Chapter 2

Review of Literature
The ovarian changes and the uterine endometrial changes during the female sexual cycle depend completely on the gonadotrophic hormones FSH and LH secreted by the anterior pituitary gland (West, 1990). Gonadal hormones contain basic steroid units and are synthesised mainly from the cholesterol and acetyl CoA. During the different phases of menstrual cycle, these hormones are released at different rates which will bring about changes in functions of different organs of the body. To meet with the constantly changing situation, respiratory system has organised its own compensatory mechanism (West, 1990). Respiratory system will adjust the rate of ventilation as environmental conditions vary, as metabolic demands are altered or as the physical characteristic of the ventilatory apparatus are modified by growth, senescence or disease (Berne and Levy, 1988).

Among the physiological correlates of the menstrual cycle, increase in alveolar ventilation has long been found in the LP (Lyons, 1968). Progesterone is thought to be the main physiological agent responsible for the pre-menstrual fall of alveolar CO₂ (1) because the cyclic changes disappear with the menopause and (2) progestational agents increases in ventilation (Tylor, 1960; Lyons and Huang, 1968) and respiratory chemosensitivity in females (Zwilich et al., 1978). Changes in sensitivity of autonomic nervous system (Little and Zahn, 1974) EEG activity (Gautray, 1969; Greutzfeldt et al., 1976) and reaction time (Mehta et al., 1977) also suggest cyclic menstrual changes in CNS sensitivity to stimuli. These studies were designed to test the hypothesis that hyperventilation produced by the stress of life events is more likely to produce psychosomatic symptoms during the premenstrual and menstrual phases when the arterial PCO₂ is already
reduced (Little and Zahn, 1974; Mehta et al., 1977). Damas-Mora et al. (1980) observed that the lowest resting PaCO\(_2\) values occurred premenstrually but low CNS and respiratory sensitivity as expressed by high values of time of hyperventilation necessary to produce low values of CO\(_2\) were always observed in the postmenstrual phase.

Increased ventilation has consistently been found in the LP of the menstrual cycle in normal women. Damas-Mora et al. (1980) are in agreement with the finding that CO\(_2\) starts to decrease early in the luteal phase and the lowest values are seen in premenstrual phase. They also reported that women are more vulnerable to psychosomatic symptoms during the premenstrual phase, and due to this stress increases in ventilation. The sensitivity of CNS to hyperventilation always, increased during the premenstrual and menstrual phase.

In normal women hypoxic ventilatory responses are enhanced during the LP (Smith and Allan, 1982 and White et al., 1983). It is reported that during the late LP, in some asthmatic patients the symptoms are worsened and this may be due to the changes in PEFR (Hanely, 1981; Gibbs et al., 1984). Munakata et al. (1993) observed that female asthmatics have increased hypercapnic chemosensitivity during the LP which is not associated with decline in airway function. But they also reported that there was no difference in pulmonary functions between the FP and LP. It is also suggested that the arterial blood gas analysis of PaCO\(_2\) was decreased during the LP accompanied by changes in pH and consequently HCO\(_3^-\) level during the LP was significantly lower than the FP (Munakata et al., 1993).

There was a significant relationship between percent increase in hypoxic sensitivity and decrement of the resting PaCO\(_2\) that occur in the LP (Nariko-
Takano, 1984). However no significant relationship was observed between changes in hypoxic sensitivity with that of the remaining parameters studied viz. pulmonary ventilation, mean inspiratory flow, alveolar partial pressure of \( O_2 \) and \( CO_2 \). They also pointed out that intersubject variation in percent increase in resting ventilation during the LP was not associated with that of percent increase in hypoxic sensitivity. The results indicate that the combination of increase in hypoxic sensitivity to increase in ventilation during the LP is variable among subjects. The studies of Gamberale et al. (1975) however showed that even though pulmonary ventilation during work was highest in the MP, though it does not affect women’s mental work capacity.

