Review of Literature

REVIEW OF LITERATURE

Pregnancy is associated with significant anatomic and functional changes in respiration influenced by mechanical, endocrine and metabolic factors. The increasing requirement for mother and fetus for oxygen during pregnancy would be most efficiently served by smooth transport and exchange of gases through the respiratory system.

The purpose of this review is to outline the enumerated factors that influence the respiratory system during pregnancy and to discuss their effects in normal women and in those with coexisting pulmonary diseases.

Physiological changes affecting the respiratory system

Mechanical Factors

The enlarging uterus alters the position of the diaphragm and overall configuration of the thoracic cage. During pregnancy, the level of diaphragm increases maximally by 4 cm and the transverse diameter of the chest increases maximally by 2.1 cm. The subcostal angle increases progressively from an average of 68.5 degrees in early pregnancy to 103.5 degrees in late pregnancy (Thomson and Cohen, 1938). Despite alteration of the resting position of the diaphragm by pressure from enlarging uterus, diaphragmatic motion is not impaired. While in other studies, diaphragmatic excursion with total breathing was actually greater in pregnancy than in the puerperium (McGuinty, 1938; Mobius et al, 1961).

Drawing an analogy, Prowse and Gaensler (1965), have associated the decreased downward pull of the diaphragm with less negative intra-thoracic pressure and a decreased resting lung volume,

however, the range of the thoracic musculature is found to be unimpaired.

Biochemical Factors

The level of hormone progesterone is known to increase gradually from 25 ng/ml at 6 weeks to 150 ng/ml at 7 weeks (Jaffe et al, 1977; Yannone et al, 1968). This hormone has been shown to increase resting minute volume (V) and the slope of the curve of ventilatory response to changes in alveolar pCO_2 even in normal non-pregnant subjects. Likewise pregnant subjects chronically hyperventilate and demonstrate a similarly enhanced hypercapneic ventilatory drive (Lyons and Antonio, 1959). Mouth occlusion pressure was found to increase progressively during pregnancy in correlation with increasing progesterone levels. Progesterone is held responsible for the chronic hyperventilation of pregnancy either by changing the sensitivity of the respiratory centers to alveolar pCO_2, or by acting as a primary respiratory stimulant (Contreras G. et al, 1991). Estrogen may have an additional effect and cause increased irritability of the respiratory center.

The net effect on respiratory system due to changing prostaglandin concentration during pregnancy is not clear. $PGF_{2\alpha}$, a uterine smooth muscle stimulant, constricts bronchial smooth muscle, while PGE_1 and PGE_2 have bronchodilatory effect (Shaw and Moser, 1975; Hyman A. et al, 1978). Several studies have documented reversible bronchoconstriction during intravenous or intraamniotic administration of $PGF_{2\alpha}$ to induce abortion; therefore, $PGF_{2\alpha}$ may precipitate asthmatic attacks in women, with underlying airway diseases (Fishburne et al, 1972; Kreisman et al, 1975 and Smith, 1972).

The clinical relevance of changing cyclic nucleotide concentration in pregnant women is still speculative. Cyclic AMP concentration peaks twice, at 14 weeks and 34 weeks during pregnancy (Ling, 1977). Cyclic GMP excretion increases rapidly during the first trimester and then remains fairly constant throughout the duration of pregnancy.

Current theory suggests that cAMP has a bronchodilatory effect, while cGMP causes bronchoconstriction (Ziment, 1978). Again, it is not known how changes in cyclic nucleotide concentration ultimately affect bronchomotor tone in normal pregnant women or those with obstructive lung disease.

There is a two to three fold increase in free cortisol level during pregnancy. This increase in metabolically active cortisol has no known effect in normal pregnant women, but may favorably affect women with steroid responsive pulmonary disease (Sulavik, 1975; Weinberger et al, 1980).

Pulmonary function, ventilation and gas exchange

The effects of the mechanical and hormonal changes can be quantified by pulmonary function tests, measurement of minute ventilation (VE), and assessment of blood gases.

Lung volumes

A combined decrease in expiratory reserve volume (ERV) and residual volume (RV) during the second half of pregnancy produces 18% mean decrease in FRC (Cugell et al, 1953). However the VC remains unchanged, therefore, the TLC is slightly diminished at term. There is a consistent decrease in ERV in late pregnancy, with values ranging from 8% to 40 % less than non-pregnant control values. Similarly, RV at term is 7% to 22% less than control values. The net

effect of the decrease in both ERV and RV is a 9.5% to 25% decrease in FRC after fifth and sixth month of pregnancy (Cugell et al, 1953; Alaily, 1978; Baldwin, 1977; Cameron et al, 1970; Craig and Toole, 1975; Gazioglu et al,, 1970; Gee J. B. L. et al, 1967; Ihrman, 1960; Knuttgen, 1974; Rubin et al, 1956; Gerrard et al,, 1978 and Milne et al, 1977).

MBC is not significantly affected by pregnancy. TVC, FVC, PEFR, MEFR and velocity index are also not appreciably altered during pregnancy. Unchanged FEV_1 or FEV_1/FVC suggests that large airway functions are not impaired during pregnancy (Cugell et al, 1953; Alaily and Carrol, 1978; Baldwin et al, 1977; Cameron et al, 1970; Knuttgen et al, 1974; Rubin et al, 1956; Gerrard et al,, 1978).

Total pulmonary resistance, consisting of both airway and tissue resistance is significantly reduced in pregnancy (Rubin et al, 1956). A decrease in airway resistance is the major factor for the 50% reduction in total pulmonary resistance. Although a reduced FRC and hypocapnia tends to increase airway resistance, the mechanisms instigated to counter balance these changes are relaxation of bronchial smooth muscle by increased levels of cortisol, relaxin or progesterone and improved compliance secondary to pulmonary hyperventilation.

As the enlarging uterus encroaches on the diaphragm, chest wall compliance and therefore, total respiratory compliance are reduced in late pregnancy (Gee et al, 1967).

Airway closure during late pregnancy occurs either above FRC or closer to FRC then it does in the non-pregnant state. The major contributing factors to these changes are the decrease in ERV and FRC in face of an unchanged closing volume (Baldwin et al, 1977; Holdcraft et al, 1977), the potential consequence being a decrease in

ventilation to involved area of lung. Creations of regions with low ventilation perfusion ratios can adversely affect gas exchange and result in arterial hypoxemia (Weinberger S. T. et al, 1980).

Diffusing Capacity

There is no change (Krumholtz et al, 1964) or a slight increase (Gazioglu et al, 1970) in diffusing capacity of the lungs for carbon monoxide early in pregnancy, with a subsequent decrease throughout the duration of pregnancy to normal or slightly lower than normal value. The relative contribution of change in membrane diffusing capacity and pulmonary capillary blood volume to arterial hypoxemia are presently not known (Weinberger S. T. et al, 1980).

Both at rest and with exercise, VE and to a lesser extent, oxygen consumption is increased during pregnancy over the non-pregnant control values (Prowse and Gansler, 1965). Although other contributing factors have been postulated, the currently accepted explanation for the hyperventilation of pregnancy is the effect of progesterone and its respiratory stimulating properties (Weinberger et al, 1980).

Pregnancy is associated with hyperventilation that is in excess of the observed increase in oxygen consumption and results in decreased $PaCO_2$, but blood pH is maintained in a slightly alkalotic range by renal compensation (Dayal P. et al., 1972). As a result of the decrease in $PaCO_2$ and, hence $PACO_2$, alveolar pO_2 increases and PaO_2 therefore also increases (Anderson et al, 1969; Templeton et al, 1976). An abnormally high (A-a) pO_2 near term, presumably related to airway closer, partially offsets the increase in pO_2 expected from hyperventilation. There is a further decrease in PaO_2 and an increase in (A-a) pO_2 while changing from sitting to supine posture in late pregnancy (Templeton et al, 1976; Awe R.J. et al, 1979). In patients

without underlying pulmonary diseases, these changes in PaO_2 appear to have little clinical significance (Weinberger et al, 1980).

Dyspnea

Dyspnea is the most common complaint expressed some time during the course of gestation by as many as 60% to 70% of pregnant women (Prowse & Gaensler, 1965). It commences most frequently in the first or second trimester and is found to improve as the patient approaches term. Although it is still not entirely clear why gravid women feel dyspneic, the symptom does appear to be related in some way to the hyperventilation of pregnancy (Gilbert and Auchincloss, 1966).

Pulmonary function testing

Pulmonary function testing has been a major step forward in assessing the functional status of lungs as it relates to the volume of air and velocity of the airflow in and out of the lungs, the lungs and chest wall compliance, diffusion characteristics of the membrane and the therapeutic effect of drugs in respiratory disorder.

Gupta (1972) in his editorial has given a brief account of history of pulmonary functions. The history states that some experiments in pulmonary physiology were undertaken before birth of Christ by Eristratus and later by Galen in 131 – 120 BC. Hippocrates in 466 – 377 BC first suggested that main purpose of breathing is to cool the heart. Versalius in 1514 – 1564 demonstrated the role of ventilation in maintainence of life. Lower in 1631 – 1691 was the first to note the change in color of oxygenated blood. Actually the evaluation of human pulmonary function dates back to the seventeenth century. Borelli (1979) was the earliest physiologist who established an experimental inquiry into the quantity of air received by a single inspiration. Subsequently John (1846) in his treatise, on the capacity of the lungs

and on the pulmonary functions, defined the functional subdivisions of lung volume. He reported the results of vital capacity measurements performed in more than 1800 "healthy cases", relating these values to the height, age and weight of his subjects.

Physiological basis of pulmonary function testing

With great advances in pulmonary physiology and medical instrumentation during past 40 years the assessment of pulmonary functions has come to acquire a central place in the practice of pulmonary medicine. Pulmonary function tests permit an accurate and reproducible assessment of functional state of respiratory system. They offer best hope for the early detection of chronic obstructive pulmonary disease (COPD) and for objective documentation of the severity of occupational lung diseases etc.

The limitation of physiological tests is fundamental and immutable. Ironically, with the partial exception of asthma, the most common diseases of respiratory system are defined in other terms. For example emphysema is defined in terms of structure, as an abnormal enlargement of air containing spaces, distal to terminal bronchioles accompanied by destruction of alveolar tissue (Meneely et al, 1962). Chronic bronchitis is defined in terms of a symptom; namely a condition associated with cough productive of sputum on most mornings for three consecutive months since two consecutive years. The accuracy of diagnostic inferences depends on a thorough knowledge of the physiological basis of the functions measured, of pathophysiology of disease affecting those functions and of requirement for equipment protocol.

Some salient features regarding mechanics of breathing, pathophysiology of respiratory diseases and physiological basis of pulmonary function tests are discussed herewith.

During inspiration, small airways get stretched, partly due to increase in volume of lungs and partly due to negative pressure in the alveoli. Hence, airway resistance is lower during inspiration. Conversely during expiration, smaller lung volume and the positive alveolar pressure compress airways. The diameter of small airways decrease and some might collapse and close completely during forceful expiration.

Work of breathing: during breathing work is performed by respiratory muscles. Work of inspiration can be divided into three fractions: (a) first that is required to expand the lungs against the long and chest elastic forces, called compliance or elastic work; (b) second that is required to overcome the viscosity of lung and chest wall structures, called the tissue resistance work and (c) third is required to overcome airway resistance during movement of air into the lungs, called as airway resistance work (Mead and Milic-Emili, 1964). During expiration, work is done only to overcome viscous resistance. Elastic recoil of lung and thorax provides energy for viscous resistance and additional energy is dissipated as heat.

On functional basis, respiratory diseases are mainly of two types, restrictive and obstructive. In restrictive lung diseases for example fibrosis, the distensibility of lungs may be reduced, where the elastic component of the work of breathing is increased. The magnitude of which depends on the degree of expansion of the lungs. Hence, the patients with restrictive lung disease tend to take shallow breaths and increase the frequency of breathing to achieve satisfactory alveolar ventilation. In obstructive lung diseases in which airway resistance may be increased, e.g. bronchial asthma, the work required to overcome airway resistance is increased, the magnitude of which depends on the velocity of airflow. Therefore, patients with

obstructive lung disease tend to take slow breath. They achieve satisfactory alveolar ventilation by increasing the tidal volume.

Pathophysiology of airway resistance: Airway resistance is increased as in bronchial asthma due to bronchospasm and due to mucosal edema and secretions as in chronic bronchitis. It is also increased if any type of swelling obstructs the airways from within or presses on the airways from outside.

