REVIEW OF LITERATURE
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The reproductive life of a woman depends entirely upon the phenomenon of ovulation. The reproductive process results from a complex series of interaction of hypothalamus, pituitary ovary and genital tract. Ovary plays the role in coordinating interactions of these component organs to bring about normal ovarian function.

Normal ovarian functions result in two major classes of product—sex steroid hormones and ova. Both are products of the follicular apparatus interacting with surrounding stromal elements under the stimulus of hormones secreted by pituitary which is controlled by the pituitary which is controlled in turn by hypophysiotrophic hormones (Rose and Wiele, 1974).

Disorders of ovulation are relative frequent and are responsible for infertility in about 15-20% of patients. These disorders include anovulation, oligo-ovulation and luteal phase defect (Moghissi and Wallach, 1983).

Corner (1927) was the first to suggest anovulatory menstrual cycles in women. Since then incidence of anovulation as a cause of infertility has been reported by various authors (Saha, 1961 and Israel, 1967). In a study of 291 infertile couples, anovulation was found to be the cause of infertility in 50.2% cases (Thomas and Forrest, 1980).
Such cycles in which an ovarian follicle matures to the point to rupture but fails to rupture and no corpus luteum is formed, was described by Novak. The presence of an anovulatory cycle or anovular amenorrhoea is physiological in women only at puberty and at menopause. However, it is an important cause of infertility. Anovulatory cycles alternating with normal cycles referred to as 'Oligo-ovulatory cycles' (Garcia and coworkers) are of relatively common occurrence.

Recent review concerning the mechanism of ovulation and its failure have been put forward by Bettendorff (1965), Betella (1967), Rennels (1967) and Wallach (1967) and are in agreement on the following principal factors.


Intrinsic alterations in the pituitary gland involving changes in the FSH and LH ratio may also cause anovulation.

Poor ovarian responsiveness undoubtedly leads to failure to ovulate. Sopena (1961) described the adnexitic ovary, in which the tunica albuginea cannot pierced owing to inflammatory fibrosis. Perhaps some similar situation is present in stein leventhal ovary (Greenblatt, 1961; Greenblatt et al, 1963). Mayer and Cochrane (1962) as well as Strassman (1945) have indicated
that premature death of the oocyte determined follicular
atresia and inability to the follicle to rupture.

Koreman et al (1965) found increased testosterone
levels in blood in patients with anovulatory cycles.
Greenblatt (1961) observed occurrence of anovulatory cycles
after prolonged androgen therapy and postulated that the
same mechanism was involved in infertility owing to hyper-
corticism. Lucis et al (1966) noted increased 17-keto-
steroid values in cases with anovulatory cycle.

and Zener (1961) reported the occurrence of anovulatory
cycles in association with the androgenital syndrome.

Severe hypothyroidism produces amenorrhoea hypogon-
adism, hypogenitalium while moderate forms of hypothyroidism
may be compatible with normal menses and normal genital
development with no major changes other than anovulation.

Definite proof of ovulation is the establishment
of pregnancy or the recovery of an ovum from the oviduct.
Direct observation of a corpus luteum which the presence
of a stigma by endoscopy or laprotomy is considered strong
evidence of ovulation (Moghissi, 1980). Presumptive
evidence may be obtained by assessment of corpus luteum
hormones or their peripheral effect on the reproductive
tract (Allende, 1956; Moghissi, 1980).

Determination of the precise time of ovulation
has proven elusive since a long time, various techniques
are commonly performed for detection of ovulation.
Progesteron stimulates endometrial gland maturation and decidual transformation of the endometrial stroma.

METHODS OF DIAGNOSIS

There is no single validated diagnostic tool that is both highly sensitive and specific in detecting ovulation. All existing methods suffer from major flaws.

