INTRODUCTION

The placenta plays a several roles throughout pregnancy including enabling gas exchange, transporting nutrients, eliminating fetal waste, preventing the rejection of the fetal allograft and secreting peptide and steroid hormones.[1] Placenta has been described as a "diary of intrauterine life" so examination of placenta can yield information which is important for later management of both infant and the mother. Preeclampsia and eclampsia two such disorders are affecting the mother, where placenta plays a fundamental role as all the signs and symptoms of this disease resolve after delivery of placenta. Therefore, placenta is a focus of interest for studying. [2]

Early placental development:

The development of the placenta is a continuous process that begins at the time of fertilization. The first three days of the emberyo development occur in the fallopian tube then on the fourth day the morula enters the uterus. By the end of the first week post fertilization, the blastocyst implants in the uterine lining and by the end of the second week after fertilization, the trophoblast erodes deeper in the decidua and forms the lacunae. The lacunae then become the intervillous space. The progenitor villous trophoblast cells proliferate throughout gestation and differentiate along two pathways to form either the interstitial extravillous trophoblast that invades decidua or the endovascular extravillous trophoblast that invades and remodels the spiral arteries. [3]

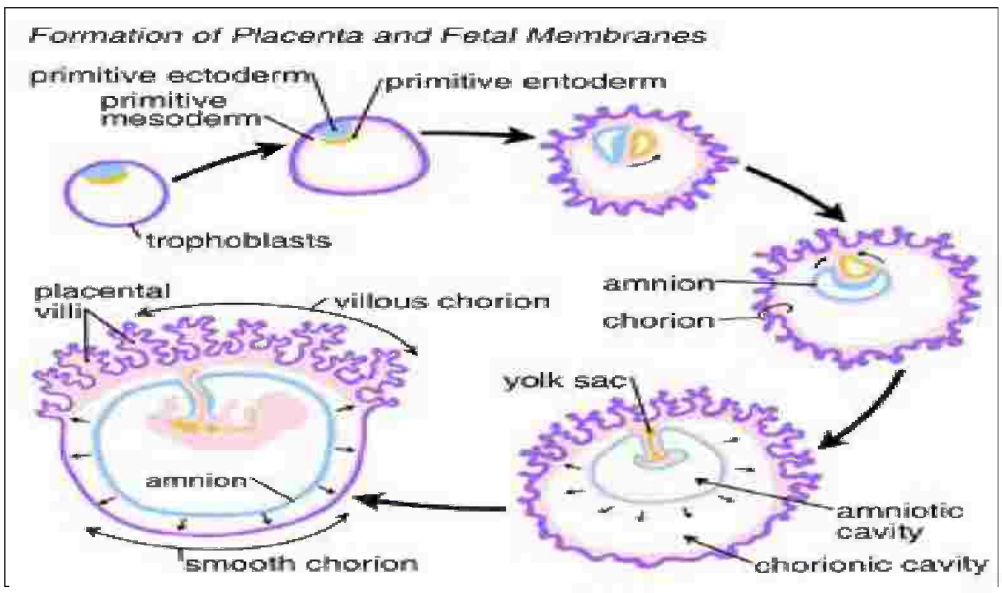


Figure (1): Demonstrates implantation of the blastocyst and early placental and fetal membrane development. [3]

During the first 12 weeks of normotensive pregnancy the endovascular cytotrophoblast invade the spiral arterial walls in the decidua and replace the muscular media. Then continuing throughout the second trimester moving into the myometrial segments of the spiral arteries establishing themselves in the muscular media leading to loss of its elasticity so it become dilated and tortuous. At term these changes can be seen at the distal portions of the radial arteries. [4]

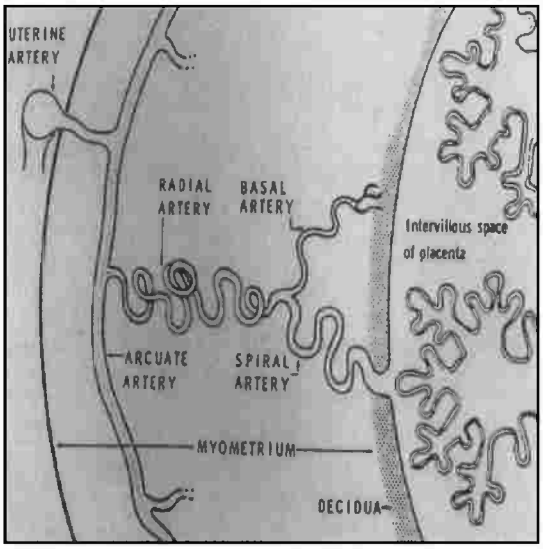


Figure (2): Anatomy of uteroplacental circulation. [4]