The characteristic diagnostic feature of airway resistance is slower expiration, so FEV_1 is reduced. This has many potential consequences. First, since expiration needs more time, respiratory frequency may be reduced. However, this cannot be done beyond a certain limit because it impairs alveolar ventilation. Second, employing expiratory muscles quickens expiration. Nevertheless, this has certain limitations. It makes the patient tired and increases the intrathoracic pressure, compresses the airways and increases the airway resistance further. Third, the next inspiration begins before expiration is complete i.e. FRC is increased. Since tidal volume remains same, person begins expiration at higher volume, and the elastic recoil of the lungs is stronger than before. This assists expiration. As disease progresses the FRC increases further and lungs are stretched more and more, till the limit of tolerance of elastic tissue is reached. This contributes to breakdown of lung tissue in chronic bronchitis leading to emphysema (Burrows et al, 1975).

The main methods of screening lung function status are assessments of ventilatory function, ventilation/perfusion ratio, diffusion measurement for gas transfer, blood gas analysis and exercise ergometry for cardio-respiratory functions. Amongst the above mentioned function tests, the widely used ventilatory function tests are forced spirometry and spirometry.

Forced spirometry

This consists of volume of air inhaled and exhaled, plotted against time during a series of ventilatory maneuvers. The curves obtained permit the determination as to whether subject has a normal pattern of ventilatory reserves or an abnormal pattern characteristic of obstructive, restrictive or mixed ventilatory abnormalities. None of these patterns are specific, although most diseases cause a predictive type of ventilatory defect(s). Spirometry alone cannot make diagnosis of specific disease, but it is sufficiently reproducible to be useful in following the course of many different diseases.

Spirometry is indicated in occupational surveys, in identifying high-risk smokers (Vestbo et al, 1990; Marezzinni et al, 1989 and Pride, 1990) and in preoperative assessment. It is useful in evaluation of impairment of treatment and of natural history of disease. It is an excellent screening test for detection of chronic airflow obstruction, but may also be useful in detecting restrictive disorders as well.

Gold (1997), believes that spirometry should be a part of the baseline clinical evaluation obtained in all adults patients. If this baseline test is abnormal or if patient has certain risk factors, the test would be repeated regularly every, one to five years.

Volume of air inhaled and exhaled with relaxed and maximal efforts can be measured easily with inexpensive equipment – a simple recording spirometer. Although normal values have been established for a spectrum of subjects of different sex, age, size and ethnic background (Schoenberg et al, 1978 and Knudson et al, 1976), few have been reported using standards of American Thoracic Society (Crapo et al, 1981; Morris et al, 1971 and DaCasta, 1971). Subject inhaling maximally to TLC and then exhaling as rapidly and forcefully as possible records maximal effort vital capacity or FVC curve.

Several useful variables derived from the maximal effort forced vital capacity are FEV at the end of 0.5, 1, 2 and 3 seconds of FVC maneuver ($FEV_{0.5}$, FEV_1, FEV_2 and FEV_3 respectively).

FEV_1 is the measurement of dynamic volume most often useful in conjunction with FVC in analysis of spirometry. It incorporates the early effort dependent portion of the curve with enough of the midportion to make it reproducible and sensitive for clinical purposes.

FEV_1/FVC ratio as *percentage*: It declines with age (Morris et al, 1973), but abnormally decreased ratios indicate airway obstruction; normal or increased ratios do not reliably exclude obstruction particularly in presence of decreased FVC. When FVC is decreased by an interstitial process or by chest wall restriction and airways are normal, FEV_1 / FVC ratios are increased. The absence of increased ratio in patients in whom one would expect the ratio to be increased suggests the presence of concomitant airways obstruction. Absolute flow may be increased initially, probably because of outward traction of increased elastic forces on airway walls. Because flow is volume dependent, it eventually decreases in restrictive disorders without airway obstruction, although precise quantification in different type of pure restrictive disorders is not available.

Average forced expiratory flow (FEF): Two measurement of average FEF over different portions of expiratory curve have been used widely. FEF between initial 200 and 1200 ml of air exhaled ($FEF_{200-1200}$), originally called maximal expiratory flow rate (MEFR) was introduced to evaluate the portion of curve, most affected by obstruction of large airways and most responsive to bronchodilators (Cander and Comroe, 1955). Experience with this measurement suggests that it has limited clinical utility and FEF between 25% and 75% of FVC was introduced as the maximal mid expiratory flow rate (MMEFR or MMR). This measurement was intended to reflect the most

effort independent portion of the curve and the most sensitive to airflow in peripheral airways, where diseases of chronic airflow obstruction are thought to begin (McFadden and Linden, 1972 and Coiso et al, 1978). These properties have gain support from clinical experience and theoretical analysis (Hyatt R. E., 1955; Mead et al, 1967 and Pride et al, 1967) and $FEF_{25-75\%}$ is widely used currently. Both $FEF_{200-1200}$ and $FEF_{25-75\%}$ show marked variations in studies of large samples of healthy subjects, and the 95% confidence limits of normal values are so large that their sensitivity in detecting diseases in an individual subject is limited (McCarthy et al, 1975 and Cochrane et al, 1977).

Normal values

The American Thoracic Society has published a formal recommendation on selection of reference values and interpretative strategies for lung function tests including FVC, FEV_1 and FEV1/FVC for adult white and black men and women (American Thoracic Society, 1991). Predicted values can be obtained on the basis of age and height mainly.

The ATS suggests that individual laboratories use published reference equations that most closely describe the population tested in their laboratories. It is useful to compare the results observed in 20 – 40 local subjects with those provided by the intended reference equations. These local subjects should be lifetime nonsmokers selected by age, ethnic group, and sex to match the population usually studied in the laboratory.

For evaluation of respiratory impairment, except for FVC, lung volume shows poor correlation with exercise tolerance tests of so called small airway function and is too variable to be useful in respiratory impairment evaluation for multiple reasons. It involves a

larger learning effect, is more fatiguing and requires better instrumentation then simple spirometry. The social security scheme in USA mandates the use of MVV and FEV_1 in rating of impairment due to chronic airflow obstruction (Berend and Thurlback, 1982).

The prediction equation for FEV_1 recommended in 1986 ATS statement on respiratory impairment evaluation are those of Crapo and co-workers (Derenne et al, 1978). Black lung benefit program mandates the use of Knudson equation (Petty et al, 1981).

All the predicted equations commonly used by pulmonary function laboratories in United States are derived from studies of Caucasian populations. Although studies have repeatedly demonstrated racial ethnic difference in predicted values for FEV_1 and FVC, there is no consensus on what correlation factor should be applied for persons of various racial and ethnic groups. The American Medical Association recommends a correlation factor of 10% for persons of African or Asian descent (i.e. multiply Caucasian predicted values by 0.9) and many computerized spirometer automatically correct predicted values when a nonwhite racial category is selected. It is important to know what predicted values the individual laboratory is using and whether any routine adjustment for race is being applied, as well as to indicate this information in the evaluation report.

Pulmonary functions in pregnancy

The early measurement of lung volumes during pregnancy was limited to the vital capacity, since the introduction of spirometry into the clinical medicine in the middle of 19th century. It is the only fraction of lung volume that has received repeated attention but unfortunately there are discrepancies in the data available for the vital capacity. Since 1930's a number of studies were reported but interest in the pregnant women seem to have waned before the recent

enormous improvement in equipment and measurement techniques. Few studies that have been made were generally unsatisfactory as there were few patients in the sample and/or may be due to the technical differences in measuring techniques and the timing of the measurements (Hytten and Lietch, 1971).

Root and Root (1923) studied single pregnant women longitudinally and reported increase in vital capacity. In 1930, Alward found 20% decrease of vital capacity in 60 pregnant women. Enright et al, (1935) found increase in vital capacity in all 7 cases whereas Landt and Benjamin (1936) noticed it unaltered in all 19 cases in pregnancy. In the year 1938, Thomson and Cohen, pointed out that every careful study based on repeated observations of the same patients has shown a tendency towards increase of the vital capacity during pregnancy and a slight decrease after delivery. This was supported by their findings in 31 normal pregnant women in whom the mean vital capacity rose from 3260 cc in the 21st week to 3450 cc in the 40th week of gestation and dropped to 3150 cc 3 – 6 months after the delivery. They also noted as the transverse diameter of the chest increased and the long diameter diminished during pregnancy the vital capacity increased. Postpartum, when the chest configuration returned to normal, changes in the diameter of chest occurred, which were the reverse of those first described and concomitant with them, the vital capacity diminished. In their study, the pregnant women were capable of forced inspiration and expiration at a somewhat higher level than in a non-pregnant state.

Widlund et al (1945) found that vital capacity increased by 15% in second trimester and 9 % at the term. In 1953 Cugell et al, made a most detailed and comprehensive serial study of respiratory function in 19 women during normal pregnancy and again between two to six months postpartum. They found no difference between the vital

capacity measured in term and postpartum both in upright and supine position and there was no real change during the pregnancy. Vital capacity observed 3280 cc and 3300 cc in postpartum as non-pregnant data and term respectively. They also stated that during the control period, the vital capacity in supine position was almost identical to that in the upright position and was equal to the predicted volume calculated from the regression equation. The 1% increase of vital capacity at term was too small to signify a trend. They also mentioned that the dyspnea that occurs during abnormal pregnancy has no relation to changes in vital capacity.

Rubin et al (1956) found the mean vital capacity, 4 – 14 days before delivery, in 8 healthy women to be 295 cc below the mean vital capacity measured in the same women 7 – 14 weeks postpartum. This difference was statistically significant, except in three (all primigravidae) in whom fetus had moved down in the abdomen, showed no real difference. Rubin et al (1956) reviews the various studies and claim a majority as supporting their findings but they agree that the fall of vital capacity may be in later pregnancy that is at term. Vital capacity remains unchanged or increases slightly as per the study by Duncan (1962). Mean VC rose from 3260 ml in 21st week to 3450 ml in 40th week and dropped to 3150 ml 3 – 6 weeks postpartum. The upward displacement of diaphragm might be expected to decrease VC during pregnancy but such an effect fails to occur because of the increased circumferences of the chest. If reduction is observed in VC then it is interpreted as clinically pathological. The changes in lung volumes studied by Prowse and Gaensler (1965) in 9 healthy pregnant women showed no alteration in VC. Baseline measurements were obtained 4–9 months postpartum when, it was assumed, normalcy had been restored. Significant alterations were not observed in any of the lung volumes or capacities until the 5th to 6th month of pregnancy other than unchanged VC.

Bernard (1967) observed an insignificant change in VC from 3.20 L (non-pregnant state) to 3.14 L (at term), a decrease of 1%, suggesting that lung compliance was not greatly changed. VC is maintained by increase in inspiratory capacity. Preservation of VC also proves that inspite of higher end expiration there can be no true restriction of diaphragmatic movement. In 1970, Gazioglu et al, found the increase of VC of 0.3 L towards the term in a serial study of 8 normal pregnant women. They observed VC of 3.8 L, 3.9 L and 4.1 L at the 10^{th}, 24^{th} and 36^{th} week of gestation respectively with compared to 3.8 L after 10 weeks of delivery. They claim that this increase in VC was mainly by an average increase of 0.4 L in inspiratory capacity. Cameron et al, (1970) showed no significant change in VC studied on 60 pregnant women compared to 10 postpartum controls.

Shearman (1972) carried out serial study of VC during pregnancy in four normal women. The VC showed no change in two subjects and an increase in two others. In one patient, there was a slight decrease just before term. They also noticed in the supine position, VC, although lower than in the sitting position showed the same changes. Pandya et al (1972) showed that though VC increases with the advancing pregnancy (1610.3 cc and 1678.0 cc in 24 women of second trimester and 39 women of third trimester respectively), it was lower than the VC observed in postpartum period (1781.25 cc, in 20 women) and in control group (1839.65 cc). The values observed in 23 non-pregnant women of the childbearing age served as control. In 1974, Knuttgen and Emerson studied 13 pregnant women and showed significant increase in VC in pregnancy as compared to their postpartum values. Butler and Bonica (1975) have given values of VC as 3.92 L (non-pregnant) and 3.7 L (third trimester). In a serial study of 12 pregnant women Sims et al (1976) using vitalograph found no change in FVC. Baldwin et al, (1977) found VC within normal limit both in pregnancy (3.7 L) and postpartum (3.7 L) in a serial study in

19 women. They performed experiments in third trimester and during early postpartum period (2 days to 6 weeks). In the same year, Skandan et al carried out the experiment of lung volumes and VC on 75 pregnant women of 18 to 47 years of age during their last trimester and out of these, 24 pregnant women were studied within 48 hours after delivery. These were compared to those of normal adult females belonging to medical and nursing students (age 18 – 21 years) served as control. They observed significant decrease in standing VC (0.18 L) during third trimester than that of control normal non-pregnant women. Postpartum difference was 0.04 L below from the control group. A serial study of ventilatory functions was carried out by Alaily and Carrol (1978), in 38 normal primigravida during and after pregnancy. The mean VC observed were 3.76 L, 3.79 L, and 3.74 L during their 10 – 16 weeks, 20 – 24 weeks and 38 – 39 weeks of gestation respectively. Early and late postpartum values in those same subjects were 3.72 L and 3.66 L. Even after 2 – 3 months delivery they noticed the mean VC was unaltered (3.72 L). According to them the mean VC changed little during pregnancy and after delivery. The mean value for the patients agreed well with predicted value of 3.76 L based on age and height according to the nomogram of Cotes (1965). Recently in a serial study of pulmonary functions on 61 pregnant women, Milne (1979) showed no alteration of VC throughout the course of pregnancy and postpartum.

