Review of Literature
In the year 1619, Varandaus first mentioned about eclampsia in "A treatise on Gynaecology". The word 'eclampsia' does not in fact mean fits, for the original Greek word "Eklampein" meant to "flash out". This was probably because of the observation that many women who had fits and ultimately went into coma used to experience the visual symptom of flashes of light before having fits. This catastrophic complication of pregnancy was even known to Hippocrates in about 500 BC. Some other authors as Mauriceau 1668, Thomas 1684, Peu 1694 & Dela Motte 1772 referred this condition as "puerperal convulsions" in their publications.

Professor Alexander Hamilton (1781) published "A treatise of Midwifery", where on the 'Toxaemias of pregnancy' chapter he wrote, 'No disease is more dreadful and alarming in appearance than Convulsions; though they are confined to no particular period of pregnancy, they are most frequent and most dangerous in the later months. The fits come on very suddenly, generally preceded by pain about the region of the womb, anxiety at the pit of the stomach, and intolerable headache; these are soon succeeded by distortions of the body, foamings, etc. If the woman survives a few fits, and recovers her senses in the intervals, there is less danger. The child is often thrown off by the fits, at whatever period of pregnancy they occur. As the disease is always attended with the utmost hazard, and frequently kills the woman.
like a fit of apoplexy, the most skilful of the Medical profession must be immediately consulted. Convulsions may arise from the pressure of the womb only, which confines the blood in the upper parts by pressing on the arteries, or from its being too much stretched. These cases are highly dangerous because they do not admit of relief till after delivery. It is also evident that they may arise from frights, violent passions and too great evacuations, in the pregnant as well as in any other state and that they are then less alarming. The most speedy and effectual means of relief, in the first cases, consist in emptying the vessels by a bold and plentiful bleeding, opening the belly by repeated laxative glysters and afterwards keeping the woman cool and quiet and confining her to a spare diet. If there are symptoms of labour, the membranes should be broken and the delivery assisted, whenever the circumstances of the case will admit of it. The relief of the other cases should be left entirely to the usual practitioner.

While prior to 1700, the term eclampsia was merely used to refer to the scintillating visual phenomenon which accompanies neurologic affections (Bruno 1713), throughout the eighteenth century, it was used as a synonym of "convulsion" and even as late as 1880 it was still a non-specific term. Thus Henry Charlton Bastin (1837-1915) said of eclampsia, "Eclampsia and convulsions are convertible terms, meaning almost absolutely the same thing. The former term indeed is useless except for the mere purpose of literary precision. In epilepsy and in eclampsia, we have equally to do with convulsion which
are now admitted by almost all modern writers to be quite indistinguishable from one another. The former name, however, is given to convulsions which have a known tendency to recur at variable intervals; whilst the latter has been commonly applied to convulsions which are either solitary or if not exactly so, occur as a closely successive cluster or group, more or less distinctly sympathetic with some general or local bodily condition. Seeing that there is, in a very large number of cases almost nothing in the nature of the attack itself to enable a medical man called to a patient in convulsions for the first time to say whether he has to do with an attack which will be repeated or not, it is easy to understand that eclampsia is a word more frequently to be seen in books than to be heard at the bedside. In books we may read of eclampsia neonatorum, the eclampsia of parturient women and uraemic eclampsia; though the more common clinical equivalence are infantile convulsions, puerperal convulsions and uraemic convulsions. The distinction between eclampsia and epilepsy, is therefore, one which is to a very great extent purely artificial.

The use of the term eclampsia parturientium for that particular variety of fits which occur in the pregnant woman began with Sauvages (1700), but little of a specific nature emerged until, toward the end of the eighteenth century, Demanet (1795) observed, the fairly common association of antecedent edema with the convulsive state. The same observation led Rayer (1837-1841) to think of the condition as a renal disorder.

That eclampsia was definitely associated with the pregnant state and not merely an incidental illness was first recog-
nised in nineteenth century. The first foreshadowing of modern knowledge came from John Charles Weaver Lever (1843) who observed albuminuria in puerperal convulsions; it seemed apparent that the fundamental pathologic lesion was nephritis and for a long time the condition was considered to be identical with uraemia.