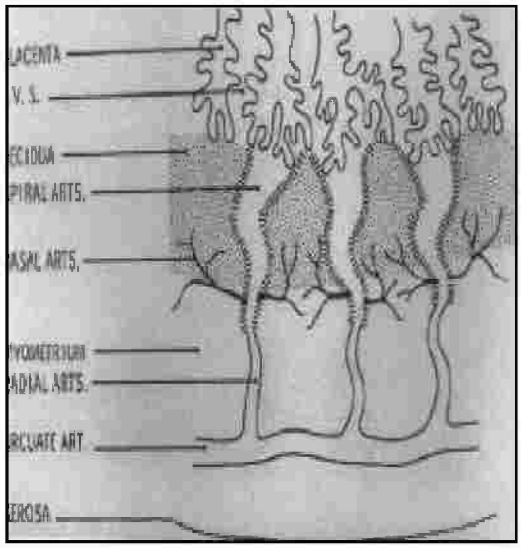


Figure (3): Fully developed physiologic changes in the uteroplacental arteries during normal pregnancy indicating the extend of trophoblastic invasion.[4]

At term the mean external diameter of the myometrial segments of the spiral arteries is approximately 500µm instead of 200- 300µm in the non pregnant state. Approximately 100- 150 converted spiral arteries supply the placental bed. Now these uteroplacental vessels have lost their ability to respond to vasoactive substances. All these changes are responsible for the increase in blood flow from 100 ml/min to 500-800 ml/min.[5] All large vessels of the pregnant uterus undergo hyperplasia and hypertrophy. Thus the increase in cross- sectional area leads to a reduction in resistance and further development of the uterine circulation which will account for the increase in uteroplacental flow during the third trimester. [4]

Morphology of the normal term placenta:

The placenta is formed from the merger of the chorion and the allantois in early pregnancy, and thus, the "afterbirth" delivered in the third stage of labor is called the chorioallantoic placenta.[3] In more than 90% of the cases, it is a disk-like, flat round to oval organ, its average diameter is 22 cm, the average central thickness is 2.5 cm and the average weight is 450gm. The fetal surface of the placenta is smooth and glistening where the umbilical cord is inserted usually eccentrically. While the uterine (maternal) surface of the placenta is opaque, as it is an artificial surface originating from laminar degenerative processes within the junctional zone that led to the easy separation of the organ. This separation process subdivides the junctional zone between placenta and uterine wall into:

- The basal plate,which is attached to the placenta and represents the maternal, uterine surface of the organ.
- The placental bed,which remains in utero.

An incomplete system of grooves subdivides the basal surface of the placenta into 10 to 40 slightly elevated areas called maternal cotyledons. [6, 7]

In nearly 10% placenta has abnormal shapes, such as placenta bilobata, placenta duplex, placenta succenturiata, placenta zonaria, and placenta membranacea, large placentas are associated with hemolytic disease of newborn, maternal diabetes mellitus, severe anemia and intrauterine fetal infections. Small placentas are associated with preeclampsia, chromosomal abnormalities, severe maternal diabetes mellitus, chronic fetal infections and intrauterine growth restriction. [7]

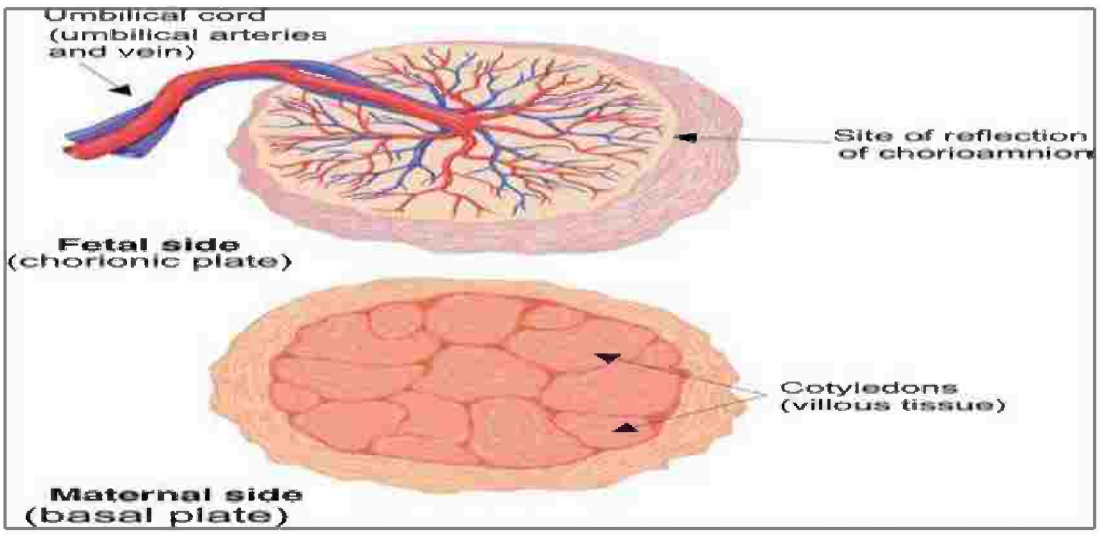


Figure (4): Illustration of the term human placenta: The upper illustration shows the chorionic or fetal side of the placenta. The umbilical cord inserts within the chorionic plate and the chorionic vessels are shown supplying each cotyledon. The basal or maternal side seen in the lower illustration is in contact with the uterine endometrium and divided into cotyledons.[7]

