REVIEW OF LITERATURE
Mens truation is a function peculiar to women. It is defined as the periodic and cyclical shedding of the progestational endometrium accompanied by loss of blood. It takes place approximately at 28 days interval between the menarche and the menopause. There is an intimate relationship between the hypothalamus, the pituitary gland the ovaries and the uterus. Each of which influences the functions of the other.

It is not known what triggers the hypothalamus to release GnRH in years prior to puberty, but it is thought that repeated small stimuli from GnRH induces the gonadotroph cells of the anterior pituitary to synthesize and to release small amounts of gonadotrophin into the circulation until eventually sufficient amounts are released to stimulate ovarian activity. Initially FSH is released with only a small amounts of LH.

Above a critical circulating concentration FSH stimulates a few sensitized follicles in the ovary to mature. FSH also induces the theca cells while sorround these follicles to secrete increasing amounts of oestrogen. The rising concentration of oestrogen feeds back to the pitutary and the hypothalamus in a negative way reducing the amount of FSH oestrogen levels continue to rise to reach a peak.
The uterus is influenced by these rising levels of oestrogen causing proliferation of the endometrium stimulating the growth of the glands and compacting the stroma. It increases the vascularity of the organ and causes the development of the myometrium. The midcycle surge of oestradiol increases the sensitivity of the pituitary gondotrophs and induces a surge release of GnRH. This is the positive feedback. The GnRH surge induces a small FSH and a large LH surge, ovulation occurs about 30 hours after the LH surge.

Following ovulation in the secretory phase of the menstrual cycle. The theca granulosa are luteinized and begin to secrete progesterone and a corpus luteum is formed by the 5th day of ovulation the corpus luteum is fully functioning.

The circulating progesterone added to the circulating oestrogen exerts a negative feedback on the hypothalamus and the pituitary causing a fall in levels of FSH and LH. Unless the released ovum is fertilized and implants within 7 days of ovulation, the corpus luteum begins to degenerate with a rapid seduction in oestrogen and progesterone. This is insufficient to support the endometrium and approximately 14+2 days after ovulation the endometrium breaks down and its blood vessels rupture causing bleeding.
THE CERVICAL CYCLE

The cervix uteri is influenced by the waxing and waning secretions of the female sex hormones. In the follicular phase the cells lining the clefts of the cervical canal/proliferate an actively secrete a thin watery mucus. This is most marked at the time of ovulation when a cascade of mucus can be seen. During the follicular phase the cervical mucus absorbs water and salts and when allowed to dry deposits crystals of sodium and potassium chloride. The ovulation cascade is related to a low content of proteins in the cervical mucus.

During the luteal phase the cervical glands become more branched and their secretion changes its physical and chemical properties. The mucus becomes more viscous and forms a more secure cervical plug. These changes are related to an increase in the amount of proteins in the mucus and to the presence of phospholipids under the influence of progesterone. The electrolyte content of the mucus is also reduced. During menstruation the cervical glands collapse and may show slight desquamation with loss of blood.

CERVICAL SECRETIONS

Cervical secretion is an alkaline mucus like the unboiled white of an egg. Cervix secretes 20-60 mg of mucus/day which increases to 700 mg/day during the menstrual cycle of a women's reproductive life. The menstrual cycle changes the cervical secretions.

**BIOCHEMICAL COMPOSITION**

Water 85-98% and mucoids and mucins, 25% amino acid chains 75%, glucose, sialic acid, albumin, globulin lipoprotein immunoglobulins, lactoferrin, enzymes like alkaline phosphatase, glucuronidase, diastase, glucose, cholesterol, sodium chloride, potassium and prostaglandins. The secretory immunoglobulins are considered as the first line of defense.

**IMMUNOGLOBULINS**

The antibody activity of serum and other body secretions is associated with a heterogeneous group of proteins collectively known as immunoglobulin. These proteins are also known as gamma globulins because of the relative electrophoretic mobility. Many antibodies migrate more rapidly than gamaglobulins and some molecules unrelated to antibodies may also migrate with the electrophoretic mobility of gamaglobulins. For these reasons the term "immunoglobulins" and symbol Ig has been suggested to designate the family
of molecules with antibody activity (Committee of
omenclature of human immunoglobulin Bull. W.H.O.

