Chapter 5

Discussion
DISCUSSION

The primary function of the lung is to supply the body with oxygen and to remove carbon dioxide and for that, the lungs must be adequately ventilated. Ventilation may be defined as the process of movement of air in and out of the lungs. This distinguishes ventilation from respiration, which involves complex chemical and physiological events at the cellular level. In health, ventilation is regulated to meet the body needs under a variety of circumstances. In disease conditions, however, this process may be disrupted resulting in inadequate ventilation or excessive breathing. Respiratory care often restores adequate and efficient ventilation in such circumstances. Providing effective respiratory care demands understanding of the normal ventilatory process as well as abnormalities that affect ventilation. Moreover, gender differences in case of respiratory responses is a proposed factor in recent times. With this concept in mind, this study was undertaken to investigate whether any such respiratory variations occur in normal menstrual cycle of healthy adult females of reproductive age ranging from 18-24 years.

Menstrual cycle influences the activity of the respiratory system. This is clear from the fact that women hyperventilate during the LP of the menstrual cycle and pregnancy (Tylor, 1960; England and Farhi, 1976; Damas-mora et al., 1980). Bayliss et al. (1992) suggested that the respiratory response to progesterone is mediated at hypothalamic sites through an estrogen dependent progesterone receptor mediated mechanism requiring RNA and protein synthesis. The estrogen dependence of the respiratory response to progesterone is likely to be a consequence of the demonstrated induction of progesterone receptor RNA which in turn is controlled by the estrogen. They indicated that neural mechanism
underlying the stimulation of the respiration by progesterone were similar to those of its reproductive effects.

Anterior pituitary hormones LH and FSH and endogenous sex steroid estrogen and progesterone are the endocrine factors which control the menstrual cycle of the female. The first part of this study deals with the effect of these hormones and the menstrual cycle phases on the pulmonary responses. In the present study, a large number of pulmonary functions i.e. lung volumes and flow rates both expiratory and inspiratory flow rates were examined to see any variation exists in the different phases of the normal reproductive cycle of a normal healthy adult female. It is found that some of the lung volumes and flow rates were affected to a certain extent while majority of them were not altered. Damas Mora et al. (1980) observed the higher responsiveness of respiratory centers to CO₂ in the premenstrual (late LP) and MP. This indicates higher sensitivity of the CNS before and during menstruation. Studies are now in progress to determine the role of neurophysiological, hormonal and psychological variables in order to study their temporal correlation. It is also noticed that hyperventilation in vulnerable periods of the menstrual cycle is more likely to cause premenstrual tension syndromes than other times. Hence, the higher responsiveness of respiratory centers to CO₂ may be one of the factors, which brings about the premenstrual tension syndrome. But at the same time Damas Mora et al. (1980) observed that apart from progesterone which is believed to be a hormone causing respiratory changes, other factors also play a role in inducing menstrual changes in respiratory centers. The role of psychological factors in producing the hyperventilation is well established. The trait of personality, attitudes to menstruation and the social role of the female are very important factors which play an additional and significant role in producing the periodic
increase in ventilation and distress of the menstrual cycle. But Stahl et al. (1985) could not find any significant changes in the lung functions, i.e., the lung volumes and flow rates during the different phases of menstrual cycle. They failed to find any variation in the FEV₁ or FVC in the early part of menstrual cycle as compared to late LP in menstrual cycle. In spite of clear gender differences in susceptibility to airway diseases, they were unable to demonstrate an association between peak physiological changes in female hormone level and pulmonary function during the menstrual cycle. So it is indicated that physiological changes in female hormone level particularly progesterone, do not in themselves cause changes in pulmonary functions or airway responsiveness. During menstrual cycle, apart from hormonal levels, several other factors viz. serum lipids, lipoprotein cholesterol, plasma ACTH, cortisol and ascorbic acid level are known to vary with menstrual cycle and would also be expected to affect pulmonary functions. It is reported that normal subjects developed slow waves and had more sensitive CO₂ responses during the premenstrual or menstrual phases, which may be a factor contributing premenstrual tension. Bonekat et al. (1987) were of the opinion that diffusion capacity for carbon monoxide can vary significantly during the menstrual cycle with the highest values occurring prior to the third day of menstruation with a mean difference of 9%. These variations need to be considered when evaluating DLCO in female patients in the reproductive age group.