I. TESTS BASED ON HORMONE ASSAY
   1. Leutinizing hormone (LH)
   2. Plasma and urinary oestrogens.

II. TESTS BASED ON PERIPHERAL AND SYSTEMIC CHANGES
   1. Basal body temperature (BBT).
   2. Cervical mucus.
   3. Endometrial biopsy and dating.
   4. Vaginal cytology.
   5. Mittelschmerz
   6. Premenstrual molimena

III. OTHERS METHODS OF OVULATION DETECTION
   1. Salivary progesterone profile.
   2. Cervical and vaginal glucose.
   3. Endometrial receptors measurements - oestrogen and progesterone.
   4. Immunohistochemistry.
   5. Progesterone associated endometrial proteins (PEP).
6. Serum prolactin levels.

IV. SERIAL ULTRASONOGRAPHY

I. TESTS BASED ON HORMONAL ASSAY

Though these tests quite accurately predict the time of ovulation. They are rather expensive besides the fact that the facilities for these tests are not available at all the health centres and hospitals.

Serum estradiol demonstrates a characteristic peak approximately one to two days before LH peak (Ferin et al, 1973) and thirty seven hours prior to ovulation (MoghiSSI, 1980). Urinary estrogens reach maximum levels on the day or within one to two days of LH peak (Kohansson et al, 1971).

The preovulatory LH surge from pituitary as reflected in blood concentrations of LH is estimated to occur from 24 to 7 hours prior to ovulation (Yussman and Taymor, 1979). Younger et al (1978) described a rapid LH assay which they used to time artificial insemination. Regardless of technique used, the measurement of LH has proven useful in the detection of ovulation.

Plasma progesterone rises rapidly following ovulation reacting a peak at the mid luteal phase. Most workers found a critical level of 16 n mol/l (5 ug/ml) consistent with ovulation (Black et al, 1972; Shepheard and Senturia, 1977).

Serum progesterone could also be measured by RIA in order to evaluate corpus luteum functions. Single
mid luteal values were recommended for this purpose. Rose et al (1970) reported a midluteal progesterone value of 5 ng/ml or more as indicative of ovulation. Israel et al (1972) reported a value of 3 ng/ml in normal cycles Johanson (1972) suggested a minimum of 10 ng/ml. This variability in observations is due to pulsatile secretion and circadian rhythm of progesterone secretion (Filicori et al, 1984; Soules et al, 1988) and to the fact that mid luteal peak is short lived. An alternative was proposed by Daya (1989) - late luteal phase progesterone level in serum. It was found to be consistent specifically in discriminated value of 21 n mol/l on day 26. Adarahan et al (1974) proposed that the sum of three mid luteal progesterone values should be considered as it was never less than 15 ng/ml.

Urinary pregnanediol measurements (Jones, 1949; Stanzyk et al, 1980 and Chatterton, 1982) and salivary progesterone profile (Li et al, 1989, Vuorento et al,1990) have been tried in an attempt to simplify total progesterone measurement in the luteal phase without consistent results and further studies are awaited.

II. TESTS BASED ON THE PERIPHERAL AND SYSTEMIC CHANGES
a. Basal Body Temperature (BBT)

The interpretation of BBT chart values on the progesterone mediated mid cycle shift of temperature.
Attempts to quantify this have focussed on the magnitude
of temperature elevation. The rate of rise and the duration of temperature elevation before next menstrual period.

Jones et al (1949) described BBT as being the most sensitive indicator of ovulation but a poor indicator of quality of ovulation. Gautray et al (1981) studied BBT charts in 88 women with LPD. A normogram had been previously constructed from 46 normal cycles. The luteal phase lengths of LPD patients were plotted in this. This analysis identified 2 groups of patients. (a) First group of 29 cases was within normal limits though the luteal phase length was often borderline. In all cases slow thermal rise to reach or exceed 37°C was measured. This period could extend over 2 days and in some cases lasted for 5 days. (b) Second group of 59 cases all fell outside the normal ellipse and showed wide variation in the lengths of both proliferative and luteal phases.

Down and Gibson (1983) compared the luteal phases based on 3 BBT charts from each of 40 infertile women - 20 with LPD and 20 without LPD (proved by E.B.) They could not demonstrate any difference in the post ovulatory temperature rise between the two groups. Although the mean luteal phase length was significantly different (13.45 days in the non LPD and 11.8 days in LPD group).

b. **Cervical Mucus**

The changing pattern of ovarian steroid secretion affects the physical and chemical properties of cervical mucus which undergo cyclic changes in response to it.
(Marcus and colleagues, 1965; Moghissi and Wallach, 1983). These include changes in the morphology of cervix, viscosity and changes in chemical composition of mucus, spinbarkeit, ferning and midcycle mucorrhoea.