Figure (5): Maternal surface of a normal placenta showing Cotyledons.[6]

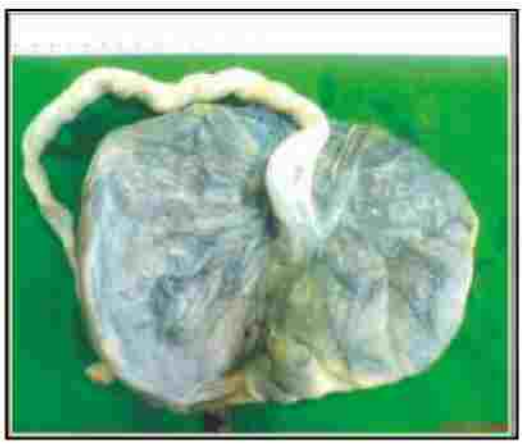


Figure (6): Fetal surface of a normal placenta and the cord.[6]

Microscopically, the placenta comprises a series of elaborately branched villous trees that arise from the inner surface of the chorionic plate and project into the cavity of the placenta. Each villous tree originates from a single-stem villus that undergoes several generations of branching until the functional units of the placenta which is terminal villi, are created. [6] Terminal villi consist of an epithelial covering of trophoblast, and a mesodermal core containing branches of the umbilical arteries and tributaries of the umbilical vein. The terminal villus has the shape of an inverted wine glass and referred as a lobule, and there may be two to three lobules within a single placental lobe, each lobule represents an individual maternal-fetal exchange unit. **[6, 8]**

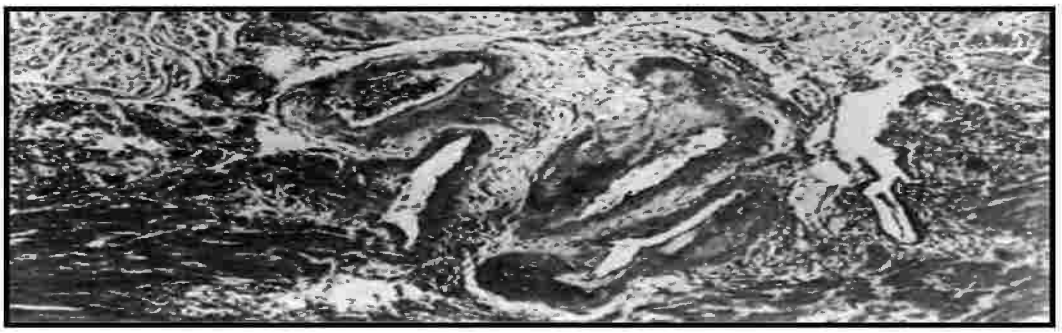


Figure (7): Microscopic picture demonstrating spiral artery at the myometrial junction showing multinucleated syncitiotrophobast and fibrinoid material replacing the internal elastic lamina.[6]

Preeclampsia and placenta:

Preeclampsia is the most common medical complication in pregnancy with a reported incidence of 2-8% among pregnancies and a major cause of maternal and fetal morbidity and mortality as it probably accounts for more than 50,000 maternal deaths worldwide each year. Pre- eclampsia/eclampsia has traditionally been called the disease of theories but as all the signs and symptoms of this disease resolve after delivery of placenta. Therefore, placenta is a natural focus of the source of this disease. [9]

Placental pathophysiology in preeclampsia "two stage model":

In pregnancies complicated with preeclampsia, the abnormal placentation is the earliest event in the development of preeclampsia (Stage 1), particularly lack of endovascular trophoblastic infiltration results in lack of uterine spiral arteriols dilatation which compromises blood flow to the maternal-fetal interface, so it is the starting point in the genesis of preeclampsia as the resulting placental hypoxia activates placental factors and induces systemic heamodynamic changes. [10, 11]

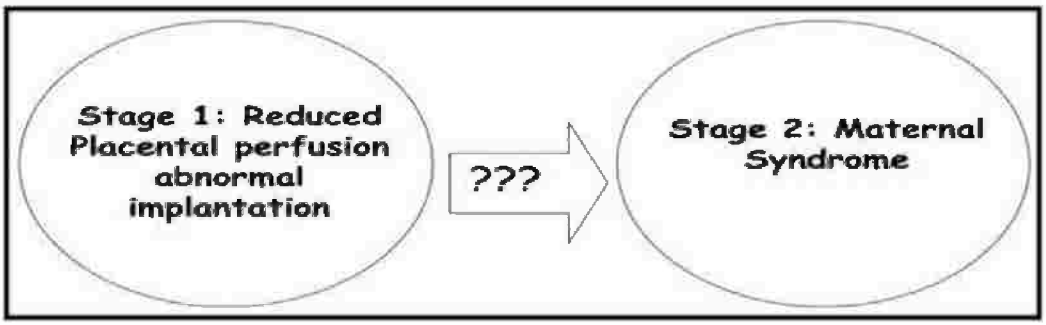


Figure (8): Two stage model: Preeclampsiaa two stage disorder, preeclampsia is initiated by reduced placental perfusion (Stage 1). This results in the release of factor(s) that leads to the maternal systemic pathophysiological changes (Stage 2).[11]