Das et al. (1991) measured the basal oxygen consumption in 32 adult women and observed that it was highest in the LP as compared to other phases where as it was almost identical to the MP and FP. The rise in the O₂ consumption was found to be a postovulatory phenomenon possibly mediated through hormones mainly progesterone. It is reported that the alveolar PCO₂ and
base excess are lower during the second half of the menstrual cycle (England and Fahri, 1976). The possible explanation behind this is due to the stimulation of ventilation by the increased concentration of the progesterone secreted by the corpus luteum. Similar effects are seen in pregnancy followed by the parenteral administration of progesterone to volunteers. The present study, showed significant difference in FEV₀.₅ and FEV₁ and FEV₁/VC% (Table 1.2 and Figure 1) in different phases of the menstrual cycle. The increase in FEV₀.₅ and FEV₁ from MP to FP and to LP was significant (P<0.05). This could be explained on the basis of higher concentration of progesterone present in the LP (Table 4.1). Increased flow rates are obtained from MP to LP with higher lung volumes. Improved flow rates are indication of effective conduction of smaller airways as seen in the LP (Table 1.5. Figures 5 and 7). Timed FEV₁ to FVC ratios are used in finding out the airway conductance. The decrease in timed vital capacity (FEV₁, FEV₀.₅ etc.) ratios indicates the caliber of smaller airways. The FEV₁ is a clinical measurement unlike more specific measurements such as pressure, flow or volume (Hales and Kazemi, 1977). It is interesting to compare the results of the present study with the conclusions made from studies of instantaneous pressure flow relations. The waterfall theory (Pride et al., 1967) or the equal pressure point theory (Mead et al., 1967) predict that the flow through the flow limiting segment of the pulmonary airways is independent of the pressure drop across it. In that case, FEV₁ would be independent of the pleural pressure developed and a greater part of FEV₁ is effort-independent.

FEV₁ remains to be the most accurate physiologic variable to find out the measurement of airway resistance. When FEV₁, FVC or FEV₁/FVC reduce to 40% of the predicted values, disease and/or a deterioration of airway function is existed. VC serves as a standard test to monitor function, which gives information
about the neuromuscular coordination and strength of the respiratory muscles. In the present study no significant variations were observed in VC during different phases of menstrual cycle even though inter variation of the subject exists. This is in accordance with the findings of variations in pulmonary functions of Judith et al. (1990) Munakata et al. (1993) reported that the increase in plasma progesterone levels during the LP did not correlate with the changes in pulmonary functions and ventilatory responses. Similar observations were also reported earlier by Weinmann et al. (1987).

FVC is recommended as an optimal method for providing follow up data with 10% change generally considered to be significant. This value is often less than the VC because the high intrapleural pressure which develops during forced expiration causes premature closure of the airways. FVC differs from VC in a way that it is devoid of time factor. The dependence of the FEV₁ on available lung volume, the force that the expiratory muscles can exert, the compliance of the lung tissues and airway resistance (Stevens et al., 1969) coupled with its relation to height, body size, age and sex confirms that FEV₁ is a function of the state of the respiratory system which substantiates its validity.

In conditions of restrictive ventilatory defects, there is restriction to the stretching of the lungs from the disease either of the lungs or of the thoracic cage, lowering the VC. If there is no airway obstructions, the lung empties quickly. In uncomplicated restrictive diseases, vital capacity is decreased, FEV₁ remains normal. In uncomplicated airway obstructions, FEV₁ is decreased while FVC can be normal or decreased. FVC is the basis for measurement of expiratory flow rates. The volumes expired in the first 0.5, 0.75, 2.0, 3.0 sec. (FEV₀.₅, FEV₀.₇₅, FEV₂, FEV₃) were also can be calculated. FEV₁/FVC ratio is used for the detection of obstructive airway disease and quantification of its severity. With normal
airway resistance, it takes shorter time for completion of forced expiration. Therefore, despite reduced absolute value of FEV₁ and FEV₆/FVC ratio is often increased. Significant reduction in FEV₆/FVC% and FEV₁/FVC% indicate better conductive properties of both large and small airways respectively. FEV₁/VC% allows the assessment of dynamic air flow. Increase in timed vital capacities viz. FEV₀.₅, FEV₁ and FEV₃ shows the increased efficiency of pulmonary function. Increased lung volumes viz. VC, FVC, MVV, FEV₀.₅ and FEV₁ etc. show the increased elastic recoil of the lung and better conductive properties of the larger airways. A decrease in FEV₁/VC% also indicates a better larger airway status. A decrease in FVC may be a factor behind muscle fatigue especially that of the expiratory muscles like internal intercostals. In a normal menstrual cycle of a female, factors like fatigue of respiratory muscles, small airway closure, blood volume changes, pulmonary oedema can cause variations in the respiratory function, which may not be easily noticed. But in the present study, consistent fluctuations were not seen in the lung volumes probably due to the fact that the subjects were normal healthy adults.

The other lung volume considered for this study was MVV. In obstructive lung disease, there is always airway obstruction and a decline in elastic recoil of the lung (air trapping) and thereby decrease in MVV. The MVV value is also decreased in presence of weakness, pain and lack of coordination. Ventilation will be faster in such incidents and MVV is well correlated with FEV. The surrounding lung gives support to the bronchial tree by radial traction. Therefore, their caliber is increased by expansion of the lungs. As lung volume decreases, the airway resistance increases rapidly. The reciprocal of resistance, conductance, has a linear relationship with the lung volumes. At low lung volumes, the airways close completely, particularly at lung bases where expansion is much less. Patients with
increased airway resistance breath at high lung volumes, which helps to reduce their high resistance.