The influence of oestrogen production in the ovary on cervical mucus secretion was demonstrated by Seguy and Simmonet (1923) and others. Oestrogen stimulates by production of clear watery alkaline acellular mucus with intense ferning and spinbarkeit, whereas progesterone inhibits the secretions of cervical epithelia producing scanty, viscous opaque mucus with low spinbarkeit and absence of ferning (Zonde K and Rozin, 1954; Roland, 1962; MacDonald, 1969 and Epstein, 1978).

Seguy and Vimeux (1933) pointed out that during the intermenstrum, the cervical mucus becomes abundant watery clear with increased stretchability and can be drawn into the thread. This capacity of cervical mucus is related to spinbarkeit. This test becomes negative after ovulation.

Papanicolaou (1946) demonstrated that when the cervical mucus is spread on a glass slide and left to dry, it crystallizes with arborization. This phenomenon in most characteristic at the time of ovulation Rydberg (1948) described the pattern as fern like, hence the name palm like reaction (P L reaction).

Campos Da Paz (1953) showed that progesterone inhibits ferning. The test can remain positive in
Anovulatory cycle until menstruation due to failing corpus luteum function, a phenomenon which can be utilized as a simple test for ovulation detection (Roland, 1952).

With preovulatory rise, the cervix softness and the os opens. After ovulation os closes again and cervix becomes firm and returns to a lower position (France, 1981). This showed that besides secretion of mucus oestrogen also acts on connective tissue and muscle of the cervix.


A characteristic pattern of proteins is seen by immunoelectrophoresis at the time of ovulation (Neme et al, 1965). On the day of ovulation albumin, alpha antitrypsin haptoglobin, lipoproteins, beta-transferrin and gammaglobulin were present, probably due to follicular rupture and discharge of its content through the fallopian tube, whereas only albumin or no protein was present before or after ovulation.

Birnberg et al (1958) studied the glucose levels in cervical mucus and found that maximum concentration occurred on the day of ovulation.

Most enzymes found in cervical mucus exhibit a cyclic pattern of a preovulatory decrease followed by post ovulatory rise (Skerlavay et al, 1968; Moghissi et al, 1976 and Takehisa, 1980).
c. **Endometrial Biopsy**

The uterine endometrium is known to demonstrate a predictable and rapid pattern of histological change over the menstrual cycle. Burch and Phelps (1943) wrote "The endometrium is the most valuable single indicator of ovarian activity in the human female and its histology. The most informative single criterion. In 1949 Jones recognized luteal phase deficiency as a clinical entity for the first time and proposed endometrial biopsy as the most quantitative test of corpus luteum function.

Noyes et al described & histological criteria used in dating of endometrium. Four pertaining to glandular epithelium (Pseudostratification of the nucleus vacuolation, secretion and mitosis) and four related to stromal changes (stromal edema predecidua, leukocyte infiltration and mitoses).

The histological dating of the luteal phase endometrium is then compared with chronological dating and a lag of more than 2 days is taken as luteal phase deficiency. The most advanced area of endometrium is taken for dating.

**Chronological dating**

It is done either retrospective or prospective.

Retrospective dating: It is based on the assumption of that luteal phase duration constantly 14 days irrespective of the length of the cycle. They day of
the day of onset of next menses (NMP). The date of onset of
next menses (NMP is taken as day 28 and the post ovulatory
day on which EB was done is calculated by backdating
from this.

**Prospective dating**: Day of ovulation is deter-
mined by BBT charts. LH surge or ultrasonographic folli-
cular monitoring. Endometrial biopsy is then timed accor-
dingly. The actual post ovulatory day is determined
prospectively from the day of ovulation.