Chhabra et al (1998) found statistically significant progressive rise of 266.16 ml in VC. They computed mean and SD of VC (ml) to be 1947.70 ± 216.6 (non-pregnant state), 1937.84 ± 239.87 (first trimester), 2052.28 ± 223.74 (second trimester) and 2071.48 ± 281.70 (third trimester). Puranik et al, 1994, reported conflicting results in their study in which the VC increases in some subjects, while decreases in some and few shows no change. They stated that such results could be due to the VC observations obtained from different

subjects with different socioeconomic status at variable periods of gestation and postpartum period. They had concluded insignificant decrease in VC probably because of increment in IC being compensated by reduced ERV from first trimester to third trimester while no change in non-pregnant and early pregnancy. They gave the values to be 2.53 ± 0.29 L (postpartum), 2.53 ± 0.12 (first trimester), 2.51 ± 0.27 L (second trimester) and 2.49 ± 0.22 L (third trimester). The lowered values are attributed to low socioeconomic status and poor nutrition of the subjects.

Singhal and Saxena (1987) showed that decrease in hemoglobin results in reduction of oxygen carrying capacity especially in third trimester and causes tissue hypoxia and accumulation of intermediary products of metabolism leading to exhaustion. Also respiratory efforts become less powerful as reflected by decrease in expiratory flow rates.

Schatz et al, (1990) accounted low maternal gestational FEV_1 during pregnancy and states that it is related to intrauterine growth. Mokapatti et al, (1991) recorded a significant decrease in FVC and FEV_1 in third trimester as compared to controls. Rao et al, (1991) observed a decrease in $FEV_{1\%}$ from 89.9 (follicular phase) to 87.7 (progestational phase). $FEV_{1\%}$ was seen to decrease significantly from 97.04 ± 4.00 in follicular phase to 94.37 ± 9.12 in luteal phase (Rajesh et al, 2000).

The FEV_1 and its ratio with VC are often measured at the same time as VC. But a very few studies that have examined flows throughout the course of pregnancy, have consistently demonstrated that no alterations are observed in the FEV_1 or the FEV_1/FVC ratio. First report on upright TVC by Cugell et al (1953) showed that 82% of the total volume was exhaled in the first second, 94% during the first two seconds and 97% in the first three seconds. All individual performances were well within normal limits. There was no significant

change in these figures at term. The non-pregnant values were 84%, 94% and 98% in first one, two and three seconds respectively. Few years later, Rubin et al, (1956) found that FEV_1/FVC ratio during pregnancy was 73.1% as compared to postpartum 80.3%. But this difference, though it seems to be lower during pregnancy was not statistically significant. The experiment was done on semi-recumbent position.

Krumholtz et al, (1964) found FEV_1 was 85% and 84% during early and late pregnancy respectively. In the serial study Cameron et al, (1970), Gazioglu et al, (1970) found FEV_1 remains constant throughout the pregnancy.

Hytten and Leitch (1971) stated that FEV_1 remains constant or is not affected during pregnancy. They further stated that rates of gas flow both average and maximum during inspiration and expiration are little altered in pregnancy Pressure required to achieve flow rate was less in pregnancy than in non-pregnant subjects, airway resistance decreases and cross sectional area of airways increases due to relaxation of smooth muscles in airways by relaxin. Shearman et al, (1972) mentioned that FEV_1 was increased by about 6% in two subjects who showed a rise in VC in a serial study of four subjects.

Raz et al, (1973) stated progesterone increases β-adrenergic activity that causes bronchodilation. Knuttgen and Emerson (1974) found insignificant change in FVC. $FEV_{1\%}$ observed by them was 86.5 ± 2.00 and 89.3 ± 1.90 prepartum and postpartum respectively. Butler and Bonica (1975) gave FEV_1 value to be 3.2 L (at term) to 3.3 L (postpartum) suggesting a decrease in FEV_1 during pregnancy. Sims et al, (1976) were unable to demonstrate any significant longitudinal changes in FEV_1/FVC or FVC in either asthma or control groups during pregnancy, or between pregnancy and non-pregnant state.

Milne et al, (1977) measured FEV_1 and FVC on three separate occasions at 8 – 11, 12 – 23 and 24 – 36 weeks of gestational age using conventional water filled spirometer. He obtained FEV_1 (lts) as 3.1, 3.05 and 3.1 and FVC as 3.69, 3.67 and 3.75 in the respective gestational weeks, showing no change in FEV_1 and insignificant increase in FVC, while ratio of FEV_1/FVC (%) 84, 82.9 and 82.5 respectively.

Recently Baldwin et al, (1977) and Milne (1979) reported the unaltered FEV_1 (3.1 L) and FVC_1/FVC percent (84%) during the course of pregnancy and postpartum. In a detailed study on 38 pregnant women, all primigravidae, Alaily and Caroll (1998) showed no statistically change of mean FEV_1 during pregnancy or after delivery. The ratio of FEV_1/FVC was within normal limits in every case. The ratio averaged 82.3% during pregnancy and 83.6% during the postpartum and the non-pregnant state; no patients had a value below 70%. This suggests the function of larger pulmonary airways was not affected in pregnancy.

Das et al, (1991) have given mean and SD values of non-smokers during pregnancy for few parameters in first (7 – 13 weeks), second (14 – 16 weeks) and third (27 – 40 weeks) trimester as: FVC (L):- 3.90 ± 0.51, 3.89 ± 0.54 and 4.00 ± 0.45; FEV_1 (L):- 3.34 ± 0.42, 3.33 ± 0.41 and 3.41 ± 0.34; $FEV_{1\%}$:- 85.75 ± 4.09, 85.75 ± 4.54 and 85.47 ± 3.87. The study indicates that all parameter are not affected by advancing pregnancy and P value for all parameter between trimesters is non-significant. In another study, Das et al, (1998) obtained FVC as 3.9 ± 0.4 L and FEV_1 as 3.36 ± 0.39 L during pregnancy, a non-significant change as compared to non-pregnant state.

Rao et al, (1991) noticed a rise in FVC (L) in progestational phase (2.76) as compared to follicular phase (2.71) while no change

(2.43) in FEV_1 (L) in follicular and progestational phase. FVC (L) was found to be significantly higher in progesterogenic phase (2.24 ± 0.35) as compared to estrogenic phase (2.11 ± 0.32) of menstrual cycle while insignificant change in FEV_1 (L/sec) was observed in follicular (1.97 ± 0.39) and luteal (2.03 ± 0.35) phase (Rajesh et al, 2000). They also state higher values in lung function while few of these are statistically significant in luteal phase as compared with follicular phase indicating possible role of progesterone causing β-adrenergic stimulation or sensitization.

Puranik (1994) found mean and SD for FVC (L) as 2.19 ± 0.25, 2.15 ± 0.28, 2.16 ± 0.27 and 2.20 ± 0.26 in first, second and third trimester and postpartum respectively, an insignificant reduction in FVC that may be due to restrictive effect of the enlarging uterus. They have also reported insignificant increase in FEV_1 and FEV_1/FVC (%). The mean and SD values for FEV_1 obtained by them are 2.00 ± 0.09 (first trimester), 2.07 ± 0.27 (second trimester), 2.10 ± 0.24 (third trimester) and 2.20 ± 0.22 (postpartum) while FEV_1/FVC (%) are 92.60 ± 5.01 (first trimester), 97.68 ± 3.53 (second trimester), 98.09 ± 3.26 (third trimester) and 99.10 ± 2.37 (postpartum).

The peripheral airway function can be measured after assessing the flow volume loops or expiratory flow rates at lower lung volume. Only two studies so far are available for maximum expiratory flow volume curves during pregnancy. No change was observed in maximum expiratory flow at 25 % or 50% of VC (Gazioglu et al, 1970; Baldwin et al, 1977). Maximum mid expiratory flow rates were found 3.1 L/sec and 3.2 L/sec during late pregnancy and early postpartum period and fell within normal limits. Mokapatti et al. (1991) noticed a decrease in mid expiratory flow rate during first trimester. Das et al. (1991) studied effect of smoking on maternal airway function and has given mean and SD values for nonsmokers during pregnancy for some

parameter in first (7 – 13 weeks), second (14 – 26 weeks) and third (27 – 40 weeks) trimester respectively as follows: $FEF_{0.2-1.2}$ (L/sec): 6.52 ±1.27, 6.70 ± 1.21and 6.87 ± 1.16; $FEF_{25-75\%}$ (L/min): 3.77 ± 0.71, 3.81 ± 0.72 and 3.90 ± 0.64. They computed statistically insignificant change in all parameter by advancing pregnancy. Das et al, again in 1998 gave values for $FEF_{0.2-1.2}$ (L/sec) as 6.70 ± 1.22 and for $FEF_{25-75\%}$ (L/min) as 3.85 ± 0.69 during pregnancy. Datta et al, found no change in FVC, FEV_1, $FEF_{25-75\%}$ and FEV_1/FVC.

Rao et al. (1991) recorded a rise in $FEF_{25-75\%}$ (L/sec) from 2.91 in follicular phase to 2.98 in progestational phase. The increase and decrease in flow rates as mentioned above could be due to increase in progesterone level during progestational phase and a decrease in progesterone level during follicular phase (Rao et al, 1991; Rajesh et al, 2000).

Fetal Growth (*Birth Weight and Intrauterine Growth*):

The ability to reach an optimal *birth weight* results from the interaction between the fetal growth potential, maternal constraining factors and the environment. The growth potential varies from race to race and from individual to individual. This is one reason for significant differences in birth weight amongst fetuses of same gestational age. For example mean birth weight of the Cheyenne Indians in the United States is 3700 gm, whereas it is only 2400 gm for new born of the Lummy tribe in New Guinea (Meridith H. C., 1970).

The fetal growth was assessed in earlier times by historical dating (last menstrual period), serial fundal height measurement and comparison with the actual size of the neonate at birth. Based on these observations infants were classified as small-for-gestational-age (SGA), appropriate for gestational age (AGA) and large for gestational

age (LGA). Although these categories were very broad and nonspecific, clinicians discovered a significant increase in perinatal morbidity and mortality for infants born either large or small for their respective menstrual age (Battaglia et al, 1967; Brenner W. E. et al, 1976; Forbes and Small, 1983 and Robert et al, 1992).

de Onis et al, (1998) quantified the magnitude and described the geographical distribution of *intrauterine growth retardation* (IUGR) in developing countries. They estimated that at least 13.7 million infants were born every year at term with LBW representing 11% of all newborns in developed countries. The rate was approximately 6 times higher than in developed countries. LBW defined as < 2500 gm, affect 16.4% of all newborns, or about 20.5 million infants each year. IUGR is defined as birth weight below the 10^{th} percentile of the birth weight for gestational age curve, represented 23.8% or approximately 30 million newborns per year. Overall, nearly 75% of all affected newborns are in Asia – mainly in South – Central Asia – 20% in Africa and about 5% in Latin America. Although some of these are healthy, small infants who merely represent the lower tail of a fetal growth distribution, in most developing countries a large proportion of newborns suffer from some degree of IUGR. These data demonstrate that many developing countries currently exceed the internationally recommended IUGR (> 20%) and LBW (> 15%) cut-off levels for triggering public health action, and that population-wide instructions aimed at preventing fetal growth retardation are urgently required.

