labor may not be appropriate. The dose should be adjusted for each individual in order to minimize the risk of overdosage.

Mao et al (82) compared the effects of a PGF gel applied intracervically to that of Gemeprost vaginal tablets in a group of 100 patients, 50 patients were treated with a vaginal tablet of Gemeprost and 50 others by the intracervical application of PGF gel. The results of this study showed the superiority of the effect on cervical dilatation of Gemeprost compared to PGF gel. The main side effect was pain which was much more frequent with Gemeprost. The superiority effect of Gemeprost compared to PGF gel could be due to the chemical differences between the two drugs, due to the excipients and their effect on absorption or to the variability in the technique of intracervical application of the gel. Insertion by the patient herself of a tablet seems easier. After comparing the two routes of administration of prostaglandins for cervical dilatation prior to an induced abortion in the first trimester, the authors feel that the use of the vaginal tablets inserted by the patients themselves on the monitoring of surgery is a safe, practical and more effective method of cervical priming than the intracervical application of the gel.

4.2.5. Tampons

4.2.5.1. Local treatment of infections

Since the introduction of vaginal tampons more than 45 years ago, the variety of products and complexity of materials used in their manufacture have steadily increased. Consequently, the effects of the tampon components on the vaginal micro organisms and on the immunological responses of the women using them are causing increasing concern. The recent association of Staphylococcus aureus and the use of superabsorbent tampons with the increased risk for

developing toxic shock syndrome in menstruating women has stimulated an interest in the biological effects of the tampon components. Significant differences were found between different kinds of tampons and tampon components in their inhibitory effect on gonococci from the peritoneal cavity of mucin-treated mice. Thus Arko R. J. and co workers (83) tested 16 different commercial tampons with the 46 strains of N. gonorrhoeae isolated from patients who had 1) disseminated gonococcal infection, 2) pelvic inflammatory disease or 3) uncomplicated gonococcal infection. In addition, aqueous extracts of selected tampons were tested for their ability to alter the resistance of mice to the subcutaneous chamber infections with N. gonorrhoeae. It was found that tampons varied significantly in their in vitro inhibition of gonococci. Playtex tampons inhibited the greatest number of gonococcal strains while Rely tampons did not show inhibitory activity with the 46 strains tested. Results of the in vitro and in vivo tests generally matched. However, the Rely tampon which showed no in vitro antigonococcal activity significantly increased the resistence of mice to the subcutaneous chamber infections when extract of the tampon was injected 30 minutes before challenge. The finding that certain tampons showed a little in vitro inhibition of gonococci but did induce significant inhibitory effects in vivo suggests the presence of host-reactive substances. Although the practical implications for the antigonococcal effects of certain tampons are not known, Lossick et al (84) reported that the women with gonococcal PID used tampons as frequently as women who did not develop PID. The present study showed that the antimicrobial effects of various tampons may vary significantly. Tampons may vary substantially in the relative composition of different fibres used in their manufacture. Thus, the observations in this study reflect the composition and chemical processes used during the manufacture of these lots. Until the inhibitory nature of the specific materials used in each tampon is known, tampons being considered for use in culture related studies should be evaluated for the possible inhibitory effects.

Although there is a variety of antifungal compounds available for the treatment of candidal vulvovaginitis it is clear that clinical efficacy of such agents may be offset in many patients who fail to

complete a full course of treatment. Long courses may be abandoned by the patients who object to the usual creams, ointments, pessaries etc. because of difficulty of application or leakage or for other aesthetic reasons. One compound, miconazole, has now been made available in the form of a coating on the absorbent vaginal tampons. Bergstein N. A. M. (85) has presented the clinical and mycological findings of a study of miconazole coated tampons in the treatment of the patients with candidal vaginitis and compares the relative efficacies of three different regimens. Group A : a tampon coated with 100 mg miconazole was inserted into vagina twice daily upto a total of fifteen tampons. Group B : one tampon was inserted into the vagina twice daily for five days. Group C : one tampon was inserted daily for five days. The results have shown that miconazole coated tampons are effective in the relief of vulvovaginal candidal infection provided they are used twice daily for at least five days. The high clinical and mycological cure rates achieved with this regimen compare favorably with the published cure rates for miconazole creams and pessaries used for longer periods. The tampons are a highly acceptable mode of presentation for the vaginal antifungal compounds; they could be used easily and continue to be used during menstruation. The present study together with trials of short courses of imidazole derivative antifungal agents shows that the three or five day treatment may be as effective as fourteen day courses in many cases.

Balsdon M. J. (86) compared the therapeutic effectiveness and acceptability to the patients of miconazole coated tampons with those of clotrimazole vaginal tablets in the treatment of vulvovaginal candidosis. The results for miconazole tampons compared favorably with those of miconazole pessaries and cream. The cure rates immediately after treatment were similar for the groups treated with miconazole coated tampons and clotrimazole tablets. The recurrence rates were lower in the tampon group but not significantly. The tampons were highly acceptable to patients as the treatment lasts only for five days and there is no leakage of medication from the vagina.

