REVIEW OF LITERATURE
American College of Obstetrics and Gynaecology (1980) defined that pre-eclampsia is the development of hypertension with proteinuria, oedema or both, induced by pregnancy after 20th week of gestation and sometimes earlier when there are extensive hydatiform changes in chorionic villi. Eclampsia is diagnosed when convulsions were not caused by the neurological diseases such as epilepsy who also has clinical criteria for pre-eclampsia.

PATHOPHYSIOLOGY

In 15th recent advances of Obstetrics and Gynaecology (1987) Moore and Redman explained pathophysiology at three levels. Primary cause requires presence of trophoblast within the uterus. Maternal adaptation to this primary problem is represented by sign and symptoms. In extreme circumstances the secondary pathology can itself initiate new or tertiary problem.

Pre-eclampsia is associated with an increase in the peripheral vascular resistance resulting in hypertension. In normal pregnancy a reduce pressor response to infusion of angiotensin II and reduced systemic vascular responsiveness but woman developing pre-eclampsia shows an abnormal increase in sensitivity to Angiotensin II. while IUGR of any cause is associated with reduced uteroplacental blood flow, flow is reduced in pre-eclampsia.
even in the absence of IUGR and more severe the pre-eclampsia, the greater the compromise.

In normal pregnancy spiral arteries of placental blood vessel are dilated and funnel shaped while in pregnancies complicated by pre-eclampsia physiological changes are confined to decidual segment of spiral arteries and do not reach the myometrial trunk. Thus there is poor placentation. Similar changes occur in IUGR without pre-eclampsia and immediate cause of placental infarction in pre-eclampsia is acute atherosclerosis.

Placental ischemia is a central part of the process and could occur via a number of different mechanisms. The failure of the normal adaptation of the spiral arteries occurring in early pregnancy.

In other situation an excessive placental mass or sclerotic uterine vessel could result in placental ischemia. Failure of normal trophoblast invasion of spiral arteries could be due to immunological factor.

In William Obstetrics 18th edition Cunningham McDonald and Gaut divided toxemia in two types: mild and severe depending upon following indicators:
INDICATORS OF PREGNANCY INDUCED HYPERTENSION

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>Mild</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diastolic B.P.</td>
<td>&lt;100 mm Hg</td>
<td>100 mm Hg or more</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>Traces to +</td>
<td>++ - +++</td>
</tr>
<tr>
<td>Headache</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Visual disturbances</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Oliguria</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Upper abdominal pain</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Se. Creatinine</td>
<td>N</td>
<td>Increased</td>
</tr>
<tr>
<td>Convulsions</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Hyperbilirubinaemia</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Liver enzyme elevation</td>
<td>Minimal</td>
<td>Marked</td>
</tr>
<tr>
<td>Fetal growth retardation</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Pulmonary oedema</td>
<td>-</td>
<td>+</td>
</tr>
</tbody>
</table>

In William Obstetrics 18th edition, it is stated that intense vasospasm is basic to the pathophysiology and this also disturb circulation of vasa vasorum leading to vascular damage.

Compromise placental perfusion from uterine vasospasm is almost certainly a major culprit in the genesis of increased perinatal morbidity and mortality associated with pregnancy induced hypertension. It was proved by various workers using direct and indirect method.
Morris, Osborn, Payling Wright (1955) found that there is significant reduction in the affective uterine blood flow associated with pre-eclampsia which develops in previously normotensive women. This reduction in probably one of the main factors responsible for the decreased placental flow described by Browne (1953). He stated that the reduction in flow appears to be direct related to the increase in diastolic blood pressure and an increase of 10 mm of Hg is associated which at best. Only half that of the normal and in severe cases the effective blood flow is only a small fraction of the normal.

Rachel B Macbay (1951) studied the oxygenation of the foetus in normal and abnormal pregnancy and concluded that there is a progressive fall in the cord oxygen levels as pregnancy maturity to term and there after the oxygen reserve at term being about 100% while there is a fall in cord oxygen level in cases complicated by pre-eclampsia, the average oxygen reserve at term being about 60%. This reduction is related to the duration of disease and its severity.