Gross et al (1959) described three main types of
immunoglobulins with antibody activity which are
immunoglobulin G (IgG), immunoglobulin M (IgM) and
immunoglobulin A (IgA). Recently two more proteins
with immunochemical characteristics related to these
immunoglobulins like immunoglobulin D (IgD), and
immunoglobulin E (IgE) has been detected. Despite the
tremendous heterogeneity all the immunoglobulins
shown structural similarity.

Immunoglobulin molecules are composed of two
kinds of polypeptide chains. Each molecule consists
of large identical polypeptide chains referred to as
heavy chains and two identical smaller ones referred
to as light chains. These polypeptide chains are held
together by disulfide bonds and by non covalent bonds
which are primarily hydrophobic. The heavy and light
polypeptide chains are synthesized on separate ribo-
somes assembled in the chains and secreted as an intact
molecule. Five immunoglobulin classes (IgG, IgA, IgM,
IgD and IgE) are recognised on the basis of structural
differences of their heavy chains.
IMMUNOGLOBULIN G (IgG)

Immunoglobulin G (IgG) is the major immunoglobulin and constitutes about 3/4 of the total gamaglobulin. The serum concentration varies from 800-1600 mg/dl in adults but intravascular pool accounts for less than half of total body immunoglobulin. About 55% is widely distributed within the extra vascular spaces. IgG molecules have half life of about 21 days and are the longest lived immunoglobulins. The total body content is in excess of 1 mg/kg body weight. On the basis of antigenic determinants within the heavy chains of IgG four isotypic sub classes of IgG molecules have been identified in the normal serum. These are IgG₁ 66%, IgG₂ 23%, IgG₃ 7% and IgG₄ 4%. It is the only globulin which is selectively transferred across the placenta giving major pretection to new born infant (Fahey, 1965).

SECRETARY IMMUNOGLOBULINS

IgA is the predominant immunoglobulin in external secretions of the respiratory tree, GIT and the genito urinary systems, in tears, saliva and colostrum. The IgA producing plasma cells are the predominant plasma cells in the sub mucosa. Secretary IgA is composed up to two IgA molecules bound to a secretory piece by disulfide bonds. The secretory piece is a polypeptide
chain with a molecular weight of 70000 daltons that is synthesized by epithelial cells. The dimeric IgA is held together by a single J chain which is also synthesized by sub mucosal plasma cells. Once the dimeric IgA chains leaves the plasma cells it enters the epithelial cells and becomes covalently bound with the secretory piece. It is then secreted in the lumen. Secretory IgA can have antibody activity to bacterial and viral antigens and toxins. They bind microorganisms and prevent their attachment to epithelial cells and administration of antigens have resulted in an enhanced production of secretory IgA in the respective organs.

**IMMUNOGLOBULIN M**

Immunoglobulin M is the protein with molecular weight 850000 daltons. IgM is also known as macroglobulin due to its high molecular weight. The rate of synthesis of IgM is only 1/20 of IgG where as their fractional catabolic rate is 2-3 times that of IgG (half life 5 days) and this accounts for low serum IgM levels (80-300 mm/dl). Little if any IgM crosses the placental barrier and the IgM present at birth is predominantly of foetal origin.

Tiselius (1937) reported fall in gammaglobulin protein in the IIIrd trimester of pregnancy and he
corelated this fall with transfer of immunity from mother to the foetus.

Brown in 1954 studied for the first time the stagewise alteration of immune globulin in pregnancy and suggested that gamma fraction of immunoglobulin is unaltered in the first trimester. Thereafter it decreases steadily in late pregnancy.

The mean IgG levels in pregnancy found by Gusdon (1969) was somewhat higher than recorded by others. Serum IgG concentration throughout later half of pregnancy differ in that they are consistently higher by 200 mg% at each week of gestation in comparison to others. Maternal and foetal IgG were equalled at 33 weeks and after that mean foetal IgG were slightly higher than maternal values.

Best et al (1969) reported greatest fall in serum IgG and IgA levels during pregnancy and this fall is linear throughout pregnancy.