Birth weight is a function of gestational age. Various maternal and infant characteristics do affect birth weight. With this view to seek the adjustment of birth weight standards for maternal and infant characteristics to improve the prediction of outcome in the SGA infants was carried out by Sciscione et al, in 1996. They correlated the maternal age and infant characteristics from normal birth pregnancies

with birth weight. They developed a formula and applied it to the second group in which they compared perinatal outcomes in normally grown infants with those who were SGA. They compared the outcome between SGA infants defined by the formula with those defined by the formula as SGA were more likely to have morbidity and mortality then those who were normally grown ($P < 0.001$). SGA infants defined by the formula had more deaths and adverse outcomes then those defined by gestational age. Thus, they concluded that adjusting birth weight standards for maternal and infants characteristics may improve the prediction of adverse outcomes.

Obstetrics ultrasonography has enhanced their ability to detect growth abnormalties, thus directing more intensive antepartum care with an improvement of perinatal outcome. Intrauterine growth and its aberrations are major concerns of modern obstetrics because birth weight is the strongest known indicator of perinatal mortality. This relationship indicates that even after controlling the gestational age, the risk of perinatal mortality increases with decreasing birth weight. (Williams et al, 1982) has focused renewed interest on this condition.

Historically IUGR has been equated with the SGA fetus (Ott, 1997) and very frequently these two terms are used in an interchangeable manner. But actually the term SGA and IUGR do not separate normal and healthy fetuses that have a weight below the 10th percentile from those who are small because of intrauterine malnutrition. This differentiation is important and ideally should be made during pregnancy, so that perinatal resources may be focused on the fetuses at the risk instead of being used for the assessment of all small fetuses. The confusion in defining these features will lessen if SGA and IUGR are not used as equivalent terms. Actually, the term IUGR should be applied to fetuses affected by a pathologic restriction in their ability to grow (Seeds, 1984; Attman and Hytten, 1989).

Currently, the most common method of screening for and identification of the SGA and suspected of the SGA and IUGR infant is the measurement of the various fetal parameters by real time ultrasound. Queenan et al, (1976) used serial BPD measurement at an attempt to diagnose IUGR. They determined 738 fetal BPD in 468 normal obstetric patients between 18 and 43 weeks in whom the size of uterus on initial examination corresponds to duration of the amenorrhea ± one week and there were no complications during the pregnancy. The mean BPD ± 2 SD is as determined for each week. They found the rate of BPD growth to be 0.26 cm/wk from 18 – 38 wks. As the comparative experimental group they studied 100 random, high-risk obstetric patients in whom again the size of uterus on initial examination corresponded to the week of amenorrhea ± one week. They observed two patterns of suspected IUGR: One showed BPD values more than 2 SD below the mean; the other manifests a decreased change in BPD. At delivery seven neonates were identified who were SGA and could not be detected in utero by single BPD measurement.

Zimmer and Divon (1992) reviewed common sonographic methods to diagnose IUGR and macrosomia reported that a single sonographic parameter is unlikely to allow an accurate diagnosis of all cases, and that such sonographic measurements are associated with a high specificity and a somewhat low sensitivity. They suggested the use of different fetal growth parameter as BPD, HC, AC, FL and amniotic fluid volume to assess IUGR. Additionally, estimated fetal weight (EFW) and morphometric ratios were computed using one or more of the mentioned variables.

William (1997) used multiple ultrasonic parameters to estimate fetal weight in utero to screen for IUGR. According to him, though various fetal morphometric ratios and/or measurements of other fetal

parameter may provide useful information, serial evaluation to assess interval growth may be necessary to clarify the diagnosis.

The abnormal intrauterine growth has typically been categorized into one of two groups – symmetric or asymmetric. Symmetrical IUGR is when the fetus is proportionately SGA in early pregnancy and is thought to be due to an early insult affecting cell membrane. Intrauterine infection (e. g. Cytomegalovirus, rubella, and toxoplasmosis), chromosomal abnormalities, structural abnormalities and genetic syndromes are among the culprits. This type of IUGR accounts for approximately one third of all cases. Asymmetric IUGR is associated with slowing of abdominal growth relative to head growth in the late second or early third trimester, with variable effects on femur growth. Long standing cases may have more significant effects on femur growth. Placental insufficiency with poor nutrient provision is thought to be operational in the majority of cases leading to hepatic glycogen utilization, fetal hepatic shrinkage and decreased abdominal circumference. Preferential shunting of blood to the fetal head leads to its continued growth at the expense of the other organs. For this categorization ultrasonography has become the most accurate diagnostic tool.

According to Campbell (1998) ultrasound dating prior to 20 weeks gestation is thought to be accurate to ± 7 days and therefore could be beneficial especially in patients at risk for IUGR, however, nearly half of all infants with IUGR are delivered from low risk patients, and the only way to provide a benefit for this low risk population would be to use routine dating ultrasound in early pregnancy, with repeat scans performed later if lagging growth is suggested by physical findings. He further supports the application of biometric parameter including fetal head size (BPD, HC) abdominal circumference size (AC), fetal length (FL and PI) and estimated fetal

weight, along with ratios of biometric measures (HC/AC, FL/AC). Thus the antenatal diagnosis of IUGR and its subtypes have been shown to be of benefit in improving perinatal outcome.

Specific pulmonary diseases in pregnancy and perinatal outcome

This section will consider the various ways in which pulmonary diseases and pregnancy interact. Most of the times, pregnancy occurs in a patient with pre-existing pulmonary disease. While in other instances, the condition is specifically associated with or is due to the patients' pregnancy as in pulmonary embolism and amniotic fluid embolism. Thus the knowledge of physiological adaptations in pregnancy proves to be the fundamental for understanding how disease states affect pregnancy and how pregnancy affects disease. A brief review of pulmonary disease and pregnancy are cited below.

Asthma in pregnancy

Asthma is a heterogeneous lung disorder the common denominator underlying all asthma is non-specific bronchial hyper-responsiveness. In addition to increased sensitivity, there is increased maximal airway narrowing and a deficient response of the airway to deep inspiration (Mabie, 1996). Furthermore asthmatics have a progressive loss of airway distension due to loss of lung elastic recoil (Pare, 1995).

A number of causes for increased airway reactivity have been proposed, including airway inflammation, abnormalities in bronchial epithelial integrity, alterations in autonomic neural control of airways, changes in bronchial smooth muscle function and abnormal airway geometry, the most popular hypothesis at present being airway inflammation. Fiberoptic bronchoscopy performed during an acute asthma attack reveals an erythematous, edematous tracheo-bronchial

tree and mucosal biopsy confirms infiltration with eosinophils, neutrophils, lymphocytes, mast cells and macrophages. The release of inflammatory mediators, such as cytokines, prostaglandins, leukotrines and histamine, is thought to lead to smooth muscle contraction, destruction of epithelial cell integrity, vasodilation with edema formation and mucous hypersecretion.

In 1961, Schaefer and Silverman retrospectively reviewed the course of 293 asthmatics compared to 30,000 non-asthmatic controls. The prevalence of asthma was found to be in 1% of cases. The course of asthma was unchanged in 93% better in 3% and worse in 4%. LBW (< 2500 gm) was present in 8.7% of asthmatics as compared to 6.3% of controls while a single maternal death was reported.

Gordan et al (1970) published the asthma experiences of the collaborative Perinatal Project. The pregnancy outcomes of 277 asthmatics were compared with 30,861 non-asthmatic controls. There was no difference in prematurity on LBW, but there was a significant increase in perinatal mortality in asthmatics (5.9% vs 3.2%). Six maternal deaths occurred, five due to asthma and one due to suicide. During the year of life, 5.7% of infants developed asthma and 18.4% had severe respiratory disease. Sixteen women (5.4% of the asthmatics group) had two abortion, three intrauterine fetal demises and one neonatal death. Three of 11 live born infants weighed < 2500 gm. Two of 10 surviving infants exhibited neurological abnormalities at 1 year of age. It was concluded that severe asthma is a very high-risk situation.

Bahna and Bjerkedal (1972) retrospectively studied the pregnancy outcome of 381 asthmatics versus 112530 normal pregnant women. They found that asthmatics had increased incidences of hyper-emesis, hemorrhage, preeclampsia, prematurity,

LBW and neonatal mortality. Malformations were not increased, nor were stillbirths or perinatal mortality.

Gluck and Gluck (1976) published a study of 47 patients with asthma and reviewed the medical literature on 1087 pregnancies complicated by asthma. They found that the course of asthma was better in 36%, worse in 23% and unchanged in 41% of patients. They concluded that mild asthma is generally unchanged in pregnancy and severe asthma usually gets worse.

Dombrowki et al (1986) retrospectively compared the pregnancy outcome in 153 asthmatics pregnancies versus 116 controls. They found an increase in smoking and chronic hypertension in asthmatics. There was no difference in gestational age at delivery, birth weight or preeclampsia. Asthmatics taking theophylline had a reduced incidence of preeclampsia (1 of 85), compared to other asthmatics (6 of 68).

Fitzsimmons et al (1986) reviewed the pregnancy outcome of 51 asthmatics requiring prednisone and/or aerosolized beclomethasone versus the control group. They found an increase in prematurity and LBW but no difference in perinatal mortality, malformations or maternal deaths in asthmatics as compared to controls.

Stenius – Aarniala et al (1988) studied the outcome of 181 asthmatics during 198 pregnancies versus 198 non- asthmatic controls. They found that 40% needed the same asthma medication during pregnancy, 18% needed less and 42% needed more. Preeclampsia and caesarian section were increased in the asthmatics group, but there was no difference in gestational age at delivery, birth weight, Apgar score or perinatal mortality. They concluded that severe asthma or steroid treatment increase the incidence of preeclampsia,

and that careful supervision should prevent most serious complications of asthma.

Schatz et al (1988) published a series of 259 asthmatics versus 295 controls from the Kaiser – Permanente Hospital in San Diego. The only difference they found in asthmatics was an increased incidence of chronic hypertension.

Lao and Huengsburg (1990) retrospectively compared the outcome of pregnancy in 87 consecutive asthmatic patients to 87 controls. Asthmatics had a higher incidence of LBW babies (< 2500 gm), which was mainly found in that not requiring bronchodilator therapy. The caesarian section rate was also higher in asthmatics probably related to a higher rate of induction of labor. Gestational age at delivery and perinatal complications were not increased in asthmatics.

Again in 1990 Schatz conducted a study on the Kaiser – Permanente Asthma and Pregnancy group to examine the relationship between intrauterine growth and serial gestation spirometry in 352 pregnancy asthmatics women who were prospectively treated and observed during pregnancy. A small ($r = 0.11$) but significant ($P < 0.04$) direct correlation was demonstrated between infants' birth weight and individual mean percent predicted FEV_1 during pregnancy. In additional, lower maternal mean FEV_1 during pregnancy was associated with increased incidences of birth weight in the lower quartile of the infants population ($P = 0.002$) and ponderal indices < 2.2 (suggested of asymmetric intrauterine growth retardation) ($P < 0.05$) but not with increased incidences of preterm (< 38 weeks) or LBW (< 2,500 gm) infants. Although lower mean birth weight occurred in infants of smoking compared with non-smoking asthmatics mothers ($P < 0.02$), the relationship of lower FEV_1 to birth weight in the lower quartile of population ($r = 3.0$, $P = 0.002$) and ponderal

indices < 2.2 (r = 2.8, P < 0.05) were shown by multivariate analysis to be above and beyond the influence of smoking and also independent of the effects of age, parity, acute asthmatics episodes, and asthma medications. These data support the hypothesis that lower maternal gestational FEV_1 during pregnancy is related to intrauterine growth retardation and suggest that the goals of gestational asthma therapy should include optimization of pulmonary function in additional to achievement of symptomatic control.

In 1992 Mabie et al, compared the pregnancy outcome of 142 asthmatics during 200 pregnancies to a control population of 22,651 without asthma. They found no difference in prematurity, intrauterine growth retardation or perinatal mortality. Eighty five percent of the patients had mild, 10% moderate and 5% severe asthma. Twelve percent of asthmatics had an exacerbation in labor, which correlates with the 10% incidence reported in the literature. An unexpected and previously unreported finding was an 18 fold higher relative risk of postpartum exacerbation of asthma in patients delivered by caesarian section then in those who delivered vaginally.

Perlow et al, in 1992, performed a retrospective, case controlled study of 183 (0.6%) asthmatics among 30,940 births while control group consisted of 130 women. Eighty-one asthmatics receiving chronic medications constituted the study group. Thirty-one of these were steroid dependent and had an increased incidence of diabetes mellitus, preterm labor, preterm rupture of the membranes and preterm delivery where caesarian section, birth weight < 1000 gm, intrauterine growth retardation, and anomalies were not increased. Fifty-one non- steroid dependent asthmatic patients had an increased incidence of preterm labor, preterm rupture of membranes, preterm delivery and caesarian section. They concluded that perinatal outcome is compromised in chronic medication dependent asthmatics.