**PLACENTAL CHANGES**

This reduced uteroplacental blood flow and oxygen supply results in various placental changes collectively termed as placental infarction and Leek and Assali (1954) concluded that acute atheros is pathognomonic lesion.
ABNORMALITIES OF UMBILICAL CORD

Several mechanical and vascular abnormalities of the umbilical cord are capable of impairing fetal placental blood flow as knots, loops, torsion, stricture, haematoma and cyst of cord.

KNOT OF THE CORD

1. False knots: results from binding of the vessels to accommodate the length of the cord.

2. True knots: results from active movements of the fetus.

Torsion of the cord: As a result of fetal movement cord normally become twisted.

Placental dysfunction due to toxemia of pregnancy was noted by Schutte et al (1971) and played an important role in the etiology of intrauterine growth retardation as observed by the author. Toxemia is responsible for the birth of hypoplastic, apathetic, growth retarded children.

Bhatia et al (1990) showed that in toxemia of pregnancy, the insult for growth retardation operates late in gestation and the babies of such mothers demonstrate a catch up growth for weight crown heel length and head circumference after birth.

Hill (1974) in Ciba foundation of symposium stated that one cannot produce significant growth retardation until 30-50% of the mass of the placenta has been lost to say nothing of the function. These structural
anomalies may well associated with disturbances in function, and the weight of placenta really tell us very little about the role it plays in determining the weight of baby.

In William's Obstetrics (18th edition) it is stated the most common placental lesion are referred to collectively as placental infarcts. These lesions are of clinical importance only when they are abundant in which case they may interfere with the function of a sufficiently large portion of placenta to hamper seriously fetal nutrition and on occasion cause fetal death. These degenerative lesions have 2 etiological factors in common:
1. Changes associated with aging of trophoblast.
2. Impairment of uteroplacental circulation causing infarction.

Tinelol and Sott (1965), in a study of placenta from 3025 pregnancies concluded that calcification in the placenta is a normal process with the amount of calcium deposited increasing in amount throughout the 3rd trimester.

Ludlow, Morris et al and Chakravorty (1955) suggested that PET can retard fetal growth since birth weight for gestational age was reduced in infants of toxemic mother, on the other hand Brask Beaudly and Sutherland (1981) concluded from their studies that toxemia of pregnancy did not retard birth weight. Baird et al (1982) and Butler et al (1969) found no reduction in birth weight at different gestational age among infants whose mother had either mild or moderate PET though severe
PET was associated with reduced birth weight. Greenwald and Maeve also observed same finding.

De Souza (1976) concluded that PET was not associated with any significant increase in the incidence of growth retarded infants or placentae. In the majority of women because PET responded favourably to treatment with bed rest and sedation, any retarding influence it may have had on fetal or placental growth was reduced. In the remaining mothers in whom PET responded less favourably to the such treatment, fetal or placental growth retardation may have occurred if pregnancy went on to term, but this was avoided by early termination of pregnancy. It is suggested therefore, that either a favourable response to treatment or early termination of pregnancy has reduced any effect of PET on fetal or placental growth retardation.

While page (1972) in his discussion of pathogenesis of pre-eclampsia and eclampsia, wrote that there is general agreement that many types of lesions are significantly more extensive in pre-eclampsia. These include increased syncytial knots or sprouts, increased number of true infarcts and retroplacental haematomas, increased loss of syncytium proliferation of cytotrophoblast and thickening of the trophoblastic basement membranes. These pathological changes leads to foetal hypoxia or death and abruptio placentae.

Quantitative difference between normal and pre-eclamptic as shown in the table below (Data of H. Fox).
Percentage incidence of selected placental lesions.