It is interesting and important from the viewpoint of historical accuracy to observe that in the same period (November 1843) J. Y. Simpson of Edinburgh published a similar observation. Similar to Lever he noted that the convulsions did not necessarily depend on chronic renal disease but usually were "a transitory morbid condition from which the patient recovers within, the course of a few days after delivery" (Munro Kerr et al, 1954). This view, however, was gradually abandoned when it was found that only a small proportion of women suffering from chronic nephritis developed eclampsias and still further modifications became necessary after it was shown that albuminuria was sometimes absent at the time of eclamptic attack by Schroeder Ingerslev (1881) and Charpentier (1883) in their series of 62, 112, 143 such cases respectively (Williams 1930).

That the liver might be involved in eclampsia was indicated by Rudolf Jurgens in 1886 and after a further article on the subject by Alexander Henri Pilliet (1859-1895), attention was shifted from the Kidneys to the liver.

Afterwards each succeeding development in medicine produced a characteristic etiologic theory for eclampsia. During the period when eclampsia was attributed to nephritis, it became
apparent that obstetricians were required to direct greater attention to the antepartum period than had been customary. One of the leaders in this movement was John Ballantyne (1861-1923). Another important figure was Etienne Tarnier (1823-1897) who found a milk diet a useful prophylactic procedure in preeclampsia.

**Evolution of treatment of eclampsia**

Thomas Willis (1684), in his "Essays of Pathology of Brain and Nervous Stock" mentioned the seventeenth century methods of coping with convulsions in pregnancy. Blood letting was a measure for lowering the blood pressure. Violent purging, colon lavage and sweating were liberally used for removal of toxins and for dehydration. Along with blood letting, other measures used by different workers were application of blisters, jalaps, cold-packs, use of drugs like croton oil, calomel, camphor and digitalis and cold water blasts over face were also recommended for averting fits.

Elimination or what was known as Dublin Method of treatment was based on the theory that toxaemia was due to excessive food intake with a drain upon the process of neutralization or to defective assimilation; thus the patients were starved (Mollroy 1936). Manning (1771) and Bland (1794) were the earliest to recommend opium in treatment of eclampsia, but the use of this drug on a large scale came much later, after Scanzoni reported its use in 1859. Jardine (1839) from Glasgow maternity hospital claimed a good result by using saline solution (0.14 per cent of sodium acetate and 0.8 percent of sodium chloride), in an amount of 100 c.c. under each breast.
Introduction of anaesthesia in the field of obstetrics by Simpson in 1847, marked the beginning of the rapid delivery method, as it was thought that removal of baby from the uterus would cause elimination of toxins, which were at that time thought to be the cause of convulsions. Debois (1850) treated his cases mainly by induction of labour.

Halbertsma (1878) was the first to introduce caesarean section in the treatment of eclampsia. Later on Saenger (1883) and Schreiber (1896) recommended this and the latter worker reported 20 per cent maternal mortality and 26 per cent perinatal loss in his series of 137 patients.

Schroeder (1873) and Leishmann (1873) used anaesthetic agents in the treatment of eclampsia. Duhrssen reported on vaginal hysterotomy at the end of 19th century but during the last decade of nineteenth century, it became apparent that such heroic measures (rapid delivery in Eclampsia) were likely to be more dangerous than the expectant treatment of the first half of the century, when little had been known about the condition and little had, consequently, been done to cure it (Mettler 1947). This resulted in a return of the conservative method of treatment in eclampsia.

The expectant treatment of eclampsia now generally employed was first described by Hastings Tweedy from Rotunda in 1896. The treatment included morphia (as a nerve sedative to control the fits and dry up excessive bronchial secretion), venesection, purgation and oxygen (if there were obstructed respiration); no nourishment or drugs were to be given by mouth throughout the
attack whether the patient was conscious or not; and above all the patients were to be kept lying on her side so that secretions could flow out of the mouth instead of down into the lungs or suction might be used to keep the mouth empty of its contents. There was to be no obstetric interference unless the os was sufficiently dilated. He especially condemned the routine induction of labour which was then the usual practice as soon as fits started (Munro Kerr, P.M. et al, 1954). Tweedy however, placed great reliance upon colon lavage and stomach wash (McIlroy 1936).