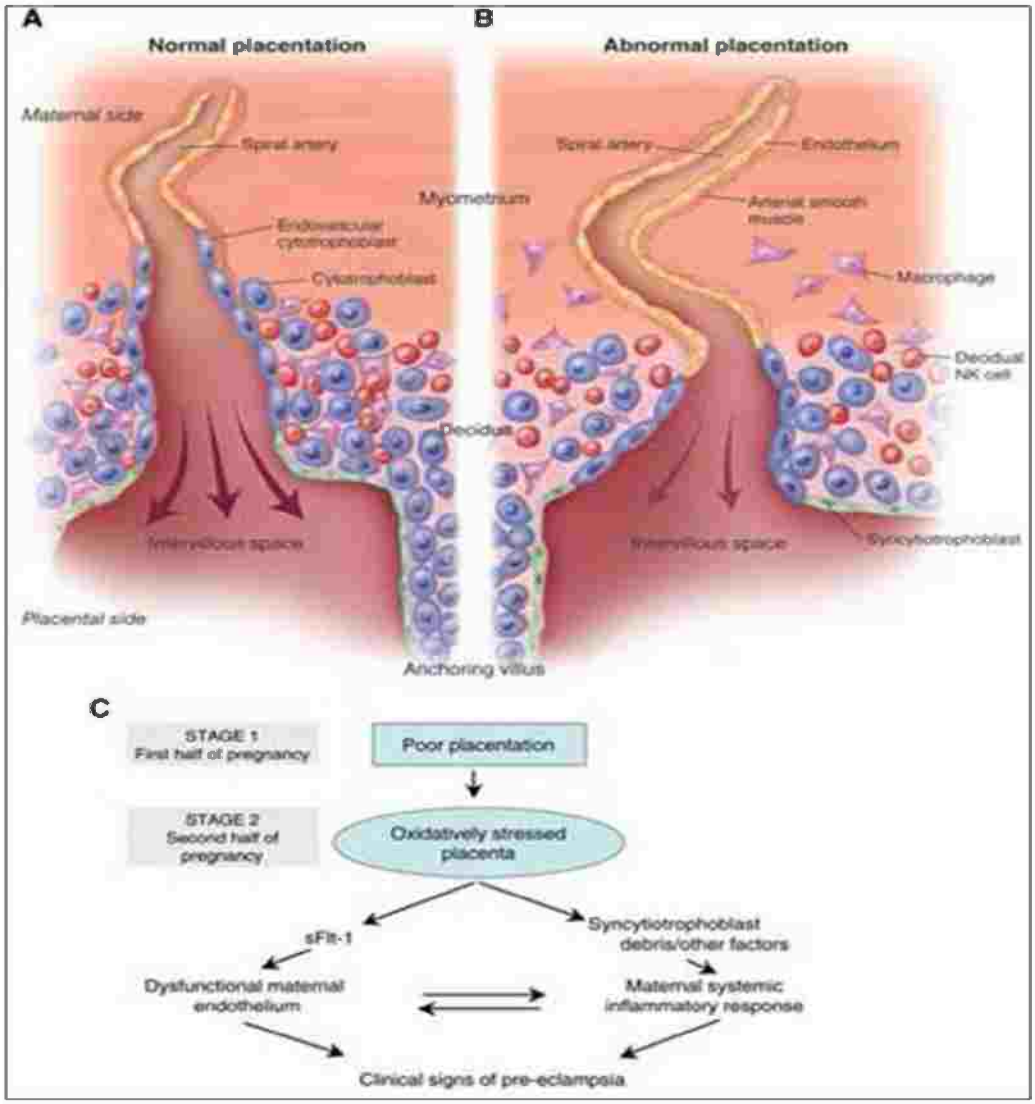


Figure (9): Diagram showing adequate trophoplastic invasion of the decidua, with subsequent dilatation of the radial arteries (A) in normal pregnancy, in comparison to inadequate invasion and poorly dilated spiral and radial arteries in preeclamptic pregnancy stage 1 (B).[10]

The maternal syndrome (Stage 2) which is the result of systemic maternal endothelial cells dysfunction resulting in vascular reactivity, activation of coagulation cascade and loss of vascular integrity. Figure (10) demonstrate the pathogenesis of maternal syndrome in preeclampsia. [11, 12]