4.2.5.2. Toxic shock syndrome and tampons

Toxic shock syndrome (TSS) is a severe, frequently life

threatening illness in which the highest incidence continues to occur among the young menstruating women who use the superabsorbant synthetic varieties of tampons. It has been demonstrated that the tampons rich in synthetic fibres provide physical chemical conditions that are optimal for S. aureus exotoxin production in general, and toxic shock syndrome toxin 1. Tierno P. M. et al (87) used an animal model to investigate the role of TSS S. aureus tampons and other vaginal bacteria. They also conducted a retrospective microbiological analysis of 60 fatal and 72 non fatal cases of human TSS. It is well known that the exotoxins of staphylococci and streptococci can enhance the lethal shock caused by the endotoxins. This is may be due to the interaction between exotoxins with reticulo endothelial system (RES). The blockage of the RES of the liver and the spleen caused by staphylococcal exotoxins can potentiate the lethal effect of endotoxins. This effect may be prevented if sufficient antibodies to exotoxins are present. The majority of TSS patients have been found to have a very low or no antibody titers to TSST- 1 and these titers have been shown to increase with the age placing the young in the highest risk category for the TSS development. The data from these experiments has suggested that the tampons provide physical and chemical conditions ideal for the proliferation of the metabolic by-products from the TSS strains of S. aureus which when combined with endotoxins become lethal. An enhancement of the lethal effect by some tampon leachables was noted with the exotoxins and the endotoxins. Whole tampons, tampon components, and some other surfactants leached from the tampons have been reported to increase the TSST- 1 when grown in the presence of blood and increased CO_2 and O_2 levels.

4.2.6. Vaginal ring

In vivo release from a vaginal ring

The first investigations on the steroid releasing contraceptive rings were described in 1970. The rings used contained medroxyprogesterone acetate and were fabricated from the biocompatible polymer, polydimethylsiloxane. This work demonstrated the advantages of the vaginal ring mainly in patient

compliance, self insertion, avoidance of the hepatic first pass effect and hence the lower steroid dosage. Subsequently a number of workers demonstrated the feasibility of this method using various ring designs and administered steroids. One of the ring designs employed the progestagen norethindrone in dosages of 50 ug/ 24 hrs and 200 ug/ 24 hrs. Unfortunately the dosages and progestagen chosen resulted in an unacceptable pregnancy rate associated with the former while the latter was associated with an unacceptably high incidence of irregular vaginal bleeding. Jackson R. et al (88) investigated a ring originally designed to release both the estrogens and the progestagens. The ring used in this study was designed to allow for the release of one or more steroids independently at near zero order rates of release. It was seen during the study that the ring was well tolerated and no expulsion took place. The results indicate that the ring is capable of releasing the drug in small quantities over a prolonged period of time with minimal decrease in plasma levels over the time tested. It seems that this delivery system would be able to produce stable plasma levels for periods longer than 21 days tested in this study.

4.2.7. Capsules

Soft jelly capsules are one of the basic spermicidal carriers. Bassol S. et al (89) have investigated if the capsular rupture and the active compound release occur earlier in the treated capsules than in the non treated capsules after their vaginal insertion and have evaluated whether the pH and vaginal infection modify the rupture time and the active compound release. The differences between the treated and non treated capsules were as following : 1) the vehicle used in the treated capsules was more hydrosoluble; 2) the jelly used in the treated capsules contained a gel and a plastificant; 3) the treated capsules received a wash with saline solution. The trial was conducted in Mexico on 96 volunteers. The results showed that most of the capsules (61 %) ruptured. The major active compound release in most of the study groups, independent of the parameters investigated, occured at minute five. Therefore, the intercourse delay period was minor with respect to the solid slow release spermicidal method most widely used by the family planning programs in Latin

America. Vaginal infections associated with the alkaline pH, multiparity and vaginal dryness play a great role in the rupture of the capsules. In women with vaginal infections, there were more cases of rupture in the treated capsules (66 %) than the non treated capsules (50 %). When the reduction percent was compared between the treated and the non treated capsules, a significant difference was found. Thus, the treated capsules offered a greater safety in terms of effectiveness than did the non treated capsules. The weight increase of the non ruptured capsules and corrugations seen on their surfaces suggested an absorption and softening by the vaginal secretions. The mean weight loss attributable to the release of the active compound at any time was not more than 42%; thus the investigators have suggested reduction of the capsular wall thickness and further postcoital tests to assess the method's effectiveness.

CONCLUSION :-

Though, a substantial amount of research has been conducted on vaginal products, there are still many of areas which need more attention. There is still not completely safe contraceptive available in the market. We need further information about in vitro tests for vaginal products. Women's opinions on the vaginal products need to be considered more seriously. We hope that this review will assist in stimulating more research of this most important topic.

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