Park and Chazotte (1994) retrospectively reviewed the perinatal outcome in women with asthma. They defined the severity of asthma in 210 cases being 40 (19%) very mild, 111 (60%) mild, 45 (24%) moderate and 14 (7%) severe on the basis of medication required. They found no difference in the incidence of preclampsia, preterm birth, birth weight, % SGA, low Apgar scores or neonatal intensive care unit admission by severity or control of asthma. Of 58 (28%) with uncontrolled asthma exacerbation occurred in 7 (12%) in first trimester, 27 (47%) in second trimester, 23 (40%) in third trimester and 4 (7%) in labour. They concluded that with modern management of asthma, they could not confirm an increased incidence of preterm birth, SGA, preeclampsia or poor perinatal outcome with increasing severity or poor control of asthma.

Kelly et al, 1995, carried out a study to analyze the impact of maternal asthma on the risk of preterm delivery and the contribution of preterm delivery to the development of childhood asthma. Two cross sectional community studies of 1872 children (5 – 11 yrs) in 1991 and 3746 children in 1993 were performed. In their study, they found that the asthmatics mothers were more likely to have a preterm delivery then non-asthmatics mothers (r = 1.49; 95% CI 1.10 to 2.02). And smoking was found to be a separate risk for preterm delivery (r = 1.35; 95% CI 1.10 to 1.65). They concluded that the maternal smoking during pregnancy and maternal asthma are independent risk factors associated with preterm delivery. Asthma in mother predisposes to preterm delivery but not growth retardation.

In 1995, Schatz et al published a prospective case control study of 486 actively managed asthmatics compared to 486 controls and were matched for age, smoking status, parity and year of delivery. The study was performed for twelve years. All subjects had complete pulmonary function testing and received obstetric care by

obstetrician. Chronic hypertension was significantly more common in asthmatics than in controls (3.7% vs 1%) while no significant difference in preeclampsia, perinatal mortality, preterm birth, LBW infants, intrauterine growth retardation or congenital malformation was observed. No medication was required in 12.3% while 24.5% inhaled bronchodilators, 38.3 % were on theophylline or cromolyn without corticosteroids, 8 % inhaled corticosteroids and 16.9 % took oral steroids. Acute episodes of asthma occurred in 11% of subjects. They concluded that the overall perinatal prognosis for women with well-managed asthma during pregnancy is comparable to that for the non-asthmatic population. Possible reasons for the difference in adverse perinatal outcome reported were - more effective management of asthma, better study design accounting for smoking and African – American race, exclusion of patients with multiple gestations, improved perinatal management of high risk pregnancies, type II errors and a cohort with less severe asthma than in other studies. Influence of asthma in pregnancy on labor and the new born was studied by Minerbi – Codish et al, (1998) to examine the relation of asthma in pregnancy, its severity and its treatment to the labor process, maternal and fetal parameters. Hundred and one consecutive asthmatic women with singleton pregnancy were studied. A group of 77 non-asthmatic women, matched for age and ethnic origin, gave birth to single babies during the same period served as controls. A larger percentage of asthmatic women suffered from respiratory and urinary tract infections than in the control group ($P < 0.001$). Severe asthma was associated with a higher rate of infections than milder asthma ($P = 0.01$). The incidence of smoking was higher among asthmatic women than among controls ($P=0.037$). No association was found between socioeconomic status and smoking/infections, maternal asthma and use of corticosteroids and other factors as hypertension, diabetes, LBW (< 2500 gm), preterm delivery (< 37 weeks), adequacy of weight to gestational age and Apgar scores. Three

infants with congenital heart defects were born to asthmatic mothers. When the presentation of the fetus was not cephalic all the asthmatic mothers were delivered by caesarian section, versus only 60% in the control group (P = 0.07). They concluded that the labor and neonatal outcome in pregnant asthmatic women treated medically was good.

Summarizing the studies of asthma in pregnancy it has been shown that an increase in preterm labor, LBW, perinatal mortality, hyperemesis, preeclampsia, chronic hypertension and complicated labor occur. However, each of the studies has found a different pattern or combination of adverse outcomes. Differences in study populations regarding important patient characteristics such as race, smoking, asthma severity, degree of asthma control and medication use are likely to account for the observed variability among studies.

Other forms of obstructive diseases

There is only scant literature available regarding the interactions between pregnancy and forms of obstructive pulmonary disease other than asthma. Because emphysema in its usual form is not a disease of women in the child bearing age, there is no information about emphysema and pregnancy except for a case report in a patient with α1- antitrypsin deficiency (Giesler C. F. et al, 1977). This patient, who had the Pizz genotype and significant obstructive disease, delivered a normal infant after an uneventful labor at 38th week.

In a discussion of bronchiectasis and pregnancy, Teirstein (1965) was unable to substantiate previous statements concerning a deleterious effect of pregnancy on the course of the disease. He reported a total of 44 pregnancies in 21 patients; in only one instance was there difficulty during pregnancy or the postpartum period that could be attributed to bronchiectasis. Based on his series of patients,

he stated that uncomplicated bronchiectasis should not be considered an indication for therapeutic abortion. In another study, by Howie and Milne (1978), little changes were observed in pulmonary function, degree of dyspnea, or volume of sputum production in each of 3 pregnant women with bronchiectasis, and no evidence of intrauterine growth retardation was observed. However, Templeton (1977) has reported a woman with bronchiectasis and a prior lobectomy whose pregnancies were complicated by LBW and an intrauterine fetal death at 38th week.

The most severe obstructive functional abnormalities observed are in women with cystic fibrosis who become pregnant. However, cystic fibrosis is not an ideal model for examining the interaction between obstructive disease and pregnancy, because the functional abnormalities usually consist of a mixed picture of obstructive and restrictive disease.

Since the initial description in 1960 of pregnancy in a woman with cystic fibrosis (Siegel and Siegel, 1960), more than 10 cases have been reported (Grand et al, 1966; Novy et al, 1967; Plotz et al, 1967; Larson, 1972). Approximately half of these patients were believed to have serious and progressive pulmonary decompensation during and after pregnancy and the other half did not experience any significant adverse effects from their pregnancy (Grand et al, 1966). However, given the downhill natural course of the disease, it is difficult to assess the role of pregnancy in producing any patients' deterioration. Of 13 infants reported by Grand et al (1966), 11 were believed to be normal at birth, with 3 of these being premature. As expected by the autosomal recessive transmission of this disease, none of the infants had cystic fibrosis, although they are presumably carriers of the abnormal gene.

The role of various factors in predicting outcome of pregnancy in patients with cystic fibrosis is not entirely clear it appears that the degree of preceding lung involvement is an important determinant of patients' course, with milder disease being associated with better prognosis during pregnancy (Grand et al, 1966). A VC of one liter has been suggested as a minimal functional requirement necessary to maintain a successful pregnancy (Novy et al, 1967). However, insufficient numbers of patients with disease of this severity are available to the validity of this hypothesis. The presence of pulmonary hypertension with cor pulmonale appears to be a poor prognostic feature, and it may be that any adverse effects of hypoxemia are at least partially mediated by worsening cor pulmonale.

Restrictive lung diseases

Sarcoidosis is a multisystem disease of unknown etiology that commonly affects young adults. It is manifested by non-caseating granulomatous infiltration that occurs in a perivascular pattern. Dyspnea with or without exertion, non-productive cough and nonspecific chest pain are the most common complaints. Pulmonary function tests may reveal normal function, a restrictive pattern, or an obstructive defect, the latter inferring endobronchial sarcoid involvement (Talmadge, 1992).

The overall effects of pregnancy on the course of sarcoidosis have been studied by a number of investigations, and the results in the available series have generally been consistent. Mayock et al (1957) describes that there appeared to be a frequent ameliorating effect of pregnancy on the 10 sarcoidosis patients in 16 pregnancies. In 8 of these 10 patients, improvement in at least some of the manifestations of sarcoidosis occurred while in 2 it did not during the antepartum period. However, the abnormal findings returned within

several months of delivery in approximately one half of patients, and some had new manifestations of sarcoidosis not previously noted.

Reisfield (1958) in a study of 17 pregnancies in 10 patients with sarcoidosis, concluded that pregnancy had no consistent effect on the cause of the disease. Reisfield et al (1959) also reported a patient with respiratory insufficiency and 25% of the predicted value as VC. Despite the degree of functional lung disease, the pregnancy was successful, as it was in another patient recently described who also had marked restrictive disease (Grossman, 1977). Subsequent studies (O'Leary, 1962; Fried, 1964; Dines et al, 1967) each suggest that the condition of almost all patients with sarcoidosis either remain unchanged or improve during pregnancy. Only a rare patient seems to get worse during the antepartum period.

Scadding (1967) summarized the overall effect of pregnancy on sarcoidosis by separating patients into categories and noted certain characteristics patterns. In patients whose chest roentgen graphic changes had resolved before patient, a normal chest roentgenogram was noted throughout gestation. In those with a resolving roentgenogram before pregnancy, resolution continued through the prenatal period. Patients with inactive fibrotic residue of disease had stable chest roentgenogram, whereas those with active disease tended to have partial or complete resolution of their roentgen graphic changes during pregnancy. However, most patients in this latter group experienced an exacerbation of their disease within 3 – 6 months after delivery.

One possible explanation for the commonly observed improvement in sarcoidosis is the increased concentration of circulating corticosteroids during pregnancy (Mayock, 1957; Scadding, 1967; Sulavik, 1975). As mentioned earlier in this review, the total concentration as well as the concentration of free circulating

corticosteroids is increased during the course of pregnancy (O'Connell et al, 1969; Rosenthal et al, 1969; Brien, 1976). Even though one would expect increased concentration of steroids to ameliorate manifestations of the disease during pregnancy, there is no definite proof that this is the correct explanation for the changes observed. Because sarcoidosis in many patients improves spontaneously, it is likely that improvement in some patients is coincident with, but not due to, their pregnancy.

There is no current evidence that sarcoidosis has any adverse effects on either fertility or the course of pregnancy (Scadding, 1967; Sulavik, 1975). Although some series have observed a few patients with either miscarriages or congenital abnormalities (Mayock, 1957; Reisfield, 1958), the incidence of such problem with pregnancy or the fetus does not appear to be greater then that found in mothers without sarcoidosis (O'Leary, 1962; Scadding, 1967). It is also of interest that placental tissue examined histologically has shown no evidence of granulomatous disease (Reisfield, 1958; Given et al, 1963).

A study was conducted on nine pregnant women with interstitial and restrictive lung disease who were prospectively managed and delivered (Boggess et al, 1995). Three patients had severe disease, characterized by VC ≤ 1.5 L (50% predicted) or diffusing capacity ≤ 50% predicted. Five patients had exercise – induced oxygen desaturation, four required supplemental oxygen and five patients required corticosteroids. One patient had an adverse outcome that she delivered at 31st week and required mechanical ventilation for 72 hours. All other patients had delivered at/beyond 36 wks with no adverse intrapartum or postpartum complications. All babies were at or above 30th percentile for growth. Thus, concluding that the restrictive lung disease is tolerated in pregnancy. Exercise

intolerance is common and patients may require early oxygen supplementation. Adequate fetal growth can be achieved.

From the time of Hippocrates until the middle of the nineteenth century, it was believed that pregnancy had an overall beneficial effect on tuberculosis (Sulavik, 1975). A diametrically opposite view was taken from 1850 until the 1940's and therapeutic abortion was frequently recommended to avert the presumed deleterious effect of pregnancy (Flanagan et al, 1959). Hedvall (1955) in a series of 276 women whose tuberculosis remained stable throughout the course of pregnancy found that 13.4% exhibited deterioration during the first postpartum year. He came to the conclusion that pregnancy and labor seldom have a harmful effect on women with tuberculosis.

Gierke (1956), in a study of 930 women with pulmonary tuberculosis, found progression of disease in 90 cases within the first 6 weeks after delivery, despite the fact that antenatal course was favorable in 70 of these 90 patients. Several theories have been proposed to explain this phenomenon, including rapid hormonal changes, postpartum descent of the diaphragm, the nutritional strain of lactation, and insufficient sleep from the time demands of a newborn infant (Selikoff et al, 1965).

