Introduction

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The human pregnancy is a unique state, in which virtually all maternal systems are dramatically altered in order to permit the sustenance and growth of intrauterine conceptus. Most authentically, pregnancy represents one of the best examples of selective adaptation in terms of respiratory physiology. A wide variety of physiologic changes that occur during pregnancy influence the maternal respiratory function and gas exchange. The major factors that alter respiratory functions are mechanical and biochemical changes that routinely accompany the pregnant state. Although such changes generally have measurable effects on pulmonary function tests, ventilation and gas exchange, the physiologic sequelae are rarely perceived by the pregnant woman.

The available data concerning respiratory physiology during pregnancy generally suggests a distinct pattern of changes. The functional residual capacity (FRC) decreases during the second half of pregnancy as a combined result of a decreased expiratory reserve volume (ERV) and to a lesser decrease, in reserve volume (RV). In contrast, total lung capacity (TLC) and vital capacity (VC) are both preserved. Flows as measured by FEV1 and FVC are normal, whereas specific conductance is normal or even increased. There does appear to be any change in small airway function, because closing volume (CV) and maximal expiratory flow volume curves do not demonstrate abnormality. Diffusion capacity is frequently unchanged, although an increase in early pregnancy and a decrease in late pregnancy have been observed in some patients.

Pregnancy is associated with significant hyperventilation that is in excess of observed increase in oxygen consumption and is postulated to be a result of increased progesterone. This hyperventilation results in a decreased $PaCO_2$ but blood pH is

maintained in a slightly alkalotic range by renal compensation. As a result of the decrease in $PaCO_2$ and $PACO_2$, alveolar PO_2 increases and PaO_2 therefore also increases. However an abnormally high (A – a) PO_2 near term, presumably related to airway closure, partially offsets the increase in PO_2 expected for hyperventilation.

Under these physiological variations when a patient with underlying pulmonary disease becomes pregnant, not only experiences the effects of normal mechanical and biochemical events, but may also find the natural course of her pulmonary disease altered. As the FRC is reduced approximately 20% at term, the oxygen reserve is diminished. Consequently, the maternal respiration may be further compromised in the presence of airway diseases.

Airway diseases are classified as restrictive and obstructive respiratory diseases, widely evaluated by pulmonary function tests. Restrictive lung diseases, characterized by stiffness i.e. decreased compliance of lung parenchyma are characterized by a rather symmetrical decrease in lung volumes, TLC, VC, a normal or even increased RV and FRC and an increased FEV_1 to FVC ratio with relatively normal expiratory flow rates, are encountered frequently in general population. Moreover, patients with restrictive pulmonary disease show a correlation between the degree of ventilatory impairment and hypoxemia during pregnancy, for e.g., in scoliosis, a restrictive lung disorder an increased perinatal and maternal morbidity has been reported by Betz et al (1987). Certain previous studies have indicated that such pregnancies can be successful after proper intervention; however, the children may be of low birth weight, usually due to premature delivery (Novy, et al, 1967; Hung et al, 1975; Pitchard et al, 1984; Ratto et al, 1988; Boggess et al, 1995).

The obstructive lung diseases show normal or decreased VC, increased RV and FRC but normal TLC, except for emphysema, in

which TLC is increased, presumably owing to increased lung compliance. Even the maximum expiratory flow rates and maximum breathing capacity (MBC) are decreased. Example, the incidence of asthma in pregnancy that is estimated to be 0.4 to 1.3 percent and is by far the most commonly encountered obstructive disorder (Mintz, 1976; Awadh et al, 1995). Earlier studies have shown the effects of pregnancy on the asthmatic patients to be variable and unpredictable (Weinstien et al, 1979). Although in most patients asthma remains unchanged, symptoms are more likely to get worse than to improve and in several studies, patients with severe asthma antedating pregnancy uniformly become worse and the majority required hospitalization (Turner et al, 1980 and Gipson et al, 1986). Additionally, asthmatic patients are likely to repeat the same pattern with subsequent pregnancies (Jenson et al, 1953; Williams et al, 1967).

The effect of asthma on fetal outcome has been studied without clear conclusions (Nobel et al, 1988 and Turner et al, 1986). While some studies have suggested that premature birth, low birth weight, increased perinatal mortality rates, and even neurological impairment in infants may occur in severely asthmatic mothers (Gordan et al, 1970 and Bahana et al, 1972). There are other studies where no significant influence of asthma on fetal outcome has been noted (Sims et al, 1976 and Das et al, 1991).