Maroulis et al (1971) observed that concentration of serum IgG diminishes with each successive trimester, whereas concentration of other two immunoglobulin IgM and IgA were either unchanged or had no consistent trend. The lowering of serum IgA concentration was statistically significant. They found statistically
significant difference of IgG concentration between second and third trimester and control group.

Ganguli et al (1980) reported a decrease in IgG levels during pregnancy up to parturition. IgG and IgM levels were higher in the first trimester than those of controls. The raised IgG and IgM levels dropped to normal during terminal stage of pregnancy with further fall in IgG and IgM levels at the time of parturition. No change was observed in IgA levels during pregnancy.

In 1941 Kerr W.R. and Robertson, M. first suggested the production of local antibodies by the vagina who observed the presence of agglutinins to trichomonally affected foetus of heifers.

In 1943 Kerr and Robertson again observed the same findings in infected heifers they also showed that these antibodies were probably responsible for the disappearance of the organism from the vagina after oestrus.

Pierce (1946) has found that agglutinating antibody to trichomonas foetus appears in the vaginal mucus of infected cows earlier at higher titres than in the serum.

Kerr and Robertson (1953) demonstrated the independance of local vaginal and serum antibodies in trichomoniasis of cattle confirming their earlier
observation which further strengthened the view that local production of antibodies occur in the female genital tract.

Huges (1937) gathered the evidence of local vaginal antibody production against foetus affected by vibrio in cattle.

Batty and Warral (1955) have observed the evidence of local production of antibodies against diphtheria toxoid and tetanus toxoid in vaginal and uterine walls.

Kerr (1955) has demonstrated that local antibodies are found in vaginal mucus when cattle are infected with bordetella abortus.

Ven Kaula et al (1957) have reported from their studies with radioisotope labelled (I^13) albumin that exogenously administered (I/V route in their case) substances were rapidly excreted by the human cervical glands and are concentrated in the cervical mucus. They have also observed that patients in the progestational phase of the menstrual cycle, seemed to concentrate radioiodine in the cervical mucus more rapidly and to a higher levels than those in the early phase of the menstrual cycle.

Lindhl et al (1956) reported the appearance of antisperm agglutinin in the cervical secretion of
human females shortly after ovulation and in the second trimester of pregnancy.

In 1958 Geslonitz et al have demonstrated the presence of anti A and anti B agglutinins in the cervical secretions of normal women.

Teponga (1959) has informed the findings of earlier workers that cattles infected with vibro foetus also showed local antibody production to these organism in the vaginal mucus.

Strauss (1961) observed the occurence of antibodies to typhoid bacillus following local inoculation in human vaginal mucus. She further noticed better response to vaginal inoculation for production of local antibodies as compared to production of serum antibodies following parenteral immunization in human females.

Solish et al (1961) studied the random samples of human cervical mucus (82) and observed the presence of isohaemagglutinins observation on multiple samples obtained from 41 women failed to suggest any correlation between antibody titre and phase of menstrual cycle.

Moghissi et al (1962) again confirmed the presence of gammaglobulins in human cervical mucus. They hypothesized a role of these gammaglobulins in fertility.
Anzoi et al (1963) also reported the presence of gammaglobulins in human cervical mucus.

Chodirkar and Tomasi (1963) studied three types of gammaglobulins (γ^2, γ^1A and γ^1m) in human serum and various body fluids including vaginal fluid. They found that in vaginal fluid the rates of γ^2/γ^1A did not differ significantly from that of the serum.

Firemans et al (1963) reported that in cervico vaginal secretion IgA:IgG ratio is higher than that of serum and that antibody present in the secretion belongs to the secretory IgA class.

Schumacher et al (1965) studied serum proteins in human cervical mucus using immuelectrophorctic methods. They analysed cervical mucus samples during various phases of menstrual cycle in normal women. They could not find any significant difference in gammaglobulin levels during these phases. They also noticed significantly higher levels of gammaglobulin in cervical mucus of patients suffering from cervical erosion and chronic cervicitis.

Moghissi and Nenhaus (1966) did not find any remarkable change in the cervical mucus immunoglobulins throughout the menstrual cycle in four fertile normal healthy women.
Bell and Wolf (1967) demonstrated the invitro production of antibodies against diptheria toxoid by rabbit vagina following direct exposure of rabbit vagina to the antigen in vivo. They could not find any invitro production of antibodies by rabbits uterus during the same study.