Several studies have however confirmed excellent prognosis for pregnant women whose tuberculosis is treated. de March (1975) reviewed the course of 149 pregnancies in 100 women with tuberculosis, and could not document any adverse effect of pregnancy, birth, the postpartum period or lactation. There was no risk of relapse when the pulmonary disease was adequately treated, even in patients with active disease or those with persistence of post chemotherapy cavity. Most large series investigating the effect of tuberculosis on the course of pregnancy and on the newborn have concluded that pregnancy is not altered by the patients' tuberculosis (Selikoff et al,

1965 and Schaefer et al, 1975). Bjerkedal et al (1975), found a slightly increased occurrence of pregnancy complications (toxemia or vaginal hemorrhage) and difficult labor in women with tuberculosis. The most striking difference was in the risk of miscarriage, which was approximately 9-10 fold higher (20.01/1000 compared to 2.3/1000 persons) among patients with tuberculosis then control subjects. No differences were found in the number of multiple births, congenital malformations, mean gestation period, percentage of preterm infants, percentage of infants of LBW or mean birth weight. While interpreting this study, however, it is difficult to determine which factors might have contributed to the greater frequencies of miscarriage and pregnancy complications noted.

Kyphoscoliosis is the most common abnormality of the thoracic cage affecting pregnancy. Scoliosis is much more common in women then men. Usually, it does not significantly alter pulmonary function. The lungs are compressed by the distorted rib cage, resulting in atelectosis. In severe cases, chronic hypoxemia leads to cor pulmonale, increased perinatal and maternal morbidity has also been reported by Cohen et al, 1980 and Kopenhager, 1977. A more recent study by Betz et al, (1987) of 175 patients with mild to moderate scoliosis found no increase in maternal or fetal morbidity or mortality rates and a caesarian section rate lower than national average. de Sweit, (1979) reported successful deliveries, even with the VC as low as one liter.

Myasthenia Gravis Is the prototype of respiratory muscle failure and is caused by a reduction in postjunctional acetyl choline receptors secondary to circulating autoantibody. Plauch, 1983 have reported that two thirds of gravid myasthenic women either remain same or improve during pregnancy, whereas one third will become worse. The maternal mortality rate is reported at about 3 percent.

Important environmental factors

Smoking is the most significant avoidable maternal factor adversely affecting fetal growth causing intrauterine growth retardation, increase in the perinatal mortality rate and the incidence of pregnancy complications and the reduction in duration of gestation. Smoking is associated with obstructive pattern of changes in pulmonary functions.

The degree of fetal growth retardation increases with the number of cigarette smoked each day by the mother. The birth weight of infants whose mothers smoked 20 cigarettes per day is reduced by 200 gm. The birth length is also reduced. Infants of light cigarette smokers have a slight reduction in birth weight (Gluckmen and Liggins, 1954)

Davis and Gray (1976) tried to examine an association of cigarette smoking in the latter half of pregnancy with maternal weight gain and fetal growth. They studied 1159 mother – infant pairs and found nonsmokers gained significantly more weight than heavy smokers (> 15 cigarettes per day) while light to moderate smokers (1–14 cigarettes per day) were intermediate. Birth weight, length and head circumference of the infants showed a similar gradient with infants born to nonsmokers being heavier, longer and with larger head circumference than those born to heavy smokers. Covariance analysis showed that a large part of the effect of maternal smoking is mediated through maternal weight gain with only a very small additional direct effect on the fetus. This suggests that increasing weight gain by smoking mothers might prevent some harmful effects of smoking on fetal growth.

Although the weight gain of smoking mothers during pregnancy is reduced, several studies have clearly shown that IUGR is not

secondary to maternal malnutrition (Miller and Hassanein, 1964; Persson et al, 1978; Pirani, 1978).

Maternal smoking has some specific effect on the placenta of exposed pregnancies. It appears to be associated with a thinner placenta but spread over the wider area than normal, and with effect on the blood vessels at both the cellular and macroscopic level (Naeye, 1978; Christianson, 1979) that probably increases the risk of antepartum hemorrhage. The effect on birth weight seems to be mediated partially through placental vascular anomalies and acute vasoconstriction during smoking, and partially through a direct effect of the products of cigarette smoke on the fetus. The cigarette smoking habit and drinking are associated with each other and is seen to be associated with low social class, young maternal age and high parity (Butler and Alberman, 1969).

Wouters et al, (1987) reported that the carboxyhemoglobin (HbCO) concentration in fetal venous cord blood did not account for fetal growth retardation in pregnant women who smoked. On examining the fetal outcome in 77 uneventful pregnancies and relating it to venous cord HbCO levels. Thirty women were smokers and 47 were nonsmokers. Birth weight and birth weight centile were found to be substantially reduced in children of mothers who smoked and HbCO levels were found to be significantly elevated in venous cord blood of children of smoking compared with nonsmokers.

An analyses of negative effect of maternal smoking upon fetal growth, taking fetal sex into consideration, was carried out by Wertelecki et al, (1987) where they tested a then proposed criteria of fetal tobacco syndrome (FTS) on a sample of 925 primiparous black women (including 204 smokers) and their neonates. The proposed criteria that they followed include proportional growth retardation (ponderal index greater than 2.26, birth weight <2500 gm) in term

neonates. Only 19 (2%) neonates in their study fulfilled the FTS morphometric criteria, and of these only 8 had smoking mothers. Nonetheless, the negative effect of maternal smoking on fetal growth (birth weight and length) was clearly evident from their data ($P < 0.01$). When a separate analysis by fetal sex was made, it revealed that the negative effect of maternal smoking upon fetal growth was more pronounced among males than females. And so they concluded that fetal sex should be taken into account in studies of maternal smoking effects.

Usandizaga et al, (1987) examined the relationship of tobacco and pregnancy on weight of the newborn infants and weight gain of mother. They studied 865 patients with the aim to prove the hypothesis that smoking might indirectly affect maternal nutrition that influence the weight of the newborn. The weight of the newborns was found to be significantly lower in 276 of the 865 women who smoked. On selection of both groups of smoking and nonsmoking patients appropriate to the weight increase during pregnancy above and below the average value, they stated that those fetuses had an IUGR whose mothers smoked and had a lower weight gain then that average value of all pregnant women.

A population based case control study by Voigt et al (1996) was conducted to examine the relationship between maternal smoking and the occurrence of abruption placentae and to assess the joint relationship of smoking and SGA status with abruption. Cases (n = 1089) were compared with randomly selected births (n = 2323). The occurrence of placental abruption was associated with both smoking (relative risk 1.6; 95% CI 1.3 – 1.8) and SGA status (relative risk 2.6; 95% CI 2.0 – 3.3). The association with SGA status was identical for smokers and nonsmokers. Thus the increase of SGA infants in women whose pregnancies were complicated by abruption was not explained

by maternal smoking, and in some cases it was thought to result from placental dysfunction induced by the process of placental separation.

The relationship between smoking and maternal age and their combined effects on birth weight, IUGR and preterm delivery were studied in 1990 by Shi Wu Wen et al. Smoking was found to lower birth weight by decreasing fetal growth and by lowering gestational age at delivery. However, the effect of smoking on both fetal growth and gestational age is significantly greater as maternal age advances. On a multiple logistic regression model adjusting for rate, parity, marital status, maternal weight, weight gain and alcohol use, they found smoking to be associated with fivefold increased risk of growth retardation in women older than 35 but less than a twofold increased risk in women younger than 17 years. Smoking reduced birth weight by 134 gm in young women but 301 gm in women older than 35 years. Smoking in older women also was associated with more instances of preterm delivery and a lower mean gestational age when compared to women of 25 or younger.

This study does not provide information as to the mechanism of relationship between smoking and increasing age, IUGR and preterm delivery. The effect of smoking on birth weight appears in part to be mediated through vascular constriction and decreased uteroplacental blood flow. They explained it on the basis that older smokers who presumably have been smoking (for a longer duration or higher cigarette dosing of cigarette constituents) are more likely either to have chronic vascular disease or are more sensitive to the vasoconstrictive effects. The increased risk of vascular disease in non-pregnant women of similar ages exposed to cigarette smoke and pregnancy hormones (oral contraceptive) may have a similar explanation.

Das et al. (1991) et al, investigated the effect of cigarette smoking on maternal airway function during pregnancy, in a cross sectional study of 97 smokers and 175 nonsmokers at different gestational ages. The groups were comparable in age, height and weight. All subjects recruited were healthy. FVC, FEV_1, their ratio, the forced expiratory flow rates between 0.2 and 1.2 L, 25% and 75% and 75% and 85% and instantaneous flows at lung volumes of 25%, 50% and 75% were measured. All spirometric tests were unaffected by gestational age. However, all parameters of spirometry were significantly less in smokers then in nonsmokers when cumulative data during pregnancy were compared. FVC, FEV_1 and their ratio were minimally reduced (4%, $P < 0.05$; 8%, $P < 0.001$ and 4%, $P < 0.001$ respectively) in smokers as compared with nonsmokers. Larger reductions were noted in forced expiratory flow rates between 0.2 and 1.2 L (14%, $P < 0.001$) and between 25% and 75% (16%, $P < 0.001$) and in $Vmax_{75\%}$ (11%, $P < 0.001$) and 50% (13%, $P < 0.001$). Maximum reduction forced expiratory flow rates between 75% and 85% (26%, $P < 0.001$) and in $Vmax_{25\%}$ (23%, $P < 0.001$) suggests marked increase in small airway resistance and early small airway disease in smokers. The progression of small airway disease was related to the level of cigarette exposure. The results of their study demonstrate that the bronchodilatory effect expected in pregnancy is not sufficient to overcome the deleterious effects of cigarette smoking.

Jauniax and Burton (1992) carried out morphometric and ultrastructural investigation on the placental tissue of 20 heavy smokers and 20 smokers. All pregnancies were artificially terminated at 9–14 weeks gestation. When compared with values in nonsmokers, smokers had significantly increased arithmetic ($P < 0.005$) and harmonic mean thicknesses ($P < 0.05$) of the villous membrane and harmonic mean thickness ($P < 0.05$ for both) of the trophoblastic layer. No significant difference was found between the groups for the

mean number of capillary profiles per villous profile or for the mean volume fractions of the villi occupied by the trophoblast, the villous stromas or the fetal capillary lumina. At the ultrastructural level, the mean number of areas presenting with syncytiotrophoblastic necrosis was significantly ($P < 0.001$) higher in the smoking than in the nonsmoking group, whereas no difference was observed for the mean number of areas demonstrating trophoblastic basal membrane thickening. These results suggest that smoking during the first months of pregnancy induces morphologic changes, which according to the researcher may explain biologic disturbances observed during gestation and also later in pregnancy.

Aronson et al, (1993) studied the effect of maternal cigarette smoking on LBW and preterm birth. 22.5% of mothers reported smoking cigarettes during pregnancy. Mothers who smoked cigarette were twice as likely to bear LBW infants' as were nonsmokers. Cigarette smoking is one of the most preventable causes of LBW and women can be made to quit smoking during pregnancy through physician encouragement that can reduce the risk of/for LBW and have long-term benefits for her and family.

Brown et al (1995) studied the effect of prenatal maternal cigarette smoking on passive expiratory mechanics in 53 healthy infants tested early in infancy. Maternal smoking was measured by questionnaire reports of the number of cigarettes smoked per day and urine cotinine concentration (corrected for creatinine) at each visit. Respiratory system mechanics were assessed by the single breath occlusion–passive–flow–volume maneuver. In ten infants born to smoking mothers the time constant of the respiratory system was 23% reduced (0.34 vs 0.44 sec; 95% CI - 45% + 1%; $P = 0.06$). This was related to an estimated 13% decreased respiratory system compliance (4.86 vs 5.62 ml/cm H_2O; $P = 0.18$) and 10% reduction in respiratory

system resistance (P=0.56). Functional residual capacity as measured by helium dilution, was also decreased by 13% (P=0.06) in smoke exposed infants. Forced expiratory flow rates at FRC obtained by thoracoabdominal compression was reduced by 28% in infants of smoking mothers (P=0.04) as reported previously in a larger sample from this population. This study was limited by small numbers of infants exposed to smoking during pregnancy and by ethnic imbalance among the smoke exposed and unexposed group.

Soothill et al, (1996) studied the association of maternal smoking to fetal carboxyhemoglobin and blood gas levels. Eighty-one pregnant women, of these 58 were nonsmokers and 23 were smokers. Fetal blood sample by cordocentesis was taken to obtain the fetal blood gas, acid base status and maternal haemoximetry. They didn't find significant correlation between fetal HbCO and gestational age in nonsmokers and smokers. The HbCO level in the fetuses of smokers was found to be more than double that of nonsmokers.