Vassili Vassilievich Stroganoff's (1897) work in the treatment of eclampsia had been epoch-making. Before his work in Russia, eclampsia was the cause of a very high maternal mortality and surgical interference considered to be the only treatment which gave good result. Stroganoff believed that toxæmia was in the nature of an angiospasm and his conservative line of treatment was directed towards allaying spasm by sedatives and anaesthesia. He recommended that conservative methods needed a trial and allowed the pregnancy to proceed. In some cases however, as soon as the patient showed signs of recovery, labour could be gently induced for preventing recurrence of fits by rupture of the membrane. Most of the present day obstetricians treat their cases of severe 'preeclampsia' and 'eclampsia' in the line of Stroganoff, with little or no modifications.
Review of theories relating to 'Toxaemia of Pregnancy'

In the early years of the nineteenth century, the mechanical pressure theory of the causation of convulsions was generally held. During the later years, and mainly due to the increasing knowledge of the hepatic and renal lesions of the disease, the suggestion that it was due to a toxaemia gradually assumed importance. But Wooldridge (1885) and Schmorl (1893) advanced the hypothesis that thromboplastin in presence of calcium ions played some role in the etiopathogenesis of toxaemia of pregnancy. By 1895, Zweifel had designated eclampsia as the 'disease of theories'.

The first important British contribution in toxaemic theory came from James Young in 1914. Young maintained that pregnancy toxaemia was due to absorption into the maternal circulation of toxins liberated from necrotic placental foci. Zangemeister (1915) tried to explain the occurrence of toxaemia on the basis of excess of tissue fluid. Hofbauer in 1918, suggested that toxaemia of pregnancy was endocrine in origin. Solomons in 1922 thought that the disease was toxic in origin and that the specific toxin was derived from the placenta either from the villi or from the infarcts or from the blood. He also thought that excess of food might be an indirect cause of toxaemia of pregnancy.

De Wesselow & Wyatt (1922) however, did not agree with the toxaemic theory, and thought that depletion of calcium salts could increase the nervous excitability. They suggested that symptoms of eclampsia were due to a generalized vascular distur-
bance. These authors mentioned an additional theory of a rise in the fibrinogen content of the blood in toxaemia; a rise in ferment with intravascular clotting, thrombosis and damage to the parenchymatous organs as a result.

The work of Harding and Van Wyck (1922) again, directed the attention towards the dietary salt intake by pointing out that salt was responsible in the production of toxaemia of late pregnancy.

Fishberg (1922) commented that eclampsia occurred in women who had Kidney of pregnancy and eclampsia was a typical variety of hypertensive encephalopathy. No difference existed between pre-eclampsia and eclampsia other than presence or absence of convulsions. He thought it was probable that cerebral vasoconstriction was the cause of seizure, and that circulatory disturbances took place in various organs as the result of vasoconstriction. The Kidney of pregnancy could be caused by this condition.

MacIlroy (1922) quoted that the foetus and its mother might have been together in "harmonious symbiosis". If the adjustment failed, the ovum acted as a parasite and tended to poison its hostess, by special demands upon her liver. The failure of the placenta to prevent the transmission of toxic substances from or to the ovum played a considerable part in the toxaemia.

Mills (1924) believed in pituitary origin and the diagnosis was made by ophthalmoscopic examinations.

Cary (1925) observed that toxaemia was due to a toxic substance in the nature of a split product of protein molecules.
Placental autolysis was the source of toxaemia. The intestine absorbed products of bacterial origin and might form the primary foci of infection.

In 1927, Cruickshank et al., pointed out that toxaemia meant a poison in the circulation and that eclampsia was unknown among animals being only associated with the human pregnancy. The above authors thought it was a likely explanation that the placenta elaborated toxins from its circulation or from autolysis of its tissues.

Frances Ivens (1927) gave latent and autogenous infection as a cause of the toxaemias of pregnancy, especially if there were lowered resistance.

Like Fishberg, Zangemeister also thought (1927) that eclampsia occurred in association with the kidney of pregnancy, and was more marked in primigravid woman.

Titus and Dodds (1928) believed that toxaemia was a disturbance of carbohydrate metabolism and that there was a deficiency of intake with depletion of the glycogen stores and consequent damage to the liver and its functions. Eclamptic fits according to him were controllable by glucose administration.