Parish et al (1967) studied the human cervical mucus during the non menstrual interval in selected women, cervical mucus extracts contained gammaglobulins and several other types of serum proteins. These globulins included agglutinating antibodies to the A and B blood group antigens and immune type haemolytic anti A and anti B antibodies to E. coli and condida albicans. In eleven women certain antibodies were present in cervical mucus but not in serum pointing towards local antibody production.

Elstein and Pollard (1968) demonstrated the presence of immunoglobulins in progestational cervical mucus while noting down the variation of albumin level in cervical mucus in various phases of menstrual cycle.

Parish and Ward (1968) studied cervical mucus of three infertile women where other causes of infertility were excluded. They found that one woman had an IgG cytoxic antibody in her serum and cervical mucus which
caused complement mediated disruption of spermatozoal head, the second woman had antispematozoal cytotoxic antibody IgG of immobilizing type. Besides these IgG three, harmless immunoglobulins (IgG and IgA) class were also found in the three women.

Masson et al (1969) analysed biochemical composition of pooled human cervical mucus and reported the concentration of various immunoglobulin i.e. IgA 0.090 mg/ml, IgG 0.45 mg/ml, IgM 0.035 mg/ml. The IgA and IgG ratio was thus 1:5 which approximately equal to that of serum.

Hulka and Omran (1969) studied cervical mucus from 7 women with proven fertility. IgA was found to be present in concentration of 2.8-90 mg/100 ml and IgG was present in concentration of 9-4.56 mg/100 ml. IgA/IgG ratio tended to increase as the cervical mucus volume increased at mid cycle.

Elstein (1970) studied the effect of progesterone on proteins of cervical mucus. At mid cycle only albumin was present in most of the cases.

Immunoglobulin and transferrin were normally not identifiable. Shortly after ovulation transferrin and immunoglobulin reappeared in the mucus with immunoglobulins becoming quite prominent and diminishing towards
the end of luteal phase. The progesterone influence on cervical mucus was manifest as an increase in protein concentration and appearance of prominent bands of transferin and immunoglobulin.

Tourville et al (1970) made immunofluorescent studies on various tissues of human female reproductive tract including uterine tube. Endometrial, cervical and vaginal biopsy material. They demonstrated the presence of G and A and M immunoglobulins in these tissues.

G and A were the predominant immunoglobulin. Both G and A increased during the secretory phase. Moreover secretory protein was also present in these tissues thus confirming the fact that local secretion of IgA occurs in these tissues.

Waldman et al (1971) detected immunoglobulin levels in cervicovaginal secretions from 131 normal women. IgA was found in 117 with a mean of 0.22 mg/ml. IgG in 124 females with a mean of 0.12 mg/ml and IgM in 41 with a mean of 0.01 mg/ml. In 74 samples IgA was the predominant immunoglobulin class in 48 IgG was predominant and in 9 patients the two were equal. The percentage of the total immunoglobulin that was IgA averaged 69% of all the samples. In older age groups the percentage of total immunoglobulins that was IgA
decreased and IgG increased. There was significantly
greater percentage of IgG in the cervico vaginal
secretion of women over 50 as compared to women below
30 ($P \leq 0.05$). In a variety of conditions such as
pregnancy, sterility vaginitis etc. the IgA:IgG ratio
in the cervicovaginal secretions remained unchanged.
The relation with the phases of menstrual cycle also
caused no significant changes in the immunoglobulin
composition of the cervico vaginal secretion.

Chipperfield and Evans (1972) studied the formation
of immunoglobulin in the lamina propria of the endocerc-
vix in relation to specific acute local infection.
Plasma cells containing IgA, IgG, IgM were identified
immunohistochemically by the direct fluoscent
antibody method in specimens obtained by needle biopsy.
Infection by Neisseria gomorrhoeae trichomonas vagin-
itis a condida albicans was associated with an increase
in the number of fluorescing plasma cells in all three
classes, but predominantly IgA; plasma cells of IgM
class were more prominent in trichomoniasis than in
the other two infection. There was no apparent rela-
tionship with menstrual cycle, oral contraceptives or
cervical erosion. They suggested that immunoglobulin
production in the endocervical submucosa might be
considered as a mechanism required to prevent pathogenic invasion of the uterus and tubes.