Kalinka and Hanke (1996) studied the risk of IUGR and preterm delivery related to the amount of cigarettes smoked per day in the group of 551 females. In subjects smoking more than 20 cigarettes, the risk of IUGR and preterm delivery was five times as high as in the non-smoking females. The average weight of the newborn was found to be 510 gm lower in the group of the most-heavy smokers as compared with the non-smoking subjects. The study has not provided any clear evidence of pre-pregnancy smoking and the passive smoking as the risk factors for the pathologies under study.

Kendrick and Meritt (1996) studied the association of health hazards, ranging from lung cancer to low infants birth weight with cigarette smoking in 23.1 % women and 14.6% pregnant women. They summarized the current data on smoking prevalence, reviewed quitting techniques, covered topics of particular interest to physicians

caring for women, and suggests ways in which physicians may become more active in preventing smoking among teens.

Kirsten et al, (1996) evaluated the association between smoking during pregnancy and preterm birth. They collected back questionnaires, about self-smoking habits of 4111 nulliparous women with singleton pregnancy, at their 16 weeks of gestation. They found amongst overall rate of preterm delivery of 4.3%, smokers had a 40% higher risk of preterm birth compared with nonsmokers. A dose response relationship was found between smoking and risk of preterm birth. Adjustment for women's height, pre pregnancy weight, and age of mothers, marital status, education, occupational status, and alcoholic intake did not change the results. Thereby, concluding smoking increases the risk of preterm birth.

Cnattingius et al, (1997) studied the effect of smoking in preeclamptic pregnancies of 317652 nulliparous women aged 15 to 34 years. They found that the maternal smoking was associated with significantly reduced risks of mild and severe preeclampsia with relative risks of 0.6 and 0.5 respectively. In pregnancies with severe preeclampsia smoking at least 10 cigarettes per day was associated with increased rates of perinatal mortality (24-36/1000), abruption placentae (31-67/1000) and being SGA (28%-68%) whereas the corresponding smoking-related increases in rates in non-hypertensive pregnancies were considerably less. Thus, they concluded that the smokers in whom preeclampsia develops have high risk of perinatal mortality, abruption placentae and SGA infants.

Horta et al, (1997), in a historical cohort study, identified live births (n=5166) and interviewed their mothers to investigate the association between the intensity and duration of cigarette smoking during pregnancy and the frequency of low births and IUGR. Children whose mothers smoked during pregnancy had a birth weight 142 gm

lower (OR =1.59, 95% CI 1.30-1.95) than those of non-smoking mothers. There was no association found between smoking and preterm delivery assessed by the Dubowitz score. In relation to IUGR, smoking was found to be associated with an OR = 2.07 (95% CI 1.69 – 2.53). A direct dose response association was found between the number of cigarettes smoked and the risk of growth retardation. Women whose partner smoked were also found at higher risk of having a child with growth retardation. So they concluded that the effect of maternal smoking on LBW seems to be attributed to IUGR rather than preterm delivery.

To examine the relationship of cigarette consumption and exhaled carbon monoxide levels during pregnancy and to assess the effect of these smoking measures on birth weight, a study was carried out on 392 women by Secker-Walker et al, (1997). Cigarette consumption and exhaled carbon monoxide levels were recorded at the first prenatal visit and the 36 wk visit from women who smoked early in pregnancy. Analysis of variance was used to compare birth weights for differing levels of cigarette consumption and exhaled carbon monoxide. With correlation and regression analysis they found that cigarette consumption and exhaled carbon monoxide levels at both visits were associated significantly with birth weight. After the first prenatal visit, a reduction in cigarette consumption of at least nine cigarettes per day or in exhaled carbon monoxide of 8 parts per million (ppm) was associated with gain in birth weight of 100 gm or more. The proportion of LBW infants increased significantly with increasing levels of cigarette consumption and with increasing concentration of exhaled carbon monoxide. Consequently, they concluded that substantial reductions in cigarette consumption or in exhaled carbon monoxide levels after the first prenatal visit are needed to achieve gain in birth weight. Not smoking or having an exhaled

carbon monoxide levels less than 5 ppm minimizes the likelihood of having a LBW infant.

All these studies relate smoking during pregnancy with LBW and perinatal mortality, along with certain studies indicating that these risks are modifiable. Only few women who smoke stop completely while pregnant and far fewer maintain non-smoking postpartum, developing effective strategies to promote and non-smoking can significantly affect the health of mothers and child. This strategy encouraged Peterson et al, (1992) to investigate the impact of a low-cost, pregnancy specific self-help smoking cessation program on patient smoking behavior both prepartum and postpartum. The population consisted of 274 English speaking women enrolled in a large health maintenance organization, reported smoking at the time of the baseline survey or had quit within the previous three months. A control group receiving a standard obstetric care was compared with two experimental groups, one receiving the self-help material and standard care and the other receiving the material plus brief regular interaction from clinician and counseling about smoking Smoking data were observed from two additional self reported surveys conducted at 6 months gestation and approximately 8 weeks postpartum. Self reported smoking behavior was verified using a urine cotinine test, which revealed one significant difference between the groups. Among baseline smokers, neither intervention yielded significantly higher six-month non-smoking rates compared with controls, both interventions significantly increased the proportion of women who were not smoking postpartum. Among those who had quit smoking at baseline, only the more intensive intervention significantly increased maintenance of non-smoking postpartum. Thus they reported that a brief counseling, a simple charting system and improved access to educational material allowed the program to be

integrated easily into routine prenatal case at a cost of 50–111 per patient.

Further Das et al. (1998) evaluated the effects of smoking cessation before or early in pregnancy on maternal airway function and birth weight. They found all the spirometric measurements in ex smokers similar to those of nonsmokers and were significantly higher than those of current smokers. Spirometric measurements for nonsmokers, currents and ex-smokers were respectively: FEV_1 (3.36 ± 0.39, 3.09 ± 0.45 and 3.35 ± 0.32 L); $FEF_{25\%-75\%}$ (3.85 ± 0.69, 3.21 ± 0.76 and 3.86 ± 0.66 L/sec); $FEF_{75\%-85\%}$ (1.39 ± 0.35, 1.03 ± 0.35 and 1.41 ± 0.39 L/sec); $Vmax_{50\%}$ (4.35 ± 0.82, 3.76 ± 0.89 and 1.36 ± 0.65 L/sec) and $Vmax_{25\%}$ (1.91 ± 0.47, 1.47 ± 0.49 and 1.92 ± 0.46 L/sec). Mean gestational age at delivery was similar among the three groups (277 ± 11, 274 ± 12 and 274 ± 11 days for nonsmokers, current smokers and ex-smokers respectively). The mean birth weight of babies born to ex-smokers (3405 ± 511 gm) was similar to that of babies born to nonsmokers (3469 ± 461 gm), but was significantly greater than that of babies born to smoking pregnant women (3189 ± 485 gm, $P < 0.001$). Thus concluding that smoking cessation either before or at an early stage of pregnancy is associated with early, reversible increment of maternal airway function and mean birth weight that are higher than among women who continue smoking.

Attention has recently (Cole, 1986) been focused on the effects on health of passively inhaled smoke where passive smoking or side stream smoking or second hand smoking appears to be hazardous in its own way. Pedrira et al, (1985) studied the association of passive smoking and childhood respiratory illness where they found a direct relation.

Martin and Brackens (1986) investigated association of LBW with passive smoke exposure in pregnancy in a prospective study of

3891 antenatal patients. One fourth (23.6%) had not smoked cigarette during pregnancy but had been exposed to side steam smoke for at least two hours per day. Among the nonsmokers, passive smoke exposure was significantly related to delivering a LBW newborn. This relation only occurred in term ≥ 37 wks deliveries. Compared with unexposed women, the relative risk of LBW after adjustment for confounding factors was 2.17 (95% CI = 1.05-4.50). Those exposed to passive smoke delivered infants 24 gm lighter on average. There was no additive effect of passive smoking on smokers themselves. Repeating the analysis on all women with term deliveries, therefore, resulted in a slightly diminished risk of LBW due to passive smoking of 1.52 (95% CI = 0.90-2.56). The risk of LBW at term due to direct cigarette smoking was 3.54 (95% CI = 1.62-7.71). Gestational age was found unrelated to passive smoking, which appears to exert its effect primarily through growth retardation in term newborn.

Rubin et al, (1986) studied the effect of passive smoking on birth weight. 500 consecutive Dutch women who had full term babies were interview on the third and fourth day postpartum and asked about smoking in all household members. Exposure to smoking by the mother was found to reduce birth weight, and indirect or passive exposure to smoking father had nearly as large (66%) an effect. In average, birth weight was reduced by 120 gm per pack of cigarettes or cigar/pipe equivalent smoked per day by the father. This relation remained statistically significant after controlling for mother's age, parity, alcohol consumption and tobacco consumption during pregnancy, illness during pregnancy and social class and sex of the baby. The effect of passive smoking was greatest in the lower social classes.

Mathai et al, (1992) concluded a cohort study to determine the effect of passive smoking on birth weight. This group comprised of

cohort of 994 singleton live births occurring in women who had received antenatal and intrapartum care. All the women were themselves nonsmokers; 520 (52%) were passive smoking while the rest were not exposed to tobacco smoke. Infants born to passive smoking were on the average 55 gm lighter than those born to nonsmokers. Passive smoking was found to be associated with a decrease in birth weight of 63 gm (95% CI, 12-114 gm) despite of adjusting other variables known to affect birth weight.

Jedrochowski and Flak (1996) studied effects of active and passive smoking during pregnancy on the birth weight in the sample of school children. Data on main stream tobacco smoke (MSTS) and side stream tobacco smoke (SSTS) and the birth weight of children were collected by standardized interview with mothers. As expected exposure to MSTS was the single strongest factor related to the reduced birth weight. The effect was statistically significant in those respondents who confirmed the cigarette smoking in the whole prenatal period. On the basis of multiple regression model considering active and passive smoking during pregnancy, parity and gestational age, it was estimated that MSTS reduces the birth weight on an average of about 210 gm and in heavy smokers 450 gm. The effect of SSTS was to reduce birth weight by about 60 gm after accounting for the other confounders. Effects of active and passive smoking both were statistically significant. When the self reported smoking status was correlated with plasma cotinine levels in women at delivery, a substantial misclassification error has been disclosed and it resulted mainly from sensitivity (47%) of the self-reported data on smoking status. This exposure bias may lead to significant underestimation of correlation between weight < 2500 gm and tobacco smoking of mothers in pregnancy. Odds ratio (8 .0) correlated to exposure misclassification was found to be much higher than the crude odds ratio (2.9).

Ahluwalia et al, (1997) examined the association between self-reported environmental tobacco smoke (ETS) exposure (exposure to the cigarette smoke of a member) during pregnancy on birth weight, prematurity and SGA infants and to determine whether these associations differ by maternal age. Multiple logistic and linear regression analysis was used to analyze the association between ETS and birth outcomes. The mean adjusted birth among infants of nonsmoking mothers age 30 years or more was 90 gm less than infants exposed to ETS than among non-exposed. No significant association was found among infants of younger nonsmoking mothers. Similarly the risks for LBW (adjusted OR = 2.42, 95% CI 1.51-3.87) and preterm delivery (adjusted OR = 1.88, 95% CI 1.22-2.88) were elevated among older nonsmokers while LBW (adjusted OR = 0.97, 95% CI 0.76 – 1.23) and preterm delivery (adjusted OR = 0.92, 95% CI 0.76 – 1.15) were not elevated among younger nonsmokers exposed to ETS. These findings indicate that the association between ETS experiment and adverse pregnancy outcome appears to be modified by maternal age

Dejin-Karlson et al, (1998) tested the hypothesis that women who deliver SGA infants are more often exposed to passive smoke at home or at work. The study was carried out among women whose pregnancies resulted in a singleton live births (n=826), 6.7% of infants were classified as SGA. The results of this study showed that passive smoking in early gestation was shown to double woman's risk of delivering a SGA infant, independent of potential confounding factors such as age, height, weight, nationality, educational level and the mother's own active smoking (OR = 2.7). A stratified analysis indicated interaction of maternal smoking and passive smoking on relative SGA. They have concluded that considerable reduction in the incidence of SGA is attributed to maternal passive smoking.