Similar contradictory reports are available on other forms of obstructive lung diseases too, like in patients with bronchiectesis. Terstien (1965) found no evidence of intrauterine growth retardation (IUGR), while Templeton (1977) reported a case study in which two pregnancies were complicated by low birth weight and an intrauterine fetal death at 38 weeks.

Besides modification of the maternal environment by risky behavioral factor like smoking or domestic or occupational exposure to certain factors like passive smoke, pollutants or certain drugs can adversely affect the fetal growth, probably, by indirect alteration of maternal lung mechanics. At present, the most important and documented risk factor is the maternal smoking. The early structural changes in the lungs produced due to cigarette smoke are inflammation, narrowing and mucus plugging of 2 – 3 mm airways, which is considered to be the first step in the natural history of the chronic airflow obstruction. All parameters of spirometry were found to be significantly less in smokers than nonsmokers (Das et al, 1991) suggesting marked increase in small airway resistance and early development of small airway disease. The progression of small airway resistance is related to cigarette exposure. Evidences from extensive studies on pregnant women have strongly associated smoking in pregnancy with low birth weight due to either preterm delivery (Aronson et al, 1993) or intrauterine growth retardation (Horta et al, 1997; Das et al, 1998) or other adverse perinatal outcomes (Kendrick and Meritt, 1996; Cnattingius et al, 1997).

Lately, attention has been shifted to the effects of passively inhaled smoke i.e. side stream smoke or second hand smoking on maternal health. Even passive smoking is reported to carry similar hazards of its own. Again, several studies covering this aspect have found a significant association of the passive smoke exposure to low birth weight or small for gestational age babies (Martin and Bracken, 1986; Mathai et al, 1992 and Dejin et al, 1998).

During the last few decades the advances in clinical obstetrics have resulted in significant improvements in the outcome of pregnancy for both mother and infant. In fact more emphasis has been paid in the direction to assure better pregnancy outcomes

through maximizing the health of pregnant women and provided more optimal intrauterine environment for the developing fetus. During pregnancy, the fetus and vital organs grow and mature in a carefully organized, interrelated sequence. Adequate maternal nutrition, blood volume, uterine blood flow and maternal state of health contribute to adequate fetal growth. Actually, the growth and development of the fetus is determined mainly by the fetal genome, but superimposed upon this genetic regulation of fetal growth are two opposing influences. On one hand fetal growth is constrained in various ways, for e.g., the supply of nutrients to the fetus is limited by the capacity of the mother to supply and that of placenta to transfer. Other factors constraining fetal growth are poorly defined but are primarily maternal. On the other hand, hormones and tissue growth factors provide a stimulus additional to the genetically determined drive to fetal growth and differentiation.

The genetic information contained in the fertilized egg guides cell multiplication and differentiation that results in the attainment of the mature human form. A tightly programmed sequence of gene activation and suppression is necessary for development to proceed in an organized manner that would allow particular development events to occur at precise gestational ages, this program must be contained within the genome that is later translated into biochemical events on a precise time course. A genetic *counting* mechanism has been proposed by Holliday and Pugh (1975), suggesting that the cells have the ability to *count* the number of divisions it has gone through the total number of cells in term fetus lies within narrow limits and is the result of 42 successive divisions of fertilized ovum and only five further divisions are required for the fetus to attain on adult size. The genetic influence on birth weight in the normal fetus is mediated by multiple gene loci. The paternal contribution to birth weight is mediated only through his contribution to the fetus' autosomal genes and sex. The maternal

contribution is more profound, being expressed not only through the genes of the fetus, but also through the effect of her genotype on the environment of the fetus; the latter being as important as the fetal growth type itself.

Fetus rarely completely expresses its genetically determined potential for growth. To a greater or lesser degree growth is constrained by unknown factors in the fetal environment, the maternal influences are being mainly implicated. While some of these are expressions of the maternal genotype, the major component of growth constraint is independent of a direct genetic components, the phenomenon has been termed as "maternal constraint". The maternal constraint could operate in many ways. Some of the possible constraining factors are maternal nutrition, uterine influence, placental growth, perfusion, transfer of nutrients and gases, maternal diseases and fetal hormones. A large number of specific maternal factors have been shown to reduce birth size.

Maternal nutritional status is one of the factors determining maternal constraint. Malnutrition prior to or during pregnancy leads to growth retardation extending into the second generation. While poor maternal nutrition may generally have a minor effect on fetal growth, it is possible that substrate limitation may have significant effects on brain growth at critical periods of development.