A significant increase in FEF_{25-75\%} and FEF_{75\%} was observed from MP to LP (Table 1.4 and Figures 4–7). The average flow rates over the middle half of FVC—the Forced Mid Expiratory Flow—the FEF_{25-75\%}, FEF_{75-85\%} of FVC gives an insight into the status of the small airways as it is less dependant on voluntary effort. The measurement of FEF_{2-12} (L/sec) gives an idea of the condition of airflow in larger airways. FEF_{25-75\%} can be reduced by increased airway resistance or a reduction in the pressure which causes fall in the elastic recoil of the lungs. These parameters of flow rates in the present study are the simple indicators of smaller airway function and are decreased in airway diseases. Like forced expiration, the manoeuvre of forced inspiration was used to measure ventilatory capacity in the menstrual cycles of young adult females. The findings of expiration are normally similar to those of inspiration but may be higher when the elastic recoil of the lung tissue is reduced and lower when the upper airways are obstructed. Reduced expiratory flow rates indicate obstructive airways, particularly at low lung volumes (Pandya et al., 1984). When the obstruction is primarily due to the loss of elastic recoil, there is an early peak flow as the airways collapse, followed by severely reduced flow rates during sustained expiratory effort (James et al., 1975).

The second part of the present study deals with the comparison of biochemical parameters during the different phases of menstrual cycle and their relation with the respiratory functions. During normal reproductive life, women appears to have at least two natural advantages over men with respect to cholesterol related atherogenesis. This persistently high plasma HDL-C concentration may augment the removal of this lipid. The significant suppression
of the LDL-C during the LP of the menstrual cycle may represent decreased availability of an atherogenic lipoprotein to peripheral tissues. Whether this represents an estrogen action alone or in combination with other hormones is yet to be determined.

It is well known that both endogenous and exogenous sex steroids can influence plasma lipids and lipoprotein levels in serum. This part of the present study is designed to investigate variation of these factors during normal menstrual cycle in normal young females. Kim and Kalkhoff (1979) suggested that in human female, the total plasma cholesterol concentrations are different from that of male throughout the reproductive age. However, the differences between sexes appear to pass through three different phases. The cholesterol levels in female exceeds that of male between birth and puberty, although these differences are quite small. Carlson and Hardel (1977) and Morrison et al. (1977) reported that the cholesterol level is increased in males than females during reproductive life. In addition, Carlson and Ericsson (1975) noticed that in the postmenopausal state, total plasma cholesterol concentrations in women are significantly higher than in men. It is of interest that LDL-C, like the total plasma cholesterol follows the same pattern of difference between the sexes, whereas HDL-C is higher in the female irrespective of age.

Avogaro et al. (1979), Schaefer et al. (1983) and Naito (1985) reported that estrogen increases the production of apo A-I both in vivo and in vitro. In addition, estrogen administration decreases LDL-C levels in the postmenopausal women. The effect of estrogen in increasing the plasma apo A-I level is mediated via direct cell nuclear interaction causing increased apo A-I, or suppression of hepatic lipase activity leading to decreased HDL-C catabolism (Schaefer et al., 1983, Archer et al., 1986). Therefore, alterations in hormone levels associated
with menstrual cycle status should be taken into account when the effect of physical activity on plasma lipoprotein level is considered. Decreased LDL-C particle size is associated with increased triglycerides and decreased HDL-C values. Strenuous exercise induces lipolysis presumably modulates these effects (Fisher et al., 1988). The results of the investigation in the present study demonstrate major fluctuations in total serum cholesterol, HDL-C, LDL-C and to a lesser extent serum triglycerides during different phases of menstrual cycle.

Total serum cholesterol level varies significantly during the menstrual cycle in the present study (Tables 2.1 and 2.2), the MP values being lower than that of the FP and MC (Figure 8). Although serum cholesterol level was lower during the LP in presence of high progesterone levels, though they were not significantly different from the mean values of FP. The above finding in cholesterol values were in agreement with the findings of Kim et al. (1979), Hugo et al. (1985) and Suzanne et al. (1991).

The mean values of HDL-C also vary significantly in our study (Table 2.1 and Figure 8). The highest concentration was observed in the MC followed by the LP while the lowest concentration was observed in the MP. Follicular values slightly exceeds the menstrual values. This observation is in accordance with the similar observation of Lowbeer et al. (1977), Kim et al. (1979), Suzanne et al. (1991). However, Natalie et al. (1992) fails to observe any variation in the above parameters during menstrual cycle. HDL-C with its major carrier proteins may help the removal of cholesterol from tissues (Hak – Joong and Ronald, 1979; Miller et al., 1987) and promote its transport to the liver for catabolism. Moreover, plasma HDL-C levels are inversely correlated with the total cholesterol pool size. The present study demonstrates significant fluctuations in LDL-C in the phases of normal menstruating women (Table 2.1 and Figure 8). During the LP,
these concentrations were significantly lower than the values of other phases. Similar observations were also reported by Shobha et al. (1981), Hugo et al. (1985), Jones et al. (1988) and Tonolo et al. (1995). But Woods et al. (1987) fails to demonstrate significant changes in LDL-C in their studies.