<table>
<thead>
<tr>
<th>Lesions</th>
<th>Normal 200 cases</th>
<th>Pre-eclampsia 160 cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>True infarcts</td>
<td>24.6</td>
<td>44.7</td>
</tr>
<tr>
<td>Retroplacental hematoma</td>
<td>0.8</td>
<td>6.2</td>
</tr>
<tr>
<td>Cytotrophoblastic proliferation</td>
<td>1.0</td>
<td>23.1</td>
</tr>
<tr>
<td>Excess syncytitial knots</td>
<td>3.4</td>
<td>6.8</td>
</tr>
<tr>
<td>Thick basement membrane</td>
<td>4.2</td>
<td>49.1</td>
</tr>
<tr>
<td>Obliterative endoarteritis(Fetal)</td>
<td>8.8</td>
<td>32.5</td>
</tr>
</tbody>
</table>

PLACENTAL CHANGES

Robert & Nesbit (1974) in his "abnormalities and disease of the placenta and appendages" stated that placenta acquires a physiological capability to maintain foetal haemostasis by reacting sensitivity to the gas and metabolic needs of fetus. These regulatory mechanisms of the placenta are only partially understood but they involve the functioning capillaries within the placenta and the surface available for transfer in accordance with fetal needs when terminal villi are explanted for organ culture and the concentration of oxygen in the chamber is reduced from 26% to 6% morphologic changes occur in syncytiotrophoblast. The nuclei together with some cytoplasm cluster at one pole of the villus, leaving only a thin layer of cytoplasm over the basement membrane.

The distance from the inter villous space to the nearest fetal capillary is reduced by 25%, thus clustering of nuclei and thinning of the syncytial covering are
interpreted as a slow accommodation of the placenta to chronic hypoxia.

Clifford (1957) observed a high incidence of gross placental abnormalities has been reported, and in some instances of severe maternal-uterine circulatory impairment (hypertensive, cardiovascular disease, toxemia, placental dysfunction syndrome) placenta is small, meconium stained and degenerated. He reported that the placentae were abnormal in 90% of fetal death on or after day 294, 84% showed gross meconium staining, degeneration pathology i.e. changes, with or without haemorrhage were present in 34%.

Nesbitt (1974) stated that nearly every term placenta show marginal infarction. As the placenta passes into the last half or third of its existence, degenerative lesions may occur in association with aging of the trophoblast or because of changes of the utero-placental circulation which results in fibrinoid degenerative calcification and ischemic infarction. Vascular lesions of the decidua resulting in accelerated syncytial degeneration, intervillous thrombosis, and placental infarction are common occurrence in toxemia of pregnancy. Only rarely are these placentae infarct massive or of sufficient degree to produce "placental insufficiency and fetal death. In his experience infarction is considered to be a primary factor responsible for perinatal death in
only about one in 500 cases and become unable to demonstrate a precise correlation between amount and location of infarction and the clinical manifestation of toxemia.

While Bartholomew and co-workers (1938) have repeatedly emphasized the importance of intervillous hematomas and placental infarction as the characteristic lesion of eclamptic toxemia. Bartholomew (1938) stated that amount and location of infarction, the degree of vessel obstruction in the placenta and rapidity of autolysis determine whether pre-eclampsia of mild or severe degree or abruptio placental occurs. The most important "Single" entity responsible for fetal death in utero of the known causes is abruptio placental. The fetal loss varies with the degree of placental disruption and the presence and degree of associated toxemia.

Sexton and co-workers (1950) reported that the fetal mortality is as high as 66% in cases of abruptio placentae associated with severe grades of toxemia.

There is lot of controversy about the placental finding in toxemia of pregnancy. Abundance evidence suggests that during toxemia placental function is impaired, in regard to the elaboration of both enzymes and transmission but, at present there are no known pathognomonic histologic lesions common to all placentae to toxemic women, considerable evidence points to a
vascular basis for diffuse trophoblastic injury and placental dysfunction frequently noted in their disease.

**PHYSICAL GROWTH EFFECT OF TOXEMIA OF PREGNANCY ON NEWBORN (PERINATAL OUTCOME)**

Jone E Brazy and co-workers (1982) on their study of neonatal manifestation of toxemia of pregnancy observed that infants of hypertensive mother had a significantly higher incidence of somatic growth retardation. Microcephaly, low apgar score, delayed adaptation, PDA, hypotonia and GIT hypo-motility. These all correlated with the severity of maternal platelet and enzyme abnormalities. The degree of growth retardation was much greater than would have been anticipated by the duration of known maternal hypertension or symptoms and suggested that this onset of uteroplacental compromise antedated overt maternal signs and symptoms.