Waldman et al (1972) immunized 10 women intravaginally with candida albicans vaccine antibody response in cervicovaginal secretions was predominantly IgA type. There was no coincident rise in serum IgA type levels indicating local production of IgA in cervicovaginal secretion. They postulated a role of these antibodies in opsonization of candida albicans or complement mediated destruction of these organisms. Ogra and Ogra (1973) studied antibody response to poliovirus type I in serum, the nasopharynx and the secretions of the genital tract in human volunteer after intravaginal and intrauterine nasopharyngeal or intermuscular immunization with inactivated poliovaccines. Intravaginal and intrauterine immunization consistently resulted in the appearance of secretory antibody to poliovirus in the genital tract. The vaginal response was predominantly of A immunoglobulin while the response in the uterus was essentially limited to G immunoglobulin. Intramuscular immunization resulted in a delayed appearance of G response in the genital tract which could be correlated with the highest G antibody titres in the serum. No genital A response
was observed, however after such immunization these observations provided evidence for local synthesis of poliovirus antibody in the genital tract in the view of these workers.

B.M. Coughlan and Skinner (1977) studied the immunoglobulin concentrations in cervical mucus in patients with normal and abnormal cervical cytology. IgG and IgA were present in every mucus samples while IgM was only occasionally seen in some. There was an increase in the levels of IgG and IgA towards the last week of the menstrual cycle, None so far IgA. These increasing levels may serve to protect the early conceptos from potentially pathogenic infectious agents similarly patients with abnormal cervical cytology showed increased IgG and mere strikingly IgA concentration but there was no corelation between the two at any stage of the menstrual cycle. Whereas in patients with normal cervical cytology, the IgG and IgA concentrations corelated throughout the menstrual cycle. The increase in IgA concentrations in patients with abnormal cervical cytology may represent a local response to abnormal epithelial cells or to a prolonged antigenic stimulus from an exogenous or endogenous infection agent.
Amino et al (1978) studied the changes of serum antithyroid antibodies during and after pregnancy in autoimmune thyroid disease. They found a decrease in the levels of both antithyroid haemagglutination antibodies (IGHA) and antithyroid microsomal haemagglutination antibodies (MCHA) during pregnancy and a increase in the titra of these antibodies was seen after delivery. Similar transient increases in antibodies were observed after spontaneous and therapeutic abortion - These changes are attributed to the fact that maternal immunological inertness has been postulated as one mechanism for protecting the foetal allograft, as a consequence of which the levels of serum concentration of IgG, IgA and IgM should be decrease in normal pregnancy. Haemodilution occuring during pregnancy might also contribute to a the reduction in the levels. Hormonal changes associated with gestation such as increased free serum cortisol and choriomic goadotorpin have an effect on the hemostatic immune regulation preventing rejection of the foetal allograft.

Gulbir Bhatia et al (1981) studied the changes in the levels of secretory immunoglobulin in cervical mucus in normal patients with respect to the different phases of menstrual cycle, the three trimesters of
pregnancy and menopause and in women suffering from cervical pathology. As the secretory immunoglobulin are thought to represent a first line of defence a known ledge of the changes occurring consequent to infections might serve as a predictor for the graver pathologies of the cervix including malignancies. There was a decrease in the levels of IgA and IgG in mid cycle and maximum concentration was seen towards the end of the cycle. The mean values of IgG being more than IgA.

The levels of IgG and IgA were also lower in the three trimesters of pregnancy when compared to the premenstrual levels, the ratio of IgG:IgA was found to be decreased in 2nd trimester as compared to 1st and 3rd.

In pathological condition of the cervix both immunoglobulin were raised as compared to normal women and especially IgG was significantly increased. The increasing levels premenstrually are attributed to hormonal changes on the cervical mucus. Estrogen are known to cause a decrease in the concentration of immunoglobulin, whereas progesterone increases the concentration. The levels of immunoglobulins are found lower in pregnancy, due to immunosuppression occurring during pregnancy to save the foetus being a allograft in the maternal tissue.