The VLDL-C in the present study was not significantly changed during normal menstrual cycle (Table 2.1 and Figure 8). Nevertheless a slight increase in the concentration of VLDL-C was observed in the LP (Hugo et al., 1985) while studies conducted by Low-beer et al. (1977) shows that the concentration was found to be increased in the MC. The findings of Woods et al. (1987) clearly support the result of the present study in VLDL-C. There are considerable data indicating that endogenous and exogenous estrogen influences the plasma lipids and lipoprotein fractions. But a possible explanation for the negative finding in this instance may be due to the fact that the increase in estrogen level in the MC may be too transient to have an effect on VLDL-C.

The concentration of serum triglycerides showed highest value in MC than the other phases of menstrual cycle. It is well known that both endogenous and exogenous sex steroids are capable of altering cholesterol, triglycerides and lipoprotein levels in serum. Table 2.1, 2.2 and Figure 8 indicate an increase in the serum triglyceride values in the MC. While in other phases of the cycle, the values were not much different. This finding can be explained with the earlier reports of Shobha et al. (1981). As observed in the present study, Low-beer et al. (1977) also noticed low values for serum triglycerides at the end of menstruation, a rise at MC and a fall at 9th day after the MC. But according to some earlier reports, elevation of serum lipids and triglycerides is expected during premenstrual tension. However, the present investigation demonstrated comparatively low values of serum lipids and triglycerides towards the end of the menstrual cycle.
The possible explanation for this phenomenon may be due to the fact that the subjects were all healthy young students who may not experiences factors viz. malnutrition, psychological stress, etc.

In the present work, a significant decrease in bicarbonate level was observed during the LP while in other phases, the values remained more or less same (Table 2.1 and Figure 9). Sandra et al. (1976) and Chapman et al. (1997) also reported similar observation. Chapman et al. (1997) further suggested that a significant decrease in mean arterial pressure in the mid LP of the cycle was found in association with a decrease in systemic vascular resistance and an increase in cardiac output.

The plasma proteins were evaluated during different phases of the menstrual cycle (Table 2.A.1, Figures 11 and 12). The total proteins, albumins and globulins fails to show any variation while fibrinogen shows significant effects depending on the phases of the cycle. However, total proteins and albumins showed highest values during the MC while the lowest values were observed in the FP, even though not significant. Globulin values were highest in the LP and lowest in the FP. Oliver and Boyd (1953) also reported that plasma proteins did not show any evident changes during the menstrual cycle. Laurell (1968) also suggested that the proteins were not involved in haemostasis, crosomucoid was the only one which showed statistically significant change during the menstrual cycle with a maximum at menstruation.

In the present investigation, fibrinogen content showed a significant increase in the LP followed by FP (Table 2.A.1 and Figure 12). While in other phases, the concentration was almost equal. This finding is supported by the earlier works of Cederblad et al. (1977), Lebech et al. (1990), Jern et al. (1991) and Inaven et al. (1991) noticed the fibrinolytic activity was higher in the LP and
the MP than the FP. The possible explanation may be the intrauterine clotting during menstruation. Cedarblad et al. (1977) further reported that apart from fibrinogen factor II, VII and X, platelets etc. are also changed in menstrual cycle. Fibrinogen, like factors VIII and VWF is an acute phase reactant. In addition, fibrinogen level increases with increase in age, obesity, use of oral contraceptives, menopause, diabetes, smoking and mental stress while decreases with moderate alcohol intake (Blomback et al., 1992).

The haematological parameters viz. bleeding time, clotting time, prothrombin time, RBC count and WBC count did not show any significant change in this investigation during different phases of menstrual cycle (Tables 3.1 and 3.2, Figures 14–16). Normal bleeding time indicates that the platelet count as well as the health of the capillaries are normal. In deficiencies of coagulation factors, clotting time is prolonged but bleeding time may be normal because vasoconstriction and platelet plug formation may be adequate to arrest bleeding. On the other hand in purpura, the clotting time may be normal because all the coagulation factors are present but bleeding time is prolonged because vascular or platelet response may be inadequate (Blomback et al., 1992). Blood loss during menstruation or any other factor did not seem to affect the duration of bleeding time in the present study.

The reports concerning the variation of blood cell count during menstrual cycle are few and contradictory which may be due to methodological shortcomings. In the present study there is no significant changes in RBC count while an increase in WBC count was observed, though not significant in the LP (Table 3.1 and Figure 16). This is in agreement with the observation of Larsson et al. (1989) who reported no change in WBC count during different phases of menstrual cycle. But they observed a change in blood viscosity during different
phases, the lowest being at the beginning of menstrual bleeding which reaches its height on 7th day (P<0.01). Changes in plasma triglycerides, and red cell properties seem to contribute to this increase. They further suggested that plasma triglycerides paralleled this change in viscosity. The properties of red cell contributing towards viscosity are aggregation tendency and deformability of red cells (Lunt and Brown, 1996). The present finding may be of some importance for evaluating the risk of thromboembolic complications in surgery of women. It is well known that blood viscosity is one of the important factors in the development of deep venous thrombosis. Accordingly, the days between 5-15 of the menstrual cycle should theoretically convey a greater risk for thromboembolic complications after surgery than other phases of the menstrual cycle (Anderson et al., 1997). In the present study RBC count remained constant throughout the cycle.