Despite the persistent effort to decrease the incidence and improve the management of eclampsia, this obstetric complication continues to be a major cause of perinatal death world wide. Sibai et al (1982) studied neonatal outcome, growth and development in eclampsia and found that infants of eclamptic mother are at increased risk for prematurity, intrauterine growth retardation and perinatal asphyxia. Most of the immediate neonatal complications were related to prematurity and growth retardation.
Weightman (1978) observed nine times higher perinatal mortality in eclampsia but when figure was corrected for gestational age and birth weight, however, there was little difference. The perinatal problem was mainly related to preterm delivery and IUGR. All the still birth being due to intrauterine asphyxia and the neonatal death due to RDS. He concluded that foetal loss is due to placental ischemia with IUGR, asphyxia and asphyxia being further aggravated by eclamptic fits. Postnatally the RDS is the dominant problem.

Sibai et al (1983) in their discussion of pregnancy outcome with pre-eclampsia demonstrated that an infant less than 29 weeks weight 720 gm of toxemic mother perinatal survival was nil irrespective of aggressive or conservative management. In contrast, corrected neonatal survival was 94% for 29-32 weeks and 100% for gestation beyond 32 weeks. A syndrome of severe growth retardation, marked asphyxia, DIC, renal failure, interventricular haemorrhage and neonatal death was observed in ≤29 weeks gestation.
### Neonatal complications of toxaemia of pregnancy.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Gestational age in weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>7 36</td>
</tr>
<tr>
<td></td>
<td>No.</td>
</tr>
<tr>
<td>RIP</td>
<td>6/10</td>
</tr>
<tr>
<td>RDS</td>
<td>4/10</td>
</tr>
<tr>
<td>ICH</td>
<td>10/10</td>
</tr>
<tr>
<td>SGA</td>
<td>8/10</td>
</tr>
<tr>
<td>DIC</td>
<td>9/10</td>
</tr>
<tr>
<td>Renal failure</td>
<td>10/10</td>
</tr>
</tbody>
</table>
Derham and Haubins (1989) stated that primary factor in a good outcome was the duration of pregnancy at delivery or IUGR and severe maternal proteinurea were adverse factor and maternal age, diagnosis and duration of hypertension and the magnitude of the systolic and diastolic blood pressure reached seemed to be only of secondary importance in relation to fetal outcome.

HAEMATOLOGIC EFFECT OF TOXEMIA OF NEWBORNS

The presence of severe hypertension in pregnancy causes a marked imbalance in maternal homeostasis and unfavourable uterine environment for the fetus and it is seen that significant correlations between the clinical and lab abnormalities present in the infant reflect the pathophysiology of the maternal disease process. The severity of uteroplacental insufficiencies were experienced by these fetuses may be reflected in the low apgar score, high hematocrits. Increased Hb % leukopenia and thrombocytopenia etc. (Brazy et al, 1982).

It is observed that there is an increase in the Hb level in the cord blood in cases complicated by pre-eclampsia. Hovard - Sholin Finne (1966) investigated erythropoietin level in cord blood in control cases and foetus delivered after pregnancies in which the foetus is supposed to suffer an intrauterine hypoxia. The results show that increased erythropoietin level found in cord blood in infants suffering from hypoxia due to other causes.
The infants of pre-eclamptic mothers seen to show the greatest frequency of elevated erythropoitin level in cord blood indicating high risk of intrauterine hypoxia, especially in severe cases. Incidence of dysmaturity and placental infarction is high in this group. The high erythropoitin level in these infants fit in well with other reports in which reduced oxygen saturation of cord blood, elevated Hb and red cell value indicating fetal hypoxia in pre-eclamptic pregnancies were found (Finne, 1966).