Paramore (1928) also suggested derangements of metabolism which originated from excessive intraabdominal pressure. He felt that eclampsia occurred most often in the strongest type of women with good abdominal walls.

Stander (1929) postulated that the most important symptom in toxaemia was hypertension and this was caused by endocrine
dysfunction probably hyperfunction of the hypophysis. He referred to capillary spasm and increased cerebral pressure in eclampsia; he stressed the importance of decreased oxidation and the increased irritability of the whole nervous and muscular mechanism.

In the same year Tweedy (1929) of Dublin School postulated that excessive diet intake was the main cause of toxaemia and that partially digested proteins together with the proteins from the foetus were harmful.

In 1930, Whitridge Williams after taking several distinct entities into consideration, concluded that the etiology of toxaemia was still to be discovered.

Stroganoff (1930) suggested that placental syncytial elements and secretions got into the blood stream and were acted upon by the antibodies to some extent. When these elements were not neutralized, such as leucin caused change in the liver. Other products affected the Kidneys, brain and endocrines-especially the pituitary and the suprarenals. Their hormones entered the blood and angiospasm or vascular spasm was the result. Stroganoff laid great stress upon the increased nervous irritability and spasm in pregnancy.

Experiments of Anselmino & Hoffman (1931) on animals with posterior lobe injections showed results similar to eclampsia which made them believe that there existed a disturbance between the thyroid and pituitary balance and hyperfunction of the posterior pituitary played a major role.

Eden and Holland (1931) were inclined to the view that placenta was the cause.
McCallum (1932) thought that in toxaemia, there was a great disturbance of metabolism. He felt that haemorrhagic patches in liver and necrosis on post mortem examination pointed to presence of toxic substances in the portal circulation.

Browne (1932) found that whatever the cause might be of preeclamptic toxaemia, some toxic agent directly caused the symptoms and signs.

Munro Kerr (1933) pointed that late pregnancy toxaemia resulted from earlier disturbances and that early pregnancy condition need more attention.

Green Armytage (1933) quoted that "the pendulum of opinion is swinging towards the conclusion that the so-called toxaemia of pregnancy is primarily a pluriglandular endocrinal upset and that most of the symptoms were due to toxins from the bowel which primarily injure the hypophysis. Hitherto the placenta has borne the burnt of the blame".

At the same time Theobald (1933) was of the opinion that toxaemia was a deficiency disease like beri-beri which occurred due to a faulty diet.

On the other hand Baird and Shaw Dunn (1933) laid stress on the influence of previous renal lesions as a factor in the causation of eclampsia.

Disturbances of endocrine function were believed to be the cause of toxaemia of pregnancy by Goodall (1933) and Fishberg (1934).

Traut and Kuder (1934) postulated that toxic conditions caused placental infarcts (and not the converse as young believed) and could be the cause of toxaemia.
Goldblatt et al (1934) produced prolonged hypertension in experimental animals by constriction of renal arteries and postulated that ischaemic kidneys released an enzyme, renin, from its cortex which activated a plasma globulin hypertensigen, to form hypertensin, which was again a pressor substance and was responsible for hypertension.

Byrom (1938) thought that vascular system became sensitized to pressor agents in the later weeks of pregnancy and published experimental evidences to show that oestrogens were to be blamed for these changes.

Browne and Dodds (1939) suggested that potential hypertensive cases used to get their hypertensions unfolded by pregnancy.

Cheslay (1940) investigated the renal blood flow by using clearance techniques and observed no alteration of blood flow in toxaemia patients and Pickering (1945) also was of the opinion that renal ischaemia and renin release could not explain the occurrence of toxaemia as repeated injections of renin could not maintain a persistence hypertension.

Taylor et al (1943) suggested that oestrogen and progesterone could lead to the retention of sodium chloride and water. But objections to this was raised by Theobald (1946) who concluded that oestrogen and progesterone were found to be lowered in toxaemias of pregnancy and moreover the diuresis which took place after delivery was not accompanied by any sodium loss from the body.

Browne (1946) on the other hand thought that excess chorionic gonadotrophin in circulation sensitized the vascular system to pressor substances.
Seegal et al (1946) postulated that preeclampsia-eclampsia was an auto-immune disease in which the mother produced antibodies to the foreign antigens of the foetus and placenta.