Pulse oximetry and hypoxemia

Severe hypoxemia can kill a patient, or leave its victim with devastating neurological handicaps. Arterial hypoxemia is known to occur at any time during anesthesia with astonishing suddenness. Yet, until recently, devices to measure arterial oxygen levels non-invasively and continually during anesthesia have not been available.

In 1947, Comroe and Botello published their classic study of the accuracy with which clinicians assess degrees of cynosis and arterial oxygen desaturation. They disturbingly concluded that "visual impressions of cynosis are unreliable" and clinical experience made no difference in vivo oxygen measurement, anesthesiologists and other clinicians were forced to detect hypoxemia by skin and blood color or by late occurring hemodynamic deterioration. Measurement of the arterial oxygen tension in whole blood was difficult until Clark reported in 1956 the development of a polygraphic oxygen electrode coated with a semipermeable membrane that made these measurements clinically available, subsequently Huch et al, modified the Clark electrode for use on the skin of a neonate. With hyperemia caused by nearly equal to the arterial oxygen tension. In 1972, both Huch and Eberhard found that similar data could be obtained in the neonate with a heated electrode.

Following these developments, monitoring of cutaneous oxygen tension became common in neonatal intensive care units. However, poor correlation with the arterial oxygen tension has diminished enthusiasm for cutaneous oxygen monitoring in older children and adults, its primary value may be to monitor tissue oxygenation.

Pulse oximetry has its origins in the work of Nicolai et al, who in 1931 applied the Beer-Lambert law to the transmission of light through the hand to study the dynamics of tissue oxygenation. He

demonstrated that occlusion of the circulation produced an exponential fall in oxyhemoglobin and rise in deoxyhemoglobin. Kramer reported, in 1935, the continuous recording of oxygen saturation of blood flowing through unopened vessels using a spectrophotometric method. At the same time, Matthes constructed the first device to measure oxygen saturation in vivo by transilluminating the ear.

Interest in aviators' oxygenation during World War II stimulated further development. Squire and later Goldie developed oximeters that set their zero value on tissue that had been compressed to squeeze out the blood, marking the beginning of modern pulse oximeters. Millinkan, in 1942 developed a lightweight, practical aviation ear oxygen meter that he called an oximeter. Based on this work, Wood and Gracie, at the Mayo Clinic in 1949, built an oximeter with improved optics and an inflatable balloon that could make the ear bloodless for a reference setting. This device was manufactured by the Waters Company and was extensively used in research, including evaluation of hypoxia during anesthesia (Downes et al, 1961). More recently, Shaw, reported by Merrick and Hayes, developed a self-calibrating ear oximeter using eight wavelengths of light that was commercially produced in 1976 and has become the standard against which other oximeters are judged.

In 1974, Aoyagi, as reported by Nakajima et al, developed an oximeter that used the variations in volume that occurs with pulsatile arterial flow to obtain a signal representing oxygen saturation. Because of sensitivity to motion and because of its large size, the device was not widely used. Yoshiya et al, in 1980 incorporated plethysmography and oximetry in an instrument that needed no calibration or heat to determine oxygen saturation. Using of plethysmography to identify a volume change resulting from the

arterial pulsation, the device compared the light absorbance in the absence of a pulse – a zero – and in the presence of the arterial pulsation to determine arterial oxygen saturation. With this integration of plethysmography and oximetry and subsequent application of solid-state electronics, the pulse oximeter determines values within 2% those measured in vitro, bringing us close to accurate, practical non-invasive assessment of arterial oxygen saturation. Motion artifact and difficulties with low perfusion states continue to limit performance of currently available devices.

Bowes et al (1989) reviewed the theory, accuracy and clinical applications of pulse oximetry. Pulse oximetry according to them has emerged as a clinical tool in anesthesia and newborn monitoring. Oximeters measure the different absorption spectra of oxygenated and deoxygenated hemoglobin. Electronic measure of oxygenation at the peak of the pulse allow computation and display of oxygen saturated of the arterial blood almost instantly. Correlation coefficient between pulse oximetry and direct blood oxygen saturation measurement ranges from 0.77-0.99 when oxygen saturation is greater than 60%. The method is non-invasive (a clip or tape on a finger), simple to operate and adaptable to various patient population. Pulse oximetry monitors continuously and instantaneously, is responsive to change and is accurate. Factors adversely affecting the accuracy of pulse oximeter output include transducer movement, peripheral vasoconstriction, a non-pulsating vascular bed, hypotension, anemia, bring change in systemic vascular resistance, hypothermia, presence of intravascular dyes and nail polish. Pulse oximetry has been used to monitor oxygen saturation intraoperatively in the adult and neonatal intensive care units and to monitor pregnant patients and their infants at delivery. Once the advantages and limitations of pulse oximetry are recognized, this monitoring technique can play an

important role in the care of patients with cardiovascular and respiratory compromise.

Templeton (1977) studied two pregnancies in a young patient who was found to be hypoxic following a left lobectomy for bronchiectasis in childhood and he found both her pregnancies complicated by IUGR. The patient was found to be hypoxemic and although this was not marked, the absence of any other etiological factor strongly suggested that the hypoxemia was contributing to the IUGR. On the basis of above case study he indicated a necessity for further study of arterial oxygen tension in chronically hypoxemic pregnant patients.

To relate maternal hypoxemia and fetal breathing movements Manning and Platt presented a case report in 1978. The fetal breathing movements (FBM) were observed daily using a real time B-mode ultrasound method in a patient with sickle cell anemia in crisis. Observations were made on two occasions in the presence of maternal hypoxemia $pO_2 \leq 40$ mm Hg, and FBM were noted to be absent. Conversely, when maternal pO_2 was 60 mm Hg or greater, FBM were present 23% – 80% of the time. The FBM were reduced or absent within 90 minutes of maternal Demerol injection. These observations suggest that human fetal response to hypoxemia may be similar to that observed under experimental conditions in the animal fetus.

Cote et al described the incidence, duration and severity of arterial oxygen saturation as detailed by pulse oximetry in infants and children. They also determined the impact of pulse oximeter information on the anesthesia care team function. Their results, consistent with Cohen et al, (1988) clinical experience with pulse oximeter, indicated that the device was a valuable aid to the inspection, palpation and auscultation used by the anesthesiologist seeking the best care for his patient.

Awe et al, (1979) studied arterial oxygenation and alveolar arterial gradients in term pregnancy where in 23 nonsmoking pregnant women (16–34 years) free of any signs or symptoms of pulmonary disease were evaluated by arterial blood gas values, in both sitting and supine posture while closing volume was determined within 6 weeks of delivery and in the immediate postpartum period. Arterial oxygen tension was usually normal while sitting, but modest hypoxemia occurs in about 25% of healthy young women while supine. The calculated alveolar –arterial gradient (A-a) O_2 was greater than 20 mm Hg. This abnormality persisted in the immediate postpartum period. Closing volumes fell significantly after delivery, but also there was no significant relationship between changes in closing volume and the arterial oxygen tension or the (A-a) O_2.

Muller et al (1980) studied the mechanism of hemoglobin desaturation during rapid-eye-movement sleep in normal subjects and in patients with cystic fibrosis, where in they assessed 5 normal subjects (22-30 yrs) and 20 patients with cystic fibrosis (9-29 yrs). The largest decrease in arterial O_2 saturation, as monitored with an ear oximeter during sleep, occurred during rapid eye movement sleep, with a mean ± SEM decrease 2 ± 0.31% in the normal subject and 7.4 ± 1.3% in the patients in both groups. Rapid eye movement sleep was associated with a significant loss of intercostals and diaphragmatic tonic muscle activity ($P < 0.01$), as monitored with surface electrodes, and a decrease in the baseline position of the rib cage and abdomen, as recorded by magnetometer ($P < 0.01$). This suggests a decrease in FRC, which was accompanied by consistently lower arterial oxygen saturation during rapid eye movement sleep. Short periods of < 20 sec of inhibition of phasic respiratory muscle activity during rapid eye movement sleep were followed by further decrease in arterial oxygen saturation. They concluded that the desaturation during rapid eye movement sleep in all subjects was mainly due to a decrease in FRC,

leading to airway closure in the dependent lung regions. The hemoglobin desaturation was further aggravated by transient periods of hypoventilation.

Brownell et al (1985) performed complete polysomnography on 6 pregnant women at 36 wks gestation and again postpartum (2.5 - 6 months). An EEG, ECG, EMG and ECG with recording of maternal heart rate were obtained by applying the surface electrodes. To obtain fetal heart rate, surface ECG electrodes were applied to the maternal abdomen. Contrary to their expectations they found that the oxygenation was well maintained during pregnancy with even the frequency of apnea and hyponea while duration of total apnea and hyponea being significantly reduced, assuming this may be due to increased levels of progesterone during pregnancy, contributing to preservation of maternal oxygenation in late pregnancy.

Norregaard (1989) determined the effects of postural changes on lung function in pregnant women during the first, second, third trimester and postpartum. Their study comprised of 39 women represented by ten in each trimester and nine postpartum. They observed a significant decrease in FRC, PEF, and FEV_1 as a result of the postural changes. Arterial oxygenation, MVV and DLCO remained largely the same.

Douglas (1992) reviewed nocturnal hypoxemia in patients with chronic obstructive pulmonary disease where in he concentrated on the concept of "nocturnal desaturators" among patients whose arterial oxygen tension in wakeful state is above 60 mm Hg. Of 152 such COPD patients, of earlier study, 41 patients were desaturated. They defined desaturation arbitrarily as having oxygen saturation below 90% for at least 5 minutes with a trough saturation of 85% or lower. These nocturnal desaturators could not be predicted from their lung functions or symptoms. However, their mean arterial oxygen tension

during wakefulness was significantly lower (70 versus 76 mm Hg) and arterial carbon dioxide tension significantly higher (41 versus 38 mm Hg), than those who did not desaturate during sleep, thus expecting this group to desaturate more readily. He instigated hypoventilation as a major cause of hypoxemia during REM sleep in patients with COPD, with contributions also from impaired ventilation-perfusion matching and FRC reduction. And in a small minority of patients, the sleep apnea/hypopnea syndrome (SAHS) may co-exist. To explain further consequences in patients having both COPD and SAHS he stated them to be prone to developing pulmonary hypertension, right-sided heart failure and carbon dioxide retention than patients with SAHS without lung disease.

Bourne et al, (1995) investigated the nocturnal hypoxemia in late pregnancy by measuring arterial oxygen saturation continuously overnight in 13 non-pregnant (NP), 13 pregnant normotensive (NPIH) and 15 pregnant patients with a diagnosis of pregnancy-induced hypertension (PIH). The two pregnant groups did not differ in duration of pregnancy (>35 weeks) and none was in labor. There was no significant difference in age between these three groups. Mean SpO2 in NP was 98.5% (range 97%-99%). This was significantly higher than that in NPIH was 95.2% (91%-98%) and PIH was 94.9% (89%-99%). In seven pregnant patients more than 20% of the recording were with SpO2 being < 90%. They concluded that a significant number of pregnant women (> 35 weeks gestation) suffer from prolonged nocturnal hypoxemia.

Van-Hooke et al (1996) studied the effect of pregnancy on maternal oxygen saturation values by use of reflectance pulse oximetry during pregnancy in a cross section of 952 obstetric inpatients and outpatients. A group of 366 patients identified as normal were compared with abnormal subgroups. A subgroup of 64

patients with saturation measurement less than 96% was further evaluated. Their results indicated that oxygen saturation values did not change appreciably during the course of pregnancy in normal patients. Hypoxemia (saturation measurement to less than 96%) was associated with smoking and occurred more frequently with preterm labor in patients who smoked. Obesity and magnesium sulfate use appeared to be synergistic in the presence of hypoxemia. Thus they concluded that the routine use of pulse oximetry during pregnancy might not be justified. Smoking, obesity and magnesium sulfate use have some effect on oximetry in pregnant patients.

Tirosh et al, (1996) studied the effect of maternal smoking during pregnancy on sleep respiratory and arousal pattern in neonates, wherein he included ten infants who were exposed to maternal smoking during pregnancy and ten, age and sex matched control infants participated in that study. At the age of 48 hours (±10) all infants underwent a 150 – 200 minute polygraphic study in a sound proof laboratory. Respiratory and heart rates, distribution of sleep states and oxygen saturation were comparable in the two groups. The proportion of obstructive apnea events followed by arousal was significantly higher in the control group especially during quiet sleep (P=0.001). It appears that exposure to smoking during pregnancy is associated with a high arousal threshold in term infants. This finding could be of relevance in the assessment of maternal smoking as a risk factor for sudden infant death syndrome.