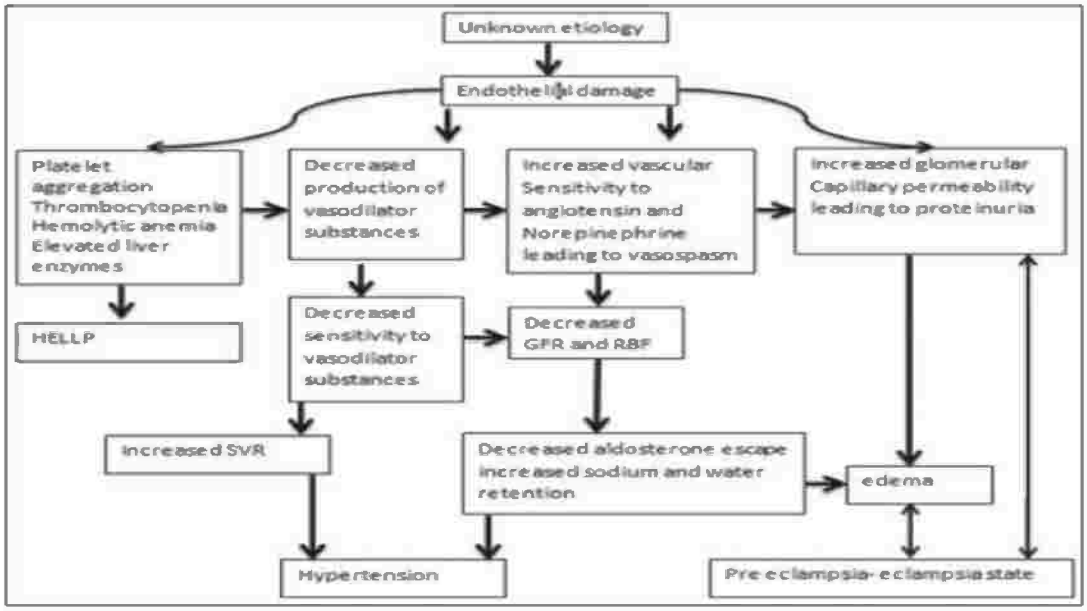


Figure (10): Demonstrate pathogenesis of the maternal syndrome (stage 2).[12]

Gross placental pathological findings in pre-eclamptic toxemia (PET):

Placental examination in pregnancies complicated by PET can show many pathological findings, but may also be grossly normal and histologically appropriate for gestational age, even in cases of fulminant toxemia. If present, placental findings can be confirmatory, but when absent should not be used to exclude disease, as term and post-partum PET are generally pathologically bland. [10]

The placental pathological findings are indicative of chronic ischemia. Grossly, chronic ischemia leads to a small placenta (trimmed weight often much less than the 10th percentile) with a thin umbilical cord (less than 1 cm in diameter).[13] Evidence of acute or chronic abruption may be seen as well Placental infarcts which is commonly pyramidal in shape and nearly always involving the base/maternal floor of the placenta it is due to occlusion of a maternal spiral arteriols. These are common at term and have no sequelae in an otherwise normal placenta. But are distinctly abnormal and rare when seen preterm or occupying greater than 5% of the estimated placental volume. More than one infarct is unusual and suggests a significant vascular occlusion. We find also small, round infarcts centrally located in the parenchyma which are less likely to involve the maternal floor to be quite characteristic of pre-term PET. [13, 14]

Figure (11): Maternal floor infarction grossly the maternal surface of the placenta has a thick ‘‘orange-rind 'covering of fibrin.[14]

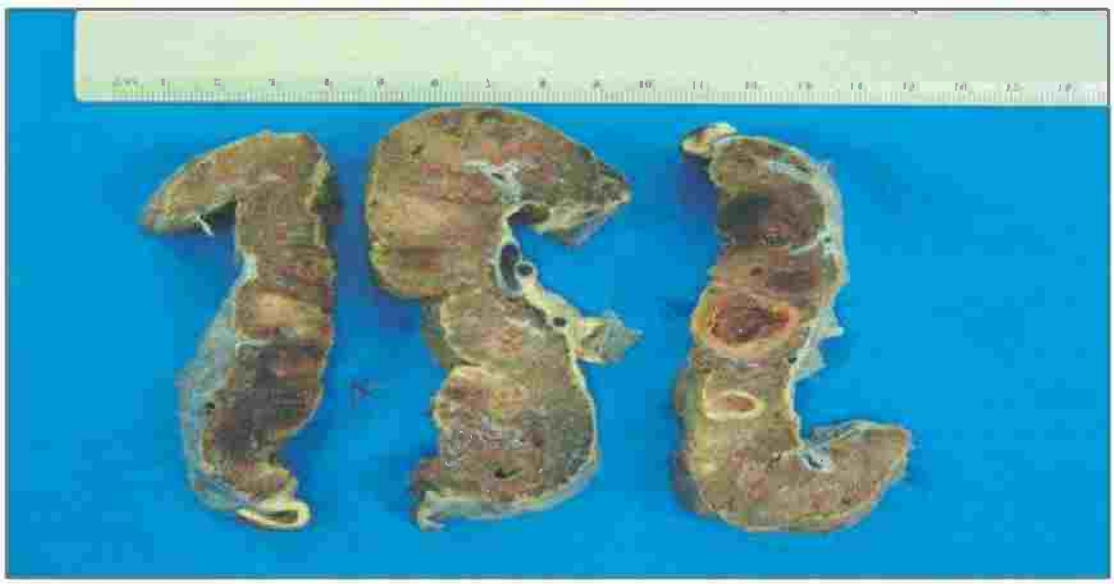
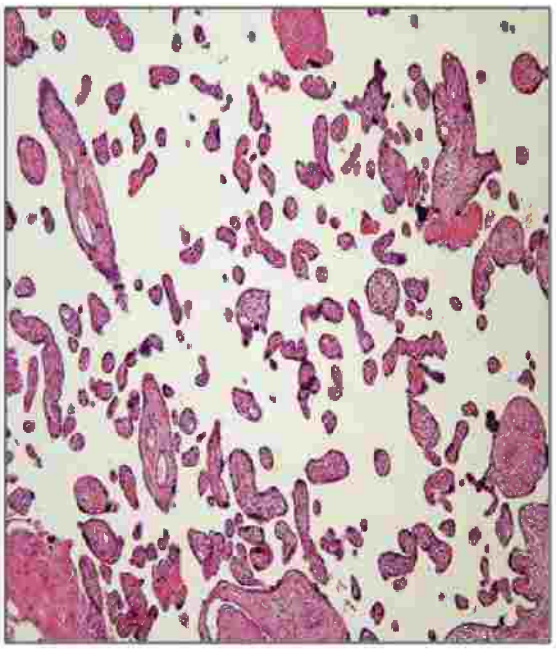