Schneider (1947) suggested the possibility of onset of acute intravascular clotting in cases of eclampsia.

Smith and Smith (1948) postulated that reduction in supply of progesterone led to abnormal metabolism of oestrogen when accumulation of "inactive oxidation products" resulted. In normal pregnancy, these inactive oxidation products stimulated the conversion of placental chorionic gonadotrophin to oestrogen and progesterone so that the balance remained; but this mechanism failed in toxaemia, and level of chorionic gonadotrophin rose at the cost of oestrogen and progesterone. As a consequence, placenta and uterine decidua became ischaemic and released a toxin into the blood stream, which was named "Menotoxin" by Smiths. It was supposed to cause preeclampsia-eclampsia by virtue of its vaso-constricting and tissue destroying properties.

Shorr (1948) described a pressor substance which he found in the blood of experimental animals, called vasoexcitor substance or V.E.M., which lend support to the Trueta shunt theory of Cortico-medullary deviation of blood flow within the Kidney substance in response to a nervous stimulus from uterine wall as a result of overdistension of uterus.

Page (1948) and Beker (1948) assumed that increased intrabdominal pressure could precipitate uterine ischaemia and thereby cellular anoxia of uterus and placenta, releasing metabolic toxins into the maternal blood stream. But Sommerville et al (1949) supported the "Menotoxin" theory of Smith & Smith. Experi-
mental support to the theory of increased intraabdominal pressure were again offered by Bastiaarnse and Mastboon (1950).

Inactivation of placental enzymes due to ischaemia were thought by some to be the cause of Toxaemia; while Ahlmark and Werko (1950) thought the enzyme responsible was 'histaminase', Thompson and Tickner (1950) postulated the 'mono-aminooxidase' theory.

Kenny et al (1950) after experimentation claimed that there existed a reduction in renal blood flow in pregnancy toxaemia.

Dieckmann (1950) thought endocrine disturbances could cause retention of sodium chloride and predispose toxaemia of pregnancy.

Scrimshaw (1950) after studying the effects of 'poor' and 'good' diet on 10,000 women opposed the views of King and Ride (1945) who postulated that Vitamin-B deficient diet could cause toxaemia; Scrimshaw observed that dietetic deficiency had no role in the etiology of toxaemia of pregnancy.

Kellar (1950) had measured the blood flow through the liver, brain, kidney, arms and skin in normal pregnancy and toxaemia subjects. Since he observed no difference in blood flow, he argued that hypertension of preeclampsia must be due mainly to an increase in the peripheral resistance caused by arteriolar vasoconstriction.

Assali (1950) observed that autonomic ganglion blocking drugs which were so effective in essential hypertension could
not control the blood pressures of toxaemia of pregnancy. He therefore concluded that the mechanism of maintaining the hypertension was entirely different in essential hypertension and toxaemias of pregnancy, being neurogenic in former and humoral in later. He thought that the widespread pathological lesions of preeclampsia-eclampsia could be explained on the basis of generalised spasm of peripheral vessels. Brill et al (1951) supported the above theory by claiming that they were able to detect ocular vasospasm with the use of flicker photometer in preeclampsia.

Schneider (1951) produced in mice liver, fibrin deposition and capillary thrombosis, just as found in human eclampsia, by intravenous injection of human placental extract and he identified the lethal factor as thromboplastin. Page et al (1951) supported the theory of Schneider that eclampsia was the result of sudden intravascular clotting. Such an occurrence could also produce a rise of fibrin degradation product in circulation. This observation could explain the occurrences of bleeding from the gums, skin petechiae and excessive bleeding from surgical incision.

In 1952, Mastboon and Lloyd on separate observations found a rise of corticosteroids in the urine of toxaemia patients. They postulated that desoxycorticosterone-poisoning had striking similarity with toxaemia of pregnancy where hypertension, oedema and albuminuria were characteristic. Both the conditions could be worsened by giving sodium chloride. It was thought that these corticosteroid substances originated either in the adrenal gland or in the placentas.
Govan (1952) believed that there was elevated gonadotrophin in toxaemia of pregnancy but according to him this came from increased excretion of pituitary gonadotrophin and were not chorionic gonadotrophin. Loraline and Matthew (1953) however, maintained that excess chorionic gonadotrophin was the background of toxaemia.