Bromberg et al (1963) observed that foetal Hb content of blood of normal full term infants varied from 64.1% to 95% while in chronic anoxemic condition in pregnancy, foetal Hb was above the normal varied from 94.5% to 100% and it is assumed that the high foetal Hb concentration in newborns of anoxemic mothers is due to adaptation of the foetus to the chronically reduced oxygen supply.

Sinha et al (1972) observed that the amount of foetal Hb and the number of nucleated R.B.C. in the cord blood of mature neonate were significantly higher in toxemia cases. This suggests that in toxemia of pregnancy the normal replacement of foetal Hb by adult Hb interfered.

Korotia et al (1976) observed that Hb intended to rise with advancing gestation of the contrary foetal Hb showed a gradual fall with advancing gestational age. Correlation between gestational age and birth weight and foetal Hb could not be established. It was concluded
that foetal Hb cannot be used as one of the induces for determining the maturity.

Jone Brazy and their co-workers (1982) on their study of "Neonatal manifestation of toxemia of pregnancy" observed that infants of hypertensive mother had a significantly higher incidence of leukopenia, Neutropenia, thrombocytopenia.

Sibai et al (1983) observed that neonatal complications in the infants of eclamptic mothers were frequent and complications were similar as reported by Brazy and associates (1982) but Sibai (1983) found similar neonatal complications in the study and control premature infants which suggest that factors other than eclampsia per se might be responsible for most of the neonatal complications in infants of eclamptic mothers and he stated that neonatal complications encountered in the study infants are not different from those reported in infants of low birth weight in other series. There was no difference in regard to thrombocytopenia, leukopenia or DIC. Moreover, there was no relation between the presence or severity of thrombocytopenia in eclamptic mothers and their infants.

Trandinger (1975) done work on platelets and IUGR in pre-eclampsia. He observed that lowest platelet count were associated with the greatest degree of IUGR with a positive correlation between platelet count and percentile birth weight.
ESTIMATION OF GESTATIONAL AGE

L.M.P.

Gestational age of foetus can be estimated by last menstrual period (L.M.P.). But due to irregularity in menstrual cycle, and illiteracy in developing countries this date may be wrong. Werner and Young (1974) observed that only 33% of mothers could be relied upon to give accurate date of L.M.P.

Fundal Height

Fundal height it also can estimate gestational age. But fallacies are also there as in multiple pregnancy, hydroamnios, transverse lie IUGR.

Biochemical Method

A. Lecithin/Sphingomylin ratio (L/S ratio) ≤ 2 indicates gestational age less than 34 weeks. Ratio which is ≥ 2 indicates gestational age of more than 38 weeks (Dutta et al, 1982; Suge, 1985).

B. Shake test:

Amniotic fluid is mixed with various strength of saline when shaken for 15 sec. with equal volume of 95% ethanol a ring of bubbles persist at the meniscus, after 15 min. of standing the sample indicating a positive test. If positive in dilution of 1:2 or greater it indicates that the fetal lung is satisfactorily mature hence gestational age is more than 35 weeks (Singh, 1985) and
correlates well with mature L/S ratio and absence of hyaline membrane disease. Creatinine level in liquor amni 72 mg% indicates gestational maturity of at least 37 weeks. It also indicates mature renal function (Singh, 1985).

Cytology

Nile Blue sulfate test of liquor Amni:
Lipid containing epithelial cells from sebaceous glands of fetal skin are shed into the amniotic fluid. With 0.1% Nile blue sulfate these lipid cells stain orange. If there are more than 20% organophilic cells it indicates gestational age of 36 weeks or more (Edward et al, 1968).

Anterior Vascular Capsules of Lens
Examination of the disappearance of anterior vascular capsule of lens (Pupillary membrane) was found useful to detect preterm infant with gestational age between 27 and 34 weeks (Hittner et al, 1977). This criterion was further confirmed by Narayan et al (1981).

Roentgenogram
Besides roentgenography fetal maturity has been assessed by long bone measurement by Bhargava et al (1977).

**Ultrasound**

Hellman (1969) suggested that linear measurement of gestational sac, which appears at 4 1/2-5 weeks after the last menstrual period, be utilised as parameter of gestational age.