It was clear from the present study that no change was observed in the clotting time throughout the menstrual cycle. In menstruation, due to the spasm of many spiral arteries supplying the uterine endometrium involution of the endometrial wall begins resulting in blood loss. But this blood loss or any other factor did not seem to affect the duration of bleeding time in the present study. An insignificant decrease in clotting time was observed in LP in the present study. It is clear from the present study that clotting time is directly proportional with fibrinogen concentration of the blood. The possible explanation for this decrease may be an increase in the concentration of the fibrinogen in the LP (Lebech and Kjaer, 1989). The process of clotting takes place quickly and the time is shortened when there is an increase in fibrinogen concentration. Prothrombin time helps in evaluating the extrinsic system of clotting which needs factors VII, X, V, prothrombin and fibrinogen and factor VIII. In practice, prothrombin time is prolonged if factors V, VII and X is deficient. Prothrombin time also did not
exhibit significant variations in this study even though FP showed the highest while MP showed the lowest value.

Correlation analysis of respiratory functions with biochemical parameters during the different phases of menstrual cycle shows only a few parameters significant and it seems that the respiratory functions were not significantly affected by biochemical parameters during the menstrual cycle. In the menstrual phase FVC had a significant negative correlation with VLDL-C while FEV_{0.5}/FVC\% had a significant positive correlation with LDL-C (Table 2.3). VC had a negative correlation with HDL-C and FIF_{50}\% had a positive correlation with LDL-C. Among the flow rates, FMFT and PIF showed significant negative correlations with VLDL-C, while FEF_{50}\% had a significant negative correlation with bicarbonate. PIF showed a significant negative correlation with VLDL-C in the menstrual phase (Table 2.4).

In FP VC and FEV_{0.5} had significant positive correlations with HDL-C while FEV_{1} had a significant negative correlation with serum triglycerides (Table 2.5). Among the flow rates FEF_{25}\% had a significant positive correlation with bicarbonate while PIF and FIF_{50}\% had significant negative correlation with HDL-C and serum triglycerides respectively (Table 2.6).

In the MC, VC, FVC and FEV_{1} exhibited significant positive correlation with HDL-C while FEV_{0.5} and FEV_{1}/FVC\% had significant negative correlation with LDL-C and VLDL-C respectively. FEV_{1} also showed a significant negative correlation with LDL-C (Table 2.7). The flow rates FEF_{25}\% and FIF_{50}\% had significant negative correlation with LDL-C. FIF_{50}\% had a significant negative correlation with serum triglycerides while FEF_{75}\% and PIF had significant positive correlation with HDL-C and VLDL-C respectively (Table 2.8).

In the LP, FEV_{1}/VC\% had significant negative correlation with VLDL-C while MVV was negatively correlated with bicarbonate. FEV_{1}/FVC\% showed a positive correlation with bicarbonate (Table 2.9). Among the flow rates FEF_{25}\%,
showed a significant positive correlation with bicarbonate and FIF$_{75}$ with LDL-C. FIF$_{25}$ had a significant positive correlation with serum triglycerides (Table 2.10).

A reduction in FEV$_1$/FVC% and flow ratio is proportional to the reduction in FVC. Increase in PIF shows better efficiency of airways. At higher lung volumes, flow rates tend to increase. FEV$_1$/FVC% indicate calibre of smaller airway while FEV$_1$/VC% shows overall assessment of dynamic airflow. A decrease in FMFT demonstrate better condition of small airways. Higher FEV$_1$ and PIF show better conductive properties of larger and smaller airways. Increased FIF indicates the efficiency of lower airways and less airway resistance. Increased flow rates show higher lung volumes and better status of airways. In this correlation analysis many other factors like the endogenous sex steroids like progesterone and physical factors viz. height, weight, age and many other factors may be directly or indirectly influenced though the exact reason for these correlation are not clearly understood.