Lung volume has an important effect on airway resistance (West, 1985). At large lung volumes, elastic recoil of the lung is high, airways widen and resistance to airflow falls (Berne and Levy, 1988). However as the lung volumes becomes smaller the structures around the lungs are relaxed so that the bronchi and bronchioles are collapsed more easily by external pressure (West, 1985). Astrand and Rodalh (1986) reported that the constriction of the bronchi results in decreased flow rates. The increase in the resistance in the upper and lower airways results in the reduction of PEF. FEF\(_{25-75\%}\), FEF\(_{75-85\%}\) and FEF\(_{02-12}\) (Govema et al., 1987). Similar observations were also reported by Vijayan et al. (1993) and Zuskin et al. (1994). They also pointed out that the values for FEF\(_{25-75\%}\) and FEF\(_{75-85\%}\) for the normal healthy women showed a negative correlation with height. They also reported that spirometric analysis of flow at low lung volumes (FEF\(_{75-80\%}\)) was more sensitive than flow measured over the middle half of the forced vital capacity. FEF\(_{25-70\%}\) in detecting small airway disease in normal women. Green et al. (1973) suggested that significant variations in maximal expiratory flow cannot be accounted for the differences in size or elastic recoil but
may be related to the airway segments of the normal persons. Schwartz et al. (1991) observed a negative correlation between pleural thickening and FVC. Miller et al. (1994) suggested that the reduction in FEV₁ can be caused as a result of air trapping. A reduction in FEV₁ and flow rates is proportional to the reduction in FVC. Therefore a reduction in FEV₁/FVC % results in obstruction of air passages.

Angelo et al. (1997) suggested that resting temperature were higher during the LP while the end-tidal tension was significantly lower in the menstruating subjects during the LP. They were of the opinion that maximum exercise performance were observed in the follicular phase.

Shakhlin (1997) reported that respiration, blood flow, O₂ intake, mental and physical performance etc. during menstrual cycle significantly altered the female status of respiratory system which varied with these changes. High economic benefits of respiratory function and high breathing reserve in the post menstrual and post ovulatory phases of the menstrual cycle found to make the female more effectively at this time (James et al., 1968). This is in agreement with the fact that the nitric oxide production is influenced by cyclical hormonal changes in women and showed an increase of more than 100% at MC (Kharitonov et al., 1994). This may be pertinent to the lower level of cardiovascular diseases in pre-menopausal women (Kharitonov et al., 1994).

Gibbs et al. (1984) reported that a number of asthma patients complained about the increase in the symptoms during or proceeding menstruation. Chandler et al. (1997) noted that the improvement of asthmatic symptoms and dyspnoea index scores after estradiole administration compared with baseline pre-menstrual period. Skobeloff et al. (1996) suggested that monthly variations in serum estradiole level may influence the severity of asthma in adult females.
Magness and Rosenfeld (1989) noted that the mean endometrial blood flow in normal cycle has a significant relation with the middle to the late FP followed by a substantial fall and a secondary slow luteal phase rise that was maintained until the onset of menstruation. There was a significant correlation between plasma estradiol levels and endometrial blood flow in the FP but not in the LP.

The respiratory stimulant effect of progesterone has been known for many years (Stahl et al., 1985). Nariko-Takano (1984) reported that the progesterone induced hyperventilation as occurs in the LP is elicited partly by mediating an increase in reflex hypoxic drive which is probably produced centrally even in hyperoxia, but the role of augmented hypoxic drive is highly variable among subjects. Schoene et al. (1981) observed that progesterone plays an important role in mediating the alterations in ventilatory response. Progesterone is thought to increase the ventilation through a central mechanism (Skatrud et al., 1978, Schoene et al., 1981 and Curtis and Allan, 1982). Skatrud et al. (1978) and Bonekat et al. (1987) found MPA which is a synthetic progestrone increases resting ventilation, the respiratory responses to hypoxia and hypercapnia and exercise ventilation in normal males. Skatrud et al. (1978) also found MPA products in the cerebrospinal fluid of their subjects added more weight to the argument that progesterone acts centrally to augment ventilation. Schoene (1981) suggested that this hyperventilation may in part be secondary to increased metabolism, reflected by the increase in body temperature after ovulation. But Damas-Mora et al. (1980) reported that factors other than progesterone also play a role in inducing the menstrual changes in the respiratory centres. The role of psychological factors in the causation of hyperventilation is well established. Traits of personality and attitude to menstruation and the female's social role are most likely to play an additional and significant role in
causing periodic increase in the ventilation during the menstrual cycle (Rand, 1968; Goldberg, 1974; Slade and Jenne, 1978). Curtis and Allan (1982) conclude progesterone and estrogen can cause hyperventilatory changes in women.