Bucht and Werko (1953) supported the renal ischaemia theory and Sophian (1953) also believed that renal cortical ischaemia caused albuminuria and ultimately led to the release of pressor substances which in turn caused hypertension and water retention as was postulated by Traueta.

Wylie (1953) however, sponsored the theory of increased abdominal pressure which caused diminution in the blood flow to the placenta, responsible for eclampsia. Walker and Turnbull (1953) brought forward the indirect evidence of reduced placental blood flow in human toxaemias of pregnancy. Browne and Veall (1953) and Morris (1955) further supported this theory by measuring the clearance rates of radioactive saline, injected through the abdomen into the uterine wall, when they found a much delayed clearance rate in toxaemia subjects. Johnson and Clayton (1957) and Dixon et al (1963) expressed similar views.

Contrary to the placental ischaemia theory, Page (1953) suggested that liberation of thromboplastin from placenta played an important role in the causation of eclampsia. McKay et al (1953) found widespread fibrin deposition in some fatal cases of eclampsia.
Kumar (1962) could produce hypertension and proteinuria in pregnant dogs after producing artificial ischaemia by tying the uterine and ovarian arteries but he failed to produce oedema.

Steblay (1962) had shown that trophoblast had antigens that crossreacted with glomerular basement membrane antigens and antibodies from one would be expected to damage the other.

Berger and Caranagh (1963) induced hypertension in intact and nephrectomized pregnant rabbits by obstructing the placental blood flow. Most of the above works were suggestive of the theory of placental ischaemia in causing preeclampsia.

By demonstrating in toxaemic patients antiplacental antibodies which were conspicuously absent in normal subjects, Hulka and Brinton (1963) suggested the immunological background.

McKay (1964) contended that the lesions of preeclampsia and eclampsia represented a generalised Shwartzman reaction to products of decidual trophoblastic degenerations. Bellar (1964) also had similar views.

McKay (1965) also observed that there existed a low grade intravascular coagulation in toxaemic subjects and convulsion was caused by sudden agglutination of platelets and formation of platelet & fibrin thrombi which in turn obstructed the cerebral microcirculation. Hjort and Rapaport (1965), Vassalli and McCluskey (1965) supported the assumption of intravascular coagulation in eclampsia. Jaamgri et al (1965) had shown that there were presence of much more (twenty times) trophoblastic tissues in the uterine vein of preeclampsia patients in comparison to the normal pregnancy.
Jeffcoate (1966) reviewed and discussed various theories of toxaemia and thought toxaemia of pregnancy still remained "disease of theories". He, however, did not include coagulation changes in his discussion.

Irino et al (1967) and Curzen (1968) supported the work of Steblay as mentioned earlier.

Bonnar et al (1969) found a raised fibrin degradation product level in toxaemic subjects. Passage of foetal white blood cells across the placental barrier was well known and Terasaki et al (1970) postulated that foetal W.B.C. stimulated the formation of antibodies in the mother. Subsequently, the fetus attempted to reject the mother, and the antigen antibody complex formed could be responsible for the fibrin deposition between placental villi, the spiral arteries and the glomerular basement membrane.

Henderson et al (1970), Bonnar et al (1971), and Birmingham Eclampsia study group (1971) reported gross depression of the plasma fibrinolytic activity, increased level of serum fibrin degradation products and reduced platelet counts in preeclamptic subjects.

Page (1972) had brilliantly collected together most of the facts and theories relating to preeclampsia into a persuasive circular argument about the causation without committing himself the most likely cause.

Thus, it is most reasonable to think that pregnancy hypertension may not have a single aetiological starting point. Fashionable theories change and the most plausible current theories about the cause of toxaemia are i) coagulopathy, ii) immune
disease and iii) increased vascular sensitivity to circulating vasopressor substance (Studd 1978).