Figure (12): Multiple fresh infarcts of placenta on cross section.[7]

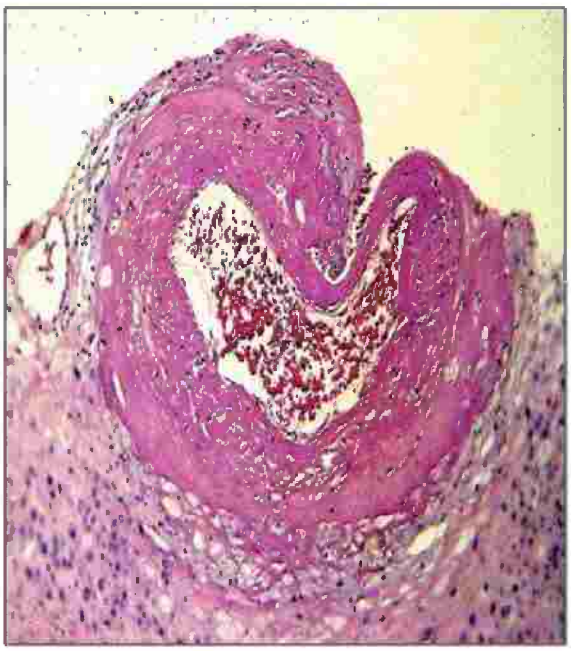
Figure (13): A normal placenta (right) and small size placenta of pre-eclampsia (left).[7]

Histological features of pre-eclamptic placenta:

The hallmark of maternal vascular disease is vascular wall damage.[14] Features characteristic of systemic, or at least uterine vascular changes due to hypertension include: muscular hypertrophy, endothelial thickening, vascular thromboses, vascular ectasia, fibrinoid necrosis of the vascular wall, presence of histiocytes in the vascular wall (atherosis), and close ''hugging'' of peripheral inflammatory cells. These features are termed ''decidual vasculopathy'' (DV) with or without atherosis. These findings are evidence of severe prolonged ischaemia to the placenta.[6] Most of the histo-pathological features associated with PET have to do with chronic placental ischaemia or maternal hypertension. These features are uncommon when PET presents at term or after delivery, but are common in preterm PET. The villous findings of ischaemia include evidence of premature branching: too many tertiary villi with large knots, lots of ''empty'' intervillous space and sclerosis of the villi.It is called villous cachexia with little cytoplasm in the villous stroma; they looked collapsed and thin and have few capillaries.[6, 13]



Figure(14): Hypermature villi. There are small, sclerotic villi with increased syncytial knots and expansive, empty intervillous space.[14]



Figure(15): A spiral artery from the adherent decidua on the maternal surface of the placenta shows acute atherosis in cases of severe preeclampia.[14]

Doppler studies of the uteroplacental circulation:

Preeclampsia is a vascular disease affecting both maternal and fetal circulation which will affect blood flow within both uterine and umbilical arteries. As Doppler techniques enable one to study flow velocity wave forms in a non-invasive way, it became one of the most ideal methods to analyze the maternal and fetal circulations and in particular that of the uterine and umbilical arteries.[15]