Endometrial biopsy is one of the most accepted
methods but there are many variables affecting the results
(a) timing of biopsy, (b) number of biopsy, (c) site of
biopsy, (d) method used for chronological dating
(e) interpretation of biopsy and inter and intra observer
variation and (f) within subject between cycle variation.

a. **Timing of biopsy**: Early work by Brewer and
Jones (1947) showed that biopsies done 4 to 6 days prior to
menses most consistently reflected the overall status of
the endometrium. According to Noyes and Haman (1953) endo-
metrial dating when EB done on 20th day, Gautray et al (1981)
21st, 22nd and 23rd day to be optimal for endometrial
biopsy.

Recently Johannisson et al (1987) did morphometric
analysis using all indices and stereologic study of endo-
metrium for the first time and measured DNA and RNA levels
in endometrium. They stated that endometrial changes
showed maximum significance around LH surge -2/-3 day
to LH +7/+8 day, where changes occur with a high degree of regularity despite the length of pre and post ovulatory phases. Want Z et al (1980, 1984) observed that biopsies taken more than 6 days before menses were out of phase more frequently. This suggested that endometrial biopsy should be taken 2-3 days prior to menses in order to avoid many false positive results. Some other studies (Soules et al, 1977, Dawns and Gibson, 1983, Shoupe et al, 1989) have also employed late luteal biopsies.

b. Number of biopsies: The required number of biopsies to be taken to firmly establish the diagnosis of LPD varies from one to three. Most studies have stressed on taking 2 biopsies to diagnose LPD (Jones et al, 1949; 1976; Soules et al, 1977; Ying et al, 1989).

c. Site of biopsy: The response to hormonal change is maximum in the superficial layers of fundus and upper anterior and posterior wall of the uterine(Falconer, 1947). The less vascular basal layer and lower segment endometrium lag behind and if biopsies are taken from these portions, there could be a higher possibility of out of phase biopsy (Wentz et al, 1980).

d. Method used for chronological dating: NMP has been traditionally used but it has many drawback. It is based on the presumption that luteal phase is of 14 days duration which has since been shown to be incorrect (Lenton et al, 1984, Johannison et al, 1987). Premenstrual spotting can confound the result if it is considered to be
the day of onset of menses. It has been postulated that endometrial biopsy could bring about earlier onset of menses probably by release of prostaglandins in the biopsy cycle.

There are various studies comparing retrospective dating with prospective methods of chronological dating. Noyes et al (1950, 1976) observed that only 38% of the women were in agreement ±2 days when histologic dating and NMP were correlated whereas 78% were in agreement when correlated with BBT. Li et al (1987) performed a study on 61 infertile women and concluded that the correlation between histologic dating and chronologic dating was found to be significantly better if the LH peak was used. Shoupe et al (1989) compared that four methods of chronologic dating NMP, BBT, LH surge and ultrasonographic monitoring when correlated with histologic dating by Noyes et al criteria in 13 parous women with normal cycles. They found NMP accurate in only 65.4% cases as compared to 76.9% with BBT, 84.6% with LH surge and 96.1% with ultrasonography.

e. Interpretation of biopsy : A lag of two or more days in histologic dating when compared to chronologic dating is considered to be sufficient to diagnose LPD in some studies) Thorney Croft, 1983, Ying et al, 1985, Tredway et al, 1987) whereas other believes in minimum lag of 3 days (Rosenfeld et al, 1980; Downs and Gibson, 1983 and Wentz et al, 1990).
Recently Davis et al (1989) found that in fertile women, 26.7% had sequentially abnormal biopsies when the criterion of lag of two or more days was used, whereas it was 5.6% when three or more days lag was the criterion.

f. Within the subject between cycle variation: Sporadic occurrence of LPD in some cycles in normal ovulating women has been repeatedly postulated (Aksael's 1980; Balasch et al, 1985 and Li et al, 1989).

COMPLICATIONS OF ENDOMETRIAL BIOPSY

These include excessive bleeding, pain, fever, vasovagal reaction and uterine perforation (Davidson et al, 1987). The more important complication is sampling in conception cycle. Rosenfeld et al (1975) observed that the likelihood of miscarriage is 10% and that of ectopic pregnancy 3%.