Present day views of Toxaemias of Pregnancy:

Definition

The unsatisfactory term 'toxaemias of pregnancy' had been variably applied to any or all disorders in which hypertension, proteinuria or oedema was evident during pregnancy or the puerperium. The Committee on Terminology of the American College of Obstetricians and Gynaecologists suggested, instead the following definition (Hughes 1972):

"Preeclampsia is the development of hypertension with proteinuria, oedema, or both, induced by pregnancy after the twentieth week of gestation and sometimes earlier when there is extensive hydatidiform changes in the chorionic villi. Eclampsia is the occurrence of convulsions, not caused by any coincidental neurologic disease such as epilepsy, in a woman who fulfills the criteria for preeclampsia".

Diagnosis:

While diagnosing preeclampsia it has to be kept in mind that mild preeclampsia may actually be one of the several diseases like preeclampsia with nephropathy, transient hypertension in women destined to develop essential hypertension in later life etc. (Studd 1978). McCartney (1964) found good number of chronic renal lesions by renal biopsy. However, renal biopsy is rarely justified during pregnancy and many nephropathies may possibly
pass undiagnosed. Patients with latent essential hypertension also pose similar problems. Subsequent developments of hypertension were found in many women who had preeclampsia-eclampsia earlier (Chasley et al, 1964). Chasley (1975) also argued convincingly that the clinical diagnosis of preeclampsia in multigravidae were often erroneous, as the underlying lesion were in reality either essential hypertension or chronic renal disease.

**Hypertension** - The hypertension of preeclampsia-eclampsia is believed to be humoral rather than neurogenic in origin and the presence of an increased vasoresponsiveness to pressor substances in preeclampsia has been established. Hunter and Howard (1961) demonstrated the presence of pressor substances in the amniotic fluid, placental and decidual extracts and subsequently in the plasma of preeclampsia cases. Recently Symonds et al (1975), contrary to the findings of Weir et al (1973) reported in the plasma of preeclampsia patients, an elevation of renin and angiotensin II, which decreased following bedrest and normalisation of blood pressure.

**Proteinuria** - Proteinuria may arise by one of the four mechanisms as follows (Hardwicke 1967):

1. Escape of normal plasma proteins through a defective glomerular basement membrane.
2. Failure of tubular reabsorption of proteins.
3. Loss of tissue proteins from renal parenchyma ureter or bladder.
4. Loss of abnormal plasma proteins.
In preeclampsia the urine was found to contain albumin, transferrin, and Ig G and thus the origin of proteinuria was believed to be a glomerular leak of normal plasma proteins of intermediate molecular size with virtually no contribution from tubular dysfunction and no detectable tissue proteins from the renal tract (Holman 1969; Studd 1973). Studd (1973) further postulated that the presence of fibrin within the glomerulus altered the functional integrity of the filtering mechanism. Later, Wood et al (1976) suggested that increase in the filtration force following raised afferent glomerular arteriolar pressure produced a "vasoactive" glomerular leak and a porous pattern emerged in more advanced cases (Studd and Wood, 1976). These changes must have a significant effect upon the coagulopathy and renal fibrination, as well as one the hypovolaemia and the oedema of preeclampsia (Studd 1975).

Oedema - It has been observed that tissue hydration, an oestrogen effect is invariable in normal pregnancy. Oedema probably occurs due to an increase in the capillary pressure and a fall in the plasma osmotic pressure due to hypocalbuminaemia of pregnancy and preeclampsia which results in the shift of body fluid from intravascular to extravascular space (Robertsen 1971). Gloeren et al (1972) used to believe that preeclampsia patients remained in a state of latent shock and its hypovolaemia might be corrected by human albumin (low salt) infusion. Mukherjee and Govan (1950) did not find any difference in the protein content of oedema fluid in preeclampsia-eclampsia in comparison to that in others. The oedema of preeclampsia is distributed pretibially,
on the extremities of the hand, in the facial tissues and may occur with an alarming speed. Although the aldosterone levels in preeclamptic patients are found to be lower than normal pregnancy yet the acute onset of oedema, highly concentrated urine etc. appear to be aldosterone mediated in origin.