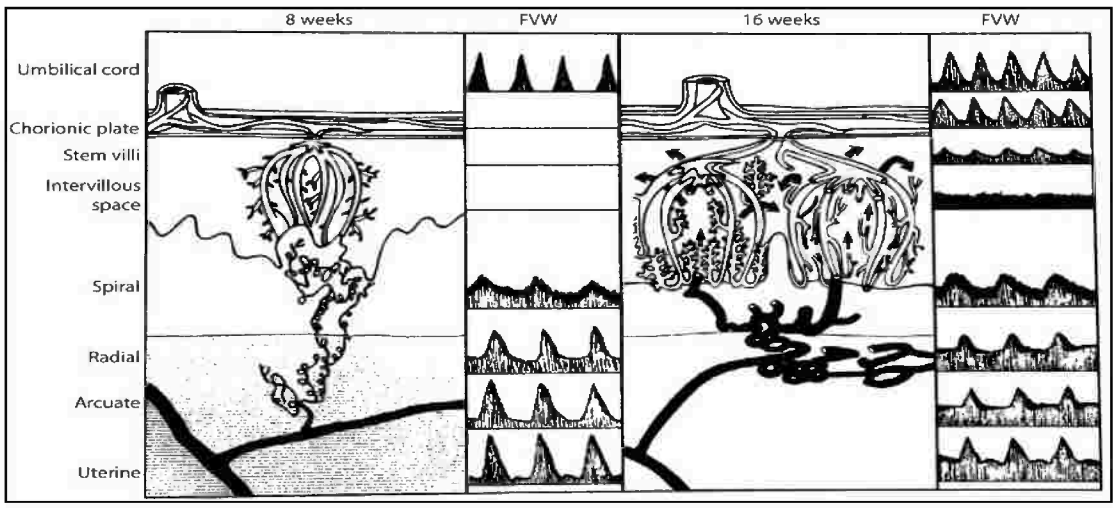


Figure (17): Flow velocity wave form obtained from both placental circulations demonesting the progressive increase in diastolic flow of uteroplacental wave forms from uterine arteries to spiral arteries and as gestational age advances.[18]

Trudinger was the first to obtain signals from arcuate and radial arteries using continuous-wave Doppler, he detected increase in S/D ratios in some but not in all high risk pregnancies as some subplacental radial and arcuate arteries are normal in the face of significant pathology in others.[19]

Umbilical artery Doppler velocimetry:

Each of two umbilical arteries originate from their respective iliac arteries course around the bladder and exit the fetus through the umbilicus forming two of the three components of the umbilical cord. Doppler sampling of the umbilical arteries can be performed at any segment along the umbilical cord. Most commonly, waveforms are obtained from a free-floating loop of cord. [15]

Umbilical arteries normally have low resistance and high blood flow from the fetus to the placenta, which further increases with advancing gestational age as the number of tertiary stem villi increase. Therefore the Doppler wave form in the first trimester of pregnancy may demonstrate absent flow or minimal diastolic flow.[15] Pathological conditions like preeclampsia that obliterate muscular arteries in tertiary stem villi result in a progressive decrease in end-diastolic blood flow until absent and reversed diastolic flow occurs during second and third trimester. Reversed diastolic flow represents the most advanced stage of placental abnormality and occurs when more than 70% of muscular arteries in tertiary stem villi are obliterated.[20]

Indices used to quantify increased umbilical artery resistance include the S/D ratio, RI and PI. Normally they decrease with advancing gestation. Values more than 95th percentile for gestational age are considered abnormal. PI appears to have greater specificity for adverse perinatal outcomes. [21]

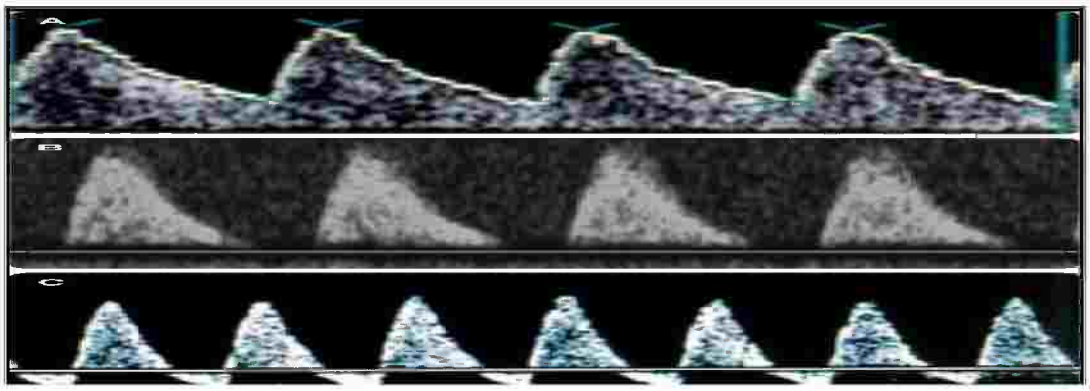


Figure (18): **(A)** Normal Blood Flow Wave Form of the Umbilical Artery. **(B)** Abnormal Umbilical Artery Blood Flow Wave Form (Absent Diastolic Blood Flow). **(C)** Abnormal Umbilical Artery Blood Flow Wave Form (Reversed Diastolic Blood Flow).[15]

Antenatal testing techniques:

Antenatal testing techniques fall into four categories and may be used simultaneously or in a hierarchical fashion. The antenatal testing technique of choice will vary depending on the perceived risk to the fetus. These categories are:

1. Fetal movement counting:

The count of ten in twelve hours can be a simple screening test that can be easily taught to the mother. [22]

2. Non-stress test:

It evaluates the reactivity of the fetal sympathetic nervous system. The positive predictive value of the nonstress test in detecting metabolic acidosis and fetal hypoxia at birth is only 44 percent.[22]

3. Biophysical profile:

The biophysical profile is the most extensively used antenatal testing technique. It is a scored test performed over 30 minutes which assesses fetal behavior by monitoring fetal body movements, breathing movements, tone, and amniotic fluid volume. [22] It is performed using real time B-mode ultrasound. A score of 0 (absent) or 2 (present) is given for each of the four observed variables as described in Table (I). The maximal score is 8 without the non-stress test and 10 with it.[22, 23]

Table (I): Scoring criteria for the biophysical profile

Fetal body movement:	3 discrete body/limb movements in 30 min	2 or fewer body/limb movements in 30 min
Fetal breathing movements (FBM):	1 episode FBM of at least 30 s duration in 30 min	Absent FBM or no episode >30 s in 30 min
Fetal tone:	1 episode of active extension with return to flexion of fetal limb(s) or trunk. Opening and closing of the hand considered normal tone.	Either slow extension with return to partial flexion or movement of limb in full extension Absent fetal movement
Amniotic fluid volume (AF):	1 pocket of AF that measures at least 2 cm in2 perpendicular planes	Either no AF pockets or a pocket <2 cm in 2 perpendicular planes

4. Umbilical Doppler velocimetry:

Umbilical artery flow can be documented using Doppler real time sonography. The semi quantitative evaluation of umbilical artery Doppler wave form pattern combining the pulsitility index (PI) values related to the visual assessment of the diastolic flow is very useful for practical use.It has reduced the incidence of perinatal death by 38% in pregnancies at risk. [24]

Methods used to evaluate newborn condition:

1. Apgar score:

This scoring system is a useful clinical tool to identify those neonates who require resuscitation as well as to assess the effectiveness of any resuscitative measures. Each of the five easily identifiable characteristics described in Table (II) heart rate, respiratory effort, muscle tone, reflex irritability, and coloris assessed and assigned a value of 0 to 2. The total score, based on the sum of the five components, determined 1 and 5 minutes after delivery.[25]

Table (II): Scoring criteria for the Apgar score.

SIGN	0 POINT	1 POINTS	2 POINTS
Heart rate	Absent	<100 bpm	>100 bpm
Respiratory effort	Absent	Slow, irregular	Good, crying
Muscle tone	Flaccid	Some flexion of extremities	Active motion
Reflex irritability	No	Grimace	Vigorous cry
Color	Blue, pale	Body pink, extremities blue	Completely pink

In 2003 the American College of Obstetricians and Gynecologists in collaboration with the American Academy of Pediatrics, lists an Apgar score of 0 to 3 beyond 5 minutes as one suggestive criterion for an intrapartum asphyxial insult.[26] A low 1-minute Apgar score alone does not correlate with the infant's future outcome. While the 5-minute Apgar score remained a valid predictor of neonatal mortality, but it is inappropriate to predict long-term neonatal outcome.[26, 27]

Neonatal outcome:

Fetal outcome in PET either high perinatal mortality rates or increased neonatal morbidity are directly related to preterm delivery [28] while Uteroplacental insufficiency, placental abruption, and low gestational age are considered the primary factors associated with a poor perinatal outcome. In addition, the influence of maternal disease severity such as degree of hypertension, increased proteinuria, or the presence of HELLP syndrome on perinatal outcome has been emphasized. [29]

So the perinatal outcome should be modulated by the obstetric management of severe preeclampsia. [28]

The Feto-Placental Weight Ratio (FPR):

Placental weight is the most common way to characterize placental growth as it reflects the laterally expanding growth of the chorionic disc and arborization of the villous and vascular nutrient exchange surface so it is the principle determinant of the ability of the placenta to translate its mass into birth weight. [30] As chorionic disk area and thickness increase, birth weight and placental weight also increase.[31]

The FPR was defined as the ratio of fetal birth weight to placental weight multiplied by 100%. It has physiologic and functional implications as it reflect the efficiency of placental function and its reserve capacity.[30] As the placenta and fetus follow different growth patterns during gestation. The human placenta follows an S-shaped growth curve (its peak growth between 28-30 weeks gestational) whereas fetal growth follows an exponential pattern (most growth occurring in the third trimester). Thus, the ratio increases with advances of gestational age till being about 6 at full term uncomplicated pregnancy. However, this ratio varies widely and differs in different countries with different placental preparations. [31]

When FPRs are compared between AGA and SGA infants based on gestational age, SGA infants are found to have lesser ratios than AGA infants. The FPR is a better indication of SGA fetuses than placental weight alone.[32] The FPR has been found to be predictive of maternal disease, obstetric outcome, perinatal morbidity and mortality and childhood growth and development. [33]