The anatomical abnormalities of the uterus may be occasionally associated with fetal growth retardation. Any factor affecting uterine blood flow too, may adversely affect fetal growth. Similarly the importance of the metabolism of the placenta in relation to regulation of fetal growth has become apparent in recent years. The growth of placenta is not synchronous with that of fetus, growing more rapidly then the fetus early in gestation so that maximal placental weight is reached at 33 week, however placental villous surface area and

vascularity continue to increase in late gestation. There exists an association between the weight of the placenta and fetus. Perhaps placental size might limit fetal growth by limiting the transfer of nutrients or by limitation of hormone production. Experimental evidences favor the view that placental mass can influence fetal growth in late gestation. Any interference with fetal and placental blood flow will have major effects on placental functions and thus on fetal growth. The umbilical blood flow increases with fetal growth but decreases in late gestation relative to fetal weight, reflecting the increased requirement for blood flow to fetal organs (Boddy, 1979).

The placental transfer of oxygen and nutrients to the fetus and the transfer of metabolic wastes from the fetus to the mother is clearly an important and influential factor in determining fetal growth. Oxygen crosses the placenta by simple diffusion and is necessary for the formation of chemical energy in the form of adenosine triphosphate. Glucose crossing the placenta by facilitated diffusion, is used in the formation of energy, provides the carbon building blocks for the synthesis of lipids, glycogen, nucleotides and other molecules. Aminoacids cross the placenta by active transport and are essential for the synthesis of proteins. Thus any persistent decrease in the availability of any of these substrates will limit the ability of the fetus to reach his or her growth potential. Likewise, maternal disorders during pregnancy are known to affect the fetal growth adversely. Fetal growth retardation has been described in mothers with bronchiectesis, asthma and other chronic lung diseases, circulatory disorders and pregnancy induced hypertension, severe anemia etc.

The endocrine influences on fetal growth can be mediated by many potential mechanisms. Hormones may affect the rate of cell divisions, the transport of glucose and amino acids. They may affect placental transport mechanisms or placental perfusion. In addition,

they may be triggers for the differentiation of tissues at specific points in development.

Thus, the rate of fetal growth represents the balance between constraining and stimulating forces acting on the genetically programmed drive to growth. In the first half of pregnancy, genetic control is dominant and give rise to relatively narrow limits of variability of patterns of fetal growth; in the second half of pregnancy, constraints and stimuli become increasingly important and given rise to greater variability of growth and maturational milestones.

The most frequent outcome indicator of fetal growth and development in human study is derived mainly from the clinical correlations with birth weight. Low weight at birth may result from one of two processes, either independently or in combination, they are shortened duration of gestation and /or retarded growth (small-for-gestational-age (SGA), low birth weight or intrauterine growth retardation). The term SGA is applied to babies with birth weight below the 10^{th} percentile for their gestational age without implications of any pathologic restriction in their growth; while the term IUGR is applied to fetuses below the 10^{th} percentile for their gestational age but being affected by pathological restriction in their ability to grow. The diagnosis of IUGR is confirmed in the neonatal period by findings such as low ponderal index (PI), decreased subcutaneous fat, hypoglycemia, hyperbilirubinemia, necrotizing enterocolitis, hyperviscosity syndrome, or any other characteristic complications of these babies.

Depending on the timing of growth restriction, as well as its etiology, infants can be either asymmetrically or symmetrically growth restricted. It was suggested that the process of fetal growth might be viewed as having three consecutive phases (Winick, 1971). The first phase is referred to as the phase of cellular hyperplasia that

encompasses the first 16 weeks of gestation. During this phase the rapid increase in cell number occurs. The second phase known as phase of concomitant hyperplasia and hypertrophy is between the 16th and 32nd weeks and involves increase in cell size and number. The third and final phase referred to as the phase of cellular hypertrophy, between 32 weeks gestation and term is characterized by a rapid increase in cell size. It is in this phase that most fetal fat deposition is thought to occur. The asymmetric growth restriction generally occurs late in the second trimester or early in the third trimester of pregnancy i.e. during the phase of growth, termed cellular hypertrophy, is attributed to placental insufficiency secondary to maternal hypertension, renal disease, heavy cigarette smoking, or diabetes with vascular diseases. The fetal brain and heart are often spared because of non-reduced blood flow, and these fetuses usually demonstrate normal musculoskeletal growth. Conversely, the symmetrically growth – restricted infant begins the process of growth restriction early, with a decrease in hyperplasia of all cells. Such fetuses not only share the growth aberration of the fetus with an asymmetric pattern but also have decreased skeletal dimensions. Factors associated with symmetrical growth restriction are chromosomal abnormalities (i.e., trisomy 18 & 13), development abnormalities secondary to teratogens (e.g. anticonvulsants and narcotics) and intrauterine fetal infections (e.g. rubella, cytomegalovirus, malaria, hepatitis A & B, toxoplasmosis, listeriosis, syphilis, and tuberculosis). In addition, cyanotic heart disease, cigarette smoking, and other causes of prolonged fetal hypoxia may result in a symmetrically growth – restricted infant.