Hedlock et al (1982) has shown that head circumference is a better predictor of gestational age than biparietal diameter.

Femur length is a more reliable ultrasonographic parameter of fetal age during later gestation (Campbell et al, 1982).

A comprehensive assessment of gestational age, based on certain neurological and physical criteria has been devised by Dubowitz et al (1970).

**Intrauterine growth retardation**

Lubchenoco's (1963) definition which defines IUGR as birth weight below 10th percentile has problem in specificity. Because of the distribution of foetal weight in general population atleast 7% of normal babies will be classified as growth retarded when 10th percentile is used to differentiate normal from abnormal fetuses.

According to Albermann and Butter (1969) birth weight less than 2.5 kg does not imply IUGR as it does not take into account the gestational age.
Usher Maclean Grewmald (1969) defined IUGR as birth weight more than 2 SD below the mean birth weight.

By weight and gestational age newborns are divided into 3 categories (Bhargava et al, 1974).

1. **Preterm** (Gestational age <37 weeks).
   a. Appropriate for gestation (AGA) and birth weight between $\pm 1$ S.D.
   b. Small for date (SFD) and birth weight below 2 S.D.
   c. Large for date (LFD) and birth weight above 2 S.D.

2. **Term** (Gestational age 37-41 weeks)
   a. Appropriate for gestation (AGA) and birth weight between $\pm 2$ S.D.
   b. Small for date (SFD) and birth weight below 2 S.D.
   c. Large for date (LFD) and birth weight above 2 S.D.

3. **Post term** (Gestational age 42 weeks or more)
   a. Appropriate for gestation (AGA) and birth weight between $\pm 1$ S.D.
   b. Small for date and birth weight below 2 S.D.
   c. Large for date (LFD) and birth weight above 2 S.D.

Singh et al (1978) have subdivided small for date babies on the basis of severity of intra-uterine growth retardation.

1. **Mild IUGR**: Babies whose birth weight falls between 3rd and 10th percentile of the standard appropriate for gestational age.
2. Severe IUGR: Babies whose birth weight falls below 2 S.D. or 3rd percentile of the standard weight for gestational age.

But Dr. Meharban Singh (1991) in his 'Care of Newborns' stated that there is a lack of consensus regarding the definition of SFD babies. Some paediatricians classify a baby as SFD of its weight falls below 10th percentile for the period of gestation, while others accept the dividing line of $\leq 2$ S.D..

Drugs in pregnancy

Any drug or chemical substance administered to the mother is able to cross the placenta to some extent unless it is destroyed or altered during passage. Placental transport of maternal substrate to the fetus and of substances from the fetus to the mother is established at about the 5th week of fetal life. Every substance used for therapeutic purposes can and does pass from the mother to foetus. Of greater importance is whether the rate and extent of transfer are sufficient to result in significant concentration within the fetus. We must discard the concept that there is a placental barrier. Drugs may affect the nutrition of the foetus by interfering with the passage of nutrients across the placenta. Alterations in placental metabolism influence the developmental of the foetus since placental integrity is a determinant of fetal growth (Summer J. Yaffe, 1982).
Fetal Abnormality

Children of mothers taking antiepileptic drugs showed a 4/3 time increased rate of malformation at birth especially cleft palate and lip, and heart abnormalities. There is probably due to the drug rather than to the disease. Withdrawal of effective therapy during early pregnancy cannot be recommended.

Folate deficiency due to altered folate metabolism also occurs with hydantoin and barbiturates anticonvulsants and is a suspected cause of fetal neural tube effects so that a folate supplements seems sensible in a women who wishes to become pregnant.

Fetal Hydantoin Syndrome

Newborn babies of mothers taking antiepileptic sometimes have reduced clotting factors, prothrombin remediable by giving vitamin K antinatally.

Benzodiazepines in Pregnancy

It is not safe and should be avoided in early pregnancy as for as possible. In late pregnancy it cross the placenta and can cause fetal a muscular hypotonia, and poor suckling. Impairment of behavioural development in the newborn is possible.