Serum cholesterol and lipids are known to vary during menstrual cycle (Cullinane et al., 1995). Serum lipids and lipoproteins have received much attention for their involvement in atherosclerosis and cardiovascular diseases. Gorden et al. (1977), Peter and Strune (1982), Wahl et al. (1983) and Hugo et al. (1985) suggested the level of serum LDL-C in the development of coronary artery diseases. On the other hand, HDL-C is inversely correlated to cardiovascular risk. They observed an increase in total and LDL-C on days 10 and 15 after menstruation. They also noted that the plasma volume coincide with peak increase in total, LDL-C and HDL-C. They concluded that the alterations in plasma volume account for approximately half of the increase in total LDL-C during the menstrual cycle. Lyons et al. (1994) were in agreement with the above view and noted that the greatest effect was in HDL-C concentrations, which increased by 12% between the times of menstruation and ovulation and remained elevated until the following premenstrual phase. The height of the peak estradiol concentration at ovulation was significantly associated with HDL-C in that phase. The increase in total cholesterol and LDL-C at ovulation was 9% and 11% respectively. So their studies demonstrated that consistent changes in plasma lipoproteins do occur during the menstrual cycle. But at the same time Naduka and Agbedana (1993) failed to observe any changes of HDL-C during the cycle even though they agreed with the changes of total serum cholesterol and triglycerides occurred during the LP as compared with the follicular phase due to the fluctuations of sex hormones. Larsson et al. (1979) found the LDL-C
in the mid LP was significantly lower (7%) than the early FP. HDL-C levels during the late follicular phase were higher (6%) than menstruation levels. They observed that the fluctuations in total cholesterol and triglycerides did not reach significance. Thus the cyclic fluctuations of LDL-C and HDL-C need to be considered in the screening and medical monitoring of women with border line lipoprotein levels as well as in the design and interpretation of results of studies involving pre-menopausal women. Tonolo et al. (1995) reported that plasma total cholesterol and LDL-C were significantly higher than basal in the preovulatory phase until progesterone levels were increased in the postovulatory phase.

Tonolo et al. (1995) reported that the physiological variation of sex hormones during the menstrual cycle in normolipidemic women influences the plasma levels of lipids and different apo-lipoproteins indicating ovarian hormones as the major physiological modulators of lipoprotein metabolism. Therefore when the lipid risk profile is evaluated in premenopausal women, the phase of the menstrual cycle should be taken into account. They also reported that HDL-C was significantly higher than the basal from day-1 to the day after LH surge and pointed out that the endogenous female sex steroids have significant effects on the circulating levels of plasma lipids and apo-lipoproteins.

Azougin et al. (1997) pointed out that HDL-C increased by 16% in the pre-ovulatory phase in comparison to the early follicular phase. Serum apolipoproteins are elevated in the pre-MC and mid-LP in comparison to the early FP. They failed to observe any change in total cholesterol, triglycerides, LDL-C, VLDL-C etc. in the menstrual cycle.