The first clinical sign of fetal growth restriction may be an abnormally low maternal fundal height measurement inappropriate for gestational age. Advances in ultrasound technology have provided the needed diagnostic accuracy for diagnosis of IUGR that is

necessary to identify fetuses included as high-risk subjects. Most important is evaluation of the fetal head (head circumference and biparietal diameter) and abdominal circumference and their ratios as well as femur length. Those at highest risk for development abnormalities are fetuses whose head growth begins to slow before 26 weeks gestation (Harvey et al, 1982). The magnitude of the clinical problem of IUGR is even more apparent when one considers that such infants have a higher perinatal mortality, a higher incidence of perinatal complications and certain development handicaps than do appropriately grown infants of similar gestational age. Thus the prevention of impaired fetal growth and subsequent neonatal complications require an understanding of those factors that influence the fetus during its intrauterine growth period and the fetal outcome, focusing primarily on maternal physiologic and metabolic adaptations during pregnancy.

Although a good number of studies concerning maternal respiratory functions are available in normal pregnant women, a paucity of data is noted in pregnant patients with respiratory diseases. In fact the pregnant women with respiratory problem pose a special challenge. Moreover, lately the role of chronic maternal respiratory illness in the modulation of fetal growth is gaining considerable interest. Many investigators have strongly related lower maternal respiratory functions to low birth weight and inclination towards intrauterine growth retardation and have explained it on the basis of possible existence of relative hypoxia or hypoxemia (Schatz et al, 1990; Mathai et al, 1992; Dejin – Karlson et al, 1998; Das et al, 1998). It is an established fact that functional residual capacity (FRC) gets progressively reduced during pregnancy. This reduced FRC in combination with increased oxygen consumption may render the parturient more susceptible to hypoxemia during periods of apnea or airway obstruction. Very few investigators so far, have actually

assessed both the small airways function and arterial oxygen saturation in women during the last trimester of their gestations, and still fewer have correlated such findings to the fetal outcome, though, arterial oxygen saturation measurement to assess hypoxemia have been rendered easy by pulse oximeter. Pulse oximetry is a non-invasive method of indirectly measuring arterial oxygen saturation, thus evaluating the patients' oxygenation status. The oxyhemoglobin curve relates oxygen saturation to arterial partial pressure of oxygen (PaO_2).

Based on these facts, the present study has been sought to examine the effect of maternal airway functions in clinically stable, otherwise in asymptomatic state on arterial hemoglobin oxygen saturation during pregnancy and their perinatal outcome, with special focus on neonatal birth weight.

Henceforth throughout the text at most places following abbreviations would be used.

AC	Abdominal circumference
BPD	Biparietal diameter
CC	Chest circumference
CO	Carbon monoxide
COPD	Chronic obstructive pulmonary diseases
CRL	Crown to rump length
CV	Closing volume
EFW	Estimated fetal weight
ERV	Expiratory reserve volume
$FEF_{0.2-1.2}$	Forced expiratory flow between 0.2 to 1.2 liters
$FEF_{25-75\%}$	Forced expiratory flow between 25-75% of FVC
$FEF_{75-85\%}$	Forced expiratory flow between 75-85% of FVC
FEV_1	Forced expiratory volume in one second

FL	Femur length
FRC	Functional residual capacity
FVC	Forced vital capacity
HbCO/COHb	Carboxy hemoglobin
HC	Head circumference
IUGR	Intrauterine growth retardation
MEFR	Maximal expiratory flow rate
P_{aCO2}	Arterial partial pressure of carbon dioxide
P_{ACO2}	Alveolar partial pressure of carbon dioxide
P_{AO2}	Alveolar partial pressure of oxygen
P_{aO2}	Arterial partial pressure of oxygen
PEFR	Peak expiratory flow rate
PI	Ponderal index: {[birth weight (gm)]/[length (cm)]^3}*100
RV	Reserve volume
SaO_2	Arterial oxyhemoglobin saturation
SpO_2	Arterial oxygen saturation determined by pulse oximeter
TLC	Total lung capacity
TV	Tidal volume
USG	Ultrasonography
VC	Vital capacity
$V_{max's}$ (25%, 50% and 75%)	Instantaneous flow rates at each quartile of FVC (25%, 50% and 75%)