In the present study, haemoglobin did not show any significant variations during the female cycle (Table 2A1) as evidenced from the changes in the correlation of haemoglobin which was not apparent since the number of RBC count remained almost constant throughout the cycle. Haemoglobin appeared to have a negative correlation with FEF$_{0-25}$ (FP) (Table 2A6) and FEF$_{25}$ in the LP. Decrease in FEV$_1$/VC% showed an overall assessment of dynamic blood flow while a higher FEF$_{0-25}$ demonstrates better efficiency of larger airways while higher FEF$_{50}$ denotes better condition of the airways. Higher lung volumes will result in higher flow rates while decreased lung volumes causes decreased flow rates.
Plasma proteins did not show significant correlation with respiratory functions. In the MP only FEV_{0.9}/FVC% showed a significant positive correlation with fibrinogen (Table 2.A.3). Flow rates FEF_{25-75}%, and FEF_{75-85}%, showed significant positive correlation with fibrinogen (Table 2.A.4). In the FP, FEV_{0.5} and FEV_{1} showed significant positive correlation with fibrinogen (Table 2.A.5) while FEF_{2-12} had a significant negative correlation with haemoglobin. FIF_{75}%, exhibited a positive correlation with fibrinogen (Table 2.A.6). In the midcycle FEV_{0.5}, FEV_{1} and FEV_{1}/VC% had significant positive correlation with fibrinogen. (Table 2.A.7). In the MC, FIF_{75}%, showed a significant positive correlation with fibrinogen while other parameters remain unaffected (Table 2.A.8). In LP, FEV_{1} had significant positive correlation with fibrinogen while FEV_{1}/VC% showed a significant negative correlation (Table 2.A.9). Expiratory flow rates FEF_{25}%, showed a significant negative correlation with haemoglobin while FEF_{25-75}%, FEF_{75-85}%, and FEF_{75}%, showed significant positive correlation with fibrinogen (Table 2.A.10). Increased trend in fibrinogen from MP to LP had a relation with corresponding increase in the expiratory flow rates viz., FEF_{25-75}%, FEF_{75-85}%, and FEF_{75}%. 

Bleeding time did not show any positive or negative correlation with any of the respiratory functions except a negative correlation with FEF_{50}% in the LP (Table 3.10). The possible reason may be the association of progesterone and ventilation in the LP, the exact mechanism of which is not clearly understood.

RBC did not show any variations in the correlation most probably because of their stable concentration throughout the menstrual cycle (Tables 3.1 and 3.2). while, WBC had a positive correlation with FEV_{0.5} and a negative correlation with FEV_{1}/VC% in the LP (Table 3.9). This shows that the respiratory functions are improved in LP due to the increased concentration of progesterone in this phase. There is a negative correlation between WBC and FEF_{25-75}% in the MC. Present
study shows an increase in WBC count in different phases of cycle which is very much related with increase in lung volumes (FEV$_{0.5}$) and negative correlation exists between WBC count and flow rates (FEF$_{25,75}$). This shows that increase in WBC count can offer a better lung volumes during menstrual cycle.

When a comparative study was undertaken between hormonal parameters viz. estrogen, progesterone, LH and FSH in the different phases of menstrual cycle significant differences in the concentration were observed (Tables 4.1 and 4.2). Estrogen showed maximum value in the MC while progesterone in the LP. But both of them were lowest in their concentration in menstrual phase. Anterior pituitary hormone, LH had a higher concentration in MC while FSH in the FP. These hormones also had minimum concentration in the menstrual phase (Table 4.2).

Cyclical changes in estrogen and progesterone affects the functions in several organs. One of these is pulmonary function in normal menstrual cycle of women. Progesterone is considered to be one of the agent which causes hyperventilation and hypocapnia during the LP of the menstrual cycle and in pregnancy. The ventilatory response to hypoxia has consistently been found to increase during the LP (Schoene et al., 1981; White et al., 1983) and during the administration of medroxy progesterone acetate – a synthetic progesterone (Zwillich et al., 1978; Schoene et al., 1980). Dempsey et al. (1986) also noticed that the regulation of ventilation in women is influenced by progesterone, which increases in blood during the LP of the menstrual cycle as well as in pregnancy. At this time resting ventilation is increased with a concurrent decrease in PCO$_2$. They further noticed that after administration of synthetic progesterone in males and animals, a similar response in ventilation were observed. From this observation it was clear that progesterone influences ventilation. Many other
investigators also supported this finding that hypoxic ventilatory response increases when blood progesterone level is raised by the administration of synthetic progesterones. Nariko-Takano (1988) observed that change in minute ventilation to change in arterial $O_2$ saturation ratio ($\Delta$VE/$\Delta$SaO$_2$) increased by 5 to 65% during the LP. The increase in hypoxic ventilatory responses were inversely correlated with decrease in resting $PCO_2$ in the LP. Munakata et al. (1993) reported that apart from this, progesterone also influences airway responsiveness. The possible explanation for this is that progesterone is known to decrease the contractility of smooth muscle of uterus, gut, gall bladder, genito urinary tract and vascular beds. In addition, exacerbation of asthmatic symptoms in the menstrual cycle is reported with the cyclical changes in the plasma progesterone level. (Juniper et al., 1987). But at the same time airway responsiveness to inhaled metacholine and histamine does not change during the menstrual cycle. (Juniper et al., 1987, Weinmann, et al., 1987) and it is improved during pregnancy. On the basis of these facts it seems difficult to consider that increased plasma progesterone levels directly affect the airway function in females. On the other hand, it is known that progesterone modifies both hypoxic and hypercapnic ventilatory responses in normal women. Increased ventilatory response may induce relative hyperventilation both at rest and during exercise (Munakata et al., 1993).