4. VAGINAL CYTOLOGY

Papanicolaou (1933) published the descriptions of variations in human vaginal smears during the menstrual cycle.

Though daily vaginal smear examination is necessary to pinpoint the time of ovulation (Riley et al, 1955; Allende, 1956; Jeffcoate, 1975) a single smear taken in the second half of the cycle reliably detects whether a corpus luteum has been formed (Jeffcoate, 1975). The progestational effects in vaginal smear in majority of cases permit a sound decision to be made whether ovulation
has occurred or not (Alende, 1956).

5. PREMENSTRUAL MOLININA

Premenstrual symptoms such as dysmenorrhoea, breast tenderness, headache, mood changes, oedema together designated as premenstrual molimina occur almost exclusively in ovulatory cycles (Magyer et al, 1978). Anovular bleeding usually occurs unannounced.

6. MITTLESCHMERZ

It is the occurrence of lower abdominal pain near the time of ovulation. The exact aetiology is unknown, but it may be due to muscular cramps in uterus, tubes or large bowel (Jeffcoate, 1975). 'O' Herlihy et al (1980) noted that the pain coincides with the day of peak plasma LH.

7. LUTEAL PHASE LENGTH

It is calculated from the day of ovulation to the last day of onset of menses. Traditionally a luteal phase less than 10 days is considered to be short. Down and Gibson (1983) compared luteal phase length of LPD and Non LPD patients based on BBT chart and observed that a luteal phase less than 11 days represented an abnormal cycle perse as well controls had longer cycle lengths. These observations support the concept that short luteal phase represents a more extreme form of LPD and taken alone. Luteal phase length is not a sensitive method of diagnosing LPD.
Hyperproteinaemia has been known to be associated with LPD (St. Michael and Dizerega, 1983) and the encouraging response of such patients to bromoeriptive has been documented years ago (del Pozo, 1979).

IV. SERIAL ULTRASONOGRAPHY

Real time ultrasonography is a relatively new imaging technique which means it is now possible to follow the follicular events directly in addition to diagnosing other gynaecological problem like fibroid, endometriosis and genital abnormalities.

The role of serial ultrasonography in detecting ovulation has been well established by various studies ('O' Herlihy et al, 1980; Queenan et al, 1980; Marinno et al, 1982; Wetzel and Hoogland, 1982; Eissa et al, 1986). Shoupe et al (1989) has clearly demonstrated the accuracy of serial transvaginal sonography used for chronological dating when correlated with histologic dating. In addition daily follicular monitoring aids us in identifying the subgroups of LPD patients with abnormal folliculodynamics so that appropriate therapy can be instituted (ovulation induction).

Abnormal folliculogenesis is 12-19% demonstrated by different studies has been defined in these studies as (1) Rupture of small follicle size (<17 mm), (2) rupture after abnormal growth (<1 mm/day for 3 days or plateau in growth for 2 days prior to rupture), (3). Lutinizied unruptured follicles.
Ying et al (1987) studied 39 patients with LPD and found that only 46% had normal sized follicles, 39% had small follicles and 15% had luteinised unruptured follicles. Hamilton et al (1990) reported a much higher percentage of cases with luteal cyst formation among infertile women nearly 50%.

**Luteinized unruptured follicle syndrome (LUFS)**

Follicles fails to rupture after undergoing apparently normal or abnormal follicular development. It has been repeatedly postulated as a cause of infertility (Marik and Hulka, 1978) and Portuondo et al, 1981). The prevalence of LUFS by laparoscopy performed 2-4 days after presumed day of ovulation (using BBT/LH surge) varied widely 6 to 79% in infertile women (Koninckx et al, 1980) as high as 47% in fertile women (Vonrell et al, 1982).

Serial ultrasonography provides a potential alternative being non-invasive early reproducible and cost effective in diagnosing LUFS (Daly OC, 1985). The incidence of LUFS by ultrasonography is roughly 10% in infertile women (Gibson et al, 1984 - 10%, Daly et al, 1985-9%, Check et al, 1984-8%, Ying et al, 1987 - 15%) however a recent report by Hamilton et al (1990) found 45% incidence of luteal cyst.