Demacker et al. (1982) suggested that the collecting time of blood sample during the menstrual cycle is critically important in interpreting changes in serum
lipids. They noted that serum cholesterol concentrations were 15% lower over the 72 hours represented by ovulation compared with the pre-MC and post MC weeks. Low-Beer et al. (1977) pointed out that cholesterol saturation of bile and the risk of developing gall stones was higher nine days after MC than at the end of menstruation. This change in bile cholesterol saturation was proceeded by a significant fall in serum lipid concentrations during the ninth day after the MC serum triglyceride and cholesterol concentrations fell respectively. Therefore, they suggested that the changes in the composition of serum and biliary lipids during the menstrual cycle are presumably due to a direct effect of sex hormones on the tissues. It is noticed that women are more likely to develop gallstones than men. The gall stones commonly found in affluent societies are rich in cholesterol especially in women taking estrogen either as a part of the contraceptive pill or for the relief of post menopausal syndrome.

The interrelation of haematological factors and pulmonary functions are not clearly understood. Bazes et al. (1971) have suggested that the correlation of DLCO which is used as an indicator for the measurement of diffusion capacities of O₂ and CO₂ and other gases for anaemia should be a routine procedure in the pulmonary function test. The DLCO falls by 7% for each 1gm/100ml fall in haemoglobin. They also found that, before and after changes in haematocrit, the DLCO changed by 6.3% for the same haemoglobin change. Anaemia is not accompanied by any other differences in other aspects of pulmonary functions at rest. But Rao et al. (1980) reported that anaemia reduces the maximal work capacity and observed that in the case of sickle cell anaemia, VC and TLC are found reduced in adult patients but in children lung volumes and flow rates didn’t show much variation. There was slight hypoxemia at rest, but FEV₁ values were normal. In extreme conditions, PPaO₂ falls. Pulmonary function changes in chronic
eosinophilia are well known. Intense leukopenia can give rise to an adult respiratory distress syndrome or respiratory failure. Laurell et al. (1968) suggested that except orosomucoid, other plasma proteins involved in haemostasis did not show any change in concentration during menstrual cycle. Lebech and Kjaer (1989) reported that fibrinogen showed a significant increase in the LP compared to the FP and MC and showed a significant positive correlation with progesterone. But they found no changes in factor VII or antithrombin III in the cycle. For coagulation studies the cycle days are more important than the phase as a whole.

Jern et al. (1991) reported that mental stress causes significant changes in leucocyte count, hematocrit, fibrinogen and Von Willbrand factor in different phases of sexual cycle. Solerte et al. (1988) pointed out that several changes occur in haematological conditions in healthy women during menstrual cycle. A number of factors such as increased blood viscosity, plasma and serum viscosity, reduced erythrocyte filtration through vessels were demonstrated during the FP and MC of the menstrual cycle. Reports suggest that heart rate, plasma volume, renal blood flow, concentration of renin–angiotensin–aldosterone system and norepinephrine are increased in LP (Spaanderman et al., 2000). These changes may be related to the estrogenic activity normally occurring during this phase of the cycle and they found several correlations between plasma concentration of estrogen, the increase of blood and plasma viscosity and reduction of erythrocyte filtration ability on day 14 of the menstrual cycle, when estrogen levels were highest. Moreover estradiol seems to influence plasma fibrinogen levels which were increased significantly during the FP and MC of the cycle. Larsson et al. (1989) carried out studies on blood chemistry and found that the
viscosity of the whole blood with hematocrit adjusted to 45% as well as that of plasma changes during the normal menstrual cycle in healthy women but no changes were found in post menopausal women. The plasma viscosity is influenced by the triglycerides and still more by fibrinogen (Beller et al., 1964). Plasma fibrinogen level reaches its peak between 21 to 28 day which is in accordance with the findings of Dorn et al. (1993). They indicated that the blood viscosity had its lowest values at the beginning of menstrual bleeding, and reached its maximum level at day 7. Properties of the red cells such as aggregation tendency and deformability may also contribute towards changes in viscosity. Blomback et al. (1992) studied the association between haemostatic components and menstrual cycle and found no direct relation between these factors and estrogen and progesterone levels.