Goodman and Goldman's Pharmacological basis of therapeutics (8th edition) stated that Mepiridine cross the placental barrier and even in reasonable analgesic
doses causes a significant increase in the percentage of babies who show delayed respiration, decreased respiratory minute volume or decreased oxygen saturation or who require resuscitation. Both fetal and maternal respiratory depression induced by mepiridine can be treated with naloxone. The fraction of drug that is bound to protein is lower in the fetus, concentration of the free drug may thus be considerably higher than in mother. Nevertheless mepiridine produces less respiratory depression in the newborn than does an equianalgesic dose of morphine or methadone.

Gerald and Thomas (1983) wrote that Diazepam freely crosses the placenta and accumulate in the fetal circulation. The fetal half life in newborns is significantly increased due to a decreased clearance of the drug. An association between diazepam and an increased risk of cleft lip/palate has been suggested. Second trimester exposure was associated with hemangioma and cardiac and circulatory defects. A dose response is likely as the frequency of newborn complications rises when closes exceed 30-40 mg or when diazepam is taken for extended periods allowing accumulation to occur.

Two major syndromes of neonatal complications have been observed:

1. Floppy infant syndrome: Hypotonia, lethargy, sucking difficulties.
2. Withdrawal Syndrome: IUGR, Tremors, irritability, hypertoncity, diarrhoea, vomiting and vigorous suckling.

2. FUROSEMIDE

Administration of the drug during pregnancy does not significantly alter Amniotic fluid volumes. Serum uric acid levels, which are increased in toxaemia, are further elevated by Furosemide. No association was found in a (1973) study between furosemide and low platelet counts in the neonate. Unlike the thiazide diuretics neonatal thrombocytopenia has been reported for furosemide. Many investigators now consider diuretics should be contraindicated in pregnancy (except CVS diseases) since they do not prevent or alter the course of toxaemia and reduces placental perfusion (Jerkener, 1973).

3. PENTAZOCINE

Severe neonatal respiratory depression may also occur with pentazocine.

4. MEPIRIDINE

Fetal problems have not been reported from the therapeutic use of mepiridine in pregnancy except when it has been given during labour. Like all narcotics, maternal and neonatal addiction are possible from its inappropriate use. Neonatal depression, at times fatal, has historically been the primary concern following obstetrical mepiridine
analysis. Its placental transfer is very rapid in cord blood (within 2 minutes), following intravenous administration. Respiratory depression in the newborn following use of the drug in labour is time and dose dependent. The incidence of depression increased markedly if delivery occurs 60 minutes or longer after injection, reaching a peak around 2 to 3 hours. Whether this depression is due to metabolites of meperidine or the drug itself is not known.

EFFECT OF DRUGS ON HEMATOLOGICAL AND PHYSICAL GROWTH OF NEWBORNS

Meharban Singh in his "Perinatal Pharmacology" (1991) stated that a drug which may be apparently safe and well tolerated by the mother may be harmful and damaging to the growing fetus e.g. magnesium sulfate when administered for the management of severe eclampsia may cause hypotonia and respiratory failure in the enonate as a result of peripheral neuromuscular block. The baby may need assisted ventilation and exchange transfusion with citrated blood to inactivate magnesium ions by forming citrate complex.

Heavy sedation during labour is associated with difficulty in initiating breathing, cerebral depression, inactivity, hypothermia, hypotonia and poor nipple feeding 1-2 days after birth.
Maternal electrolyte disturbances by diuretics are mirrored in the fetal blood. Thiazide may directly suppress the megakaryocyte and result in thrombocytopenia.

It has been observed that infant born to mothers receiving reserpine during late pregnancy developed nasal stuffiness, shuffles, respiratory difficulty with intercostal recession and lethargy.

Propranolol therapy during pregnancy may be associated with fetal malformation, IUGR hypoglycemia, Bradycardia, respiratory depression. Various anaesthetic agents given to mothers during caesarean section causes CNS depression and difficulties in initiating the breathing at birth. Halogenated hydrocarbons reaches the fetus more easily than nitrous oxide. Sudden maternal hypotension due to spinal anaesthetics may result in fetal hypoxia.