About the mechanism of action of progesterone, the reports are conflicting. A few investigators support a central mechanism while others disagree. Schoene et al. (1981) reported that progesterone is thought to increase ventilation through a central mechanism probably acting as a mediator in alternating the ventilatory responses. In males when MPA was administered, an increase in resting ventilation and decrease in arterial $CO_2$ tension (Skatrud et al.,...
1978). The fact that they found MPA in CSF of their subjects adds more weight to this argument that progesterone act centrally to augment ventilation.

In the present study, on correlation, progesterone showed a positive correlation with $\text{FEF}_{25-75\%}$ (FP), $\text{FEV}_{0.5}$, $\text{FEF}_{25-75\%}$ (MC), $\text{FEV}_{1}$, $\text{FEF}_{25-75\%}$ and $\text{FEF}_{50\%}$ (LP) while it had a negative correlation with $\text{FEV}_{1}/\text{VC\%}$ in the LP. Increased lung volumes like $\text{FEV}_{0.5}$, $\text{FEV}_{1}$ and increased flow rates, $\text{FEF}$ shows better airway response and better condition of airways. Since this is mostly observed in MC and the LP, this can be directly correlated with the increased concentration of progesterone in midcycle and LP. So the present study clearly indicate that progesterone augment ventilation in LP and midcycle.

On comparison, maximum concentration of estrogen is found in the midcycle around ovulation as observed by a number of investigators. Not many investigations are carried out to evaluate the relation of estrogen and respiratory functions. But estrogen is mainly correlated with the serum lipids in the menstrual cycle. Avogaro (1979) and Naito (1985) reported that Apolipoproteins A-I and B are major proteins of HDL-C and LDL-C and better indicators of coronary artery disease than HDL-C and LDL-C lipid constituents. Estrogen increases the production of apo A-I in vivo and in vitro. In addition estrogen administration increases LDL-C receptor activity and decreases LDL-C and apo B levels in post menopausal women. (Jensen, 1987). Estrogen has been shown to increase the concentration of the alpha lipoproteins and decrease beta lipoproteins, presumably by increased uptake of LDL-C by the liver. During menstrual cycle, estrogen levels reach its peak just prior to ovulation, but average higher levels of estrogen for a longer duration is observed in the LP of the cycle as compared to other phases. These estrogen changes are consistent with the timing of the plasma lipid responses. These results demonstrate that there is a hormonal effect on
cholesterol levels and that this effect is independent of polyunsaturated/saturated fatty acids (P:S) ratio and relative fat intake when weight is held constant (Yvonne, 1988).

Several studies have indicated a difference in the incidence of cardiovascular disease in men and pre-menopausal women while these differences are not observed in the postmenopausal women, which suggests that ovarian sex steroids may be related to some protective mechanism. Estrogen is directly related to HDL-C whereas progesterone shows an inverse relationship with the HDL-C. Furthermore, a fall in LDL-C levels has been reported during estrogen replacement therapy in post-menopausal women (Knopp et al., 1982). This is in support of fact that a higher incidence of atherosclerotic cardiovascular disease in person with high LDL-C while high HDL-C denotes decreased evidence of cardiovascular diseases. So this is a natural protective mechanism in premenopausal women against cardiac diseases. The possible mechanism is that HDL-C enhances the removal of cholesterol from tissues by HDL-C carrier protein apo A-1 and promote its transport to the liver for catabolism. Another study suggests that HDL-C may be the principal source of biliary cholesterol and its excretion represents another key process for the removal of the lipids. Decreased HDL-C concentration in middle-aged and elderly persons are associated with increased incidence of cardiovascular risks. In postmenopausal women the risk of coronary diseases is equal to men. Even though hormone replacement therapy is applied, after menopause, increased susceptibility to carcinogenesis and a role for hormone therapy is suspected (Raafat et al., 2001). It is reported that selective estrogen receptor modulators have beneficial effects on bone and cardiovascular risk factors and estrogen antagonist effect on breast and uterus by reducing serum LDL-C and total cholesterol in healthy older women (Vincenzo et al., 2001). This finding is also supported by Wild and Reis...
(2001), that selective estrogen receptor modulators are protective in nature. Doren et al. (2000) suggested that hormone replacement therapy may induce or opposite changes of both vascular resistance and lipids, even if these findings modify cardiovascular risk. But recent reports suggest that women who receive hormone replacement therapy for several years did not appear to be at risk in these cases as compared to other women (Hill et al., 2000).

A positive correlation was observed between estrogen and IVC in menstrual phase. FEF_{25-75\%} (FP), FEV_{0.5}, FEV_1, FEF_{02-12} (midcycle), FEV_{0.5}, FEV_1 and FEF_{25-75\%} (LP) were negatively correlated with estrogen. FEV_{1}/FVC\% showed a positive correlation and FEV_{1}/IVC\% showed a negative correlation with estrogen (Table 4.3 to 4.10). Here also an improvement in the expiratory flow rates showed better efficiency of airways. The study shows a positive and negative relationship of estrogen with different lung volumes and flow rates. But, there is no earlier observation or literature available about the relationship of estrogen with lung functions. Therefore, the exact role of estrogen to lung function is not known. Here also an improvement in the expiratory flow rates showed better efficiency of airways and system.

The basic factors controlling ovarian function are hypothalamic hormone GnRH, anterior pituitary hormones LH and FSH, gonadal sex hormones estrogen and progesterone. FSH is slightly elevated in the early FP and decreases throughout the cycle except in MC peak. LH shows a rise in MC called the 'LH surge' about 18 hours before ovulation. In other phases, it is almost stable in concentration. On correlation between anterior pituitary hormones and respiratory function, positive correlation of LH with FEF_{75-85\%} in MP, a negative correlation exists between LH and FP (FEV_{0.5}, FEV_1, FEF_{25\%}) a negative correlation exists between LH and MC (FEV_{0.5}, FEV_1) and a positive relationship
between LH and MC(/**EF**75%) (Table 4.3 to 4.7). The study shows a negative correlation between LH and lung functions except in **EF**75%. An increase in flow rates indicates improved conditions of both smaller and larger airways and the improvement may be due to LH.

The correlation of FSH with respiratory functions, shows a positive correlation in \( FEV_{1.5} \) in menstrual phase, \( FEV_{25-75}\% \) in MC and negative correlation of \( FEV_{1}/\text{VC}\% \) (LP)(Table 4.3 to 4.9). Out of these correlation analyses, it is noticed that apart from progesterone, other hormones are also correlated to respiratory function in a positive way at some stage of the menstrual cycle. But studies on such a variety of respiratory functions and hormonal parameters were carried out for the first time. It is assumed that estrogen, LH and FSH may have an indirect relation with respiratory functions rather than direct relationship. Progesterone level in the different phases of the menstrual cycle may influences this effect. Apart from this, many other physical and psychological factors and stress situations were also influence respiration during the menstrual cycle. But it is clearly observed that progesterone exerts a major role while other hormones to a lesser extend.

In the third section of the present study correlation of biochemical, haematological and hormonal parameters were carried out in different phases of menstrual cycle. Total serum cholesterol shows a significant negative correlation with estrogen in MC of the present study(Table 5.13). Similar observation were also reported by Christopher et al. (1997). The possible reason for the negative correlation between estrogen and total serum cholesterol may be due to the high concentration of estrogen at this phase. But such an association between estrogen and serum cholesterol is also seen in the LP (Table 5.18). This may be due to the
fact that even though estrogen remains high in LP phase its effects are opposed by high progesterone level in the LP.

HDL-C showed a positive correlation with LH in late FP (Table 5.18) around ovulation and also in MC (Table 5.13) where it had a strong correlation with estrogen and HDL-C. Christopher et al. (1997) also reported similar findings. This association of HDL-C decreases the incidence of coronary artery diseases in premenopausal women. LDL-C in the present study did not show any correlation with any biochemical or hematological parameters except estrogen in MC. This could be due to the fact that LDL-C always parallels with total serum cholesterol in menstrual cycle. This finding supports the concept that LDL-C contribute towards the total cholesterol pool as suggested by Christopher et al. (1997). Significant negative correlation was found between VLDL-C with progesterone in the LP (Table 5.18). This is in agreement with the earlier findings of Christopher et al. (1997) and clearly supports the observation that hormones influence the concentration of plasma. The negative correlation exists between triglycerides with estrogen (Table 5.8) in the present study may be due to the fact that triglycerides forms part of the total cholesterol and probably it parallels the total cholesterol in the blood.

Bicarbonate showed a negative but significant correlation with progesterone in MC of the study (Table 5.13). Similar observations were also reported by Sandra and Leon (1976). The probable reason behind this may be the increased concentration of progesterone in LP causes a primary metabolic acidosis and hyperventilation which bring about a decrease in PCO₂ and base excess, entails a considerable loss of bicarbonate.

Progesterone showed a negative correlation with hemoglobin in MP (Table 5.4). But the association of these two was not well understood.
Hematological parameters viz. bleeding time, clotting time and prothrombin time did not show any correlation with any parameter possibly because these hematological parameters remain unchanged throughout the menstrual cycle.

Among the plasma proteins, fibrinogen exerts a positive correlation with FSH in FP (Table 5.9) which is poorly understood but may be associated with the increased concentration of FSH in FP. But a positive correlation of fibrinogen with progesterone in the LP in this study (Tables 5.19 and 5.20) in accordance with the earlier report of Lebech and Kjaer (1989). WBC count showed a positive correlation with FSH in LP. However, no definite explanation can be offered for this phenomenon. It is clear from the present study that the hormonal changes in menstrual cycle affect the plasma lipids to a reasonable extent while hematological parameters to a lesser extent.