Pathophysiology

Vasospasm - Vasospasm is basic to the disease process of preeclampsia-eclampsia. The vascular constriction imposes a resistance to blood flow and accounts for the arterial hypertension. Vasospasm most likely exerts noxious effect on the blood vessels themselves, as well as the organs they supply. Circulation in the vasa-vasorum is impaired, leading to damage of the vascular walls. Alternating segmental dilatation that commonly accompanies the segmental arteriolar spasm probably contributes further to the development of vascular damage, since endothelial integrity may be compromised by stretch in the dilated segments. Moreover, angiotensin appears to have a direct action on endothelial cells causing them to contract. These events can create interendothelial leaks through which the blood constituents, including platelets and fibrinogens, can pass and be deposited subendothelially (Brunner and Gavras, 1975). These vascular changes, together with local hypoxia of the surrounding tissues, presumably lead to haemorrhage, necrosis, and other disturbances that have been observed. Deposition of fibrin is then likely to be prominent.

In addition to vasospasm, there occurs an increased

Impaired organ functions

Uteroplacental changes - While precise measurements of uterine blood flow through the placenta are lacking, there is every reason to believe that placental perfusion by the mother is reduced in case of pregnancy-induced hypertension (Gant et al, 1972).

Hertig (1945) identified in preeclampsia a lesion of the uteroplacental arteries characterized by prominent lipid rich foam cells. Zeak and Assal (1950) concluded that the pathognomic lesion in preeclampsia might be termed 'acute atherosis'. Kitzmiller (1973) identified fibrin by immunologic means. On the basis of electron microscopic studies deWolf et al (1975) described the following: "Early preeclamptic changes include endothelial damage, insudation of plasma constituents into the vessel wall, proliferation of myointimal cells, and medial necrosis. Lipid accumulates first in the myointimal cells and secondarily in macrophages". When the syndrome is fully developed, presence of placental infarcts and retarded foetal growth point to reduced placental function (Pritchard 1976).

Renal changes - During pregnancy induced hypertension, renal perfusion and glomerular filtration is diminished. However, in absence of the chronic vascular disease, complete recovery of renal functions may be expected. Sheehan (1950), Farquhar (1959),
Spargo et al (1959), Pollak et al (1960), Mautner et al (1962) observed glomerular capillary endothelial swelling and subendothelial deposits of fibrin protein material. Homogeneous deposits of an electrodense substance were found between the basal lamina and the endothelial cells and also within the cells. Vassalli et al (1963) on the basis of immunofluorescent staining, considered the material to be fibrinogen or its derivative and regarded its presence as characteristic of preeclampsia. This observation led to the present day theory that renal lesions of preeclampsia-eclampsia are the result of intravascular coagulation, initiated by something presumably thromboplastin, released from placenta (Page 1972).

An alternative suggestion that an immunologic mechanism is responsible for renal lesions came from Petrucco et al (1974), who detected IgM and IgG and sometimes complement in the glomeruli of women of preeclampsia-eclampsia.

Tubular lesions are common in eclampsia and may represent an accumulation of proteins, reabsorbed from glomerular filtrate. In rare cases, renal cortical necrosis may be found.

**Hepatic Changes** - Hemorrhagic necrosis in the periphery of the liver lobule, identified commonly at autopsy, was long considered the characteristic lesion of eclampsia. However, in non-fatal cases this lesion is not always identifiable. It is presumed that the liver lesion is the effect of the disease and not the cause.
Heart - Subendocardial haemorrhage in the interventricular septum was found in many fatal cases of preeclampsia-eclampsia.

Lungs - The Birmingham Eclampsia Study Group (1971) suggested the possibility of fibrin deposition or embolization of trophoblast in the lungs. Small haemorrhages, scattered throughout the lungs had been reported in cases of severe preeclampsia.

Brain Changes - Haemorrhages, ranging from petechiae to gross bleeding is a common feature.

Govan described fibrinoid changes as a regular finding occasionally in the walls of cerebral vessels. The lesion appeared to be present for sometime, as judged from the surrounding leuco- cytic response and infiltration by pigmented macrophages, which suggested that the prodromal neurologic symptoms and the convulsions might be related to the lesion.

Coagulation System

The level of fibrinogen and plasminogen gradually increase during normal pregnancy. Allowing for the expansion of plasma volume, a woman in late pregnancy has almost twice the amount of circulating fibrinogen and plasminogen as in the non-pregnant state. Fibrinolytic activity in plasma decreases steadily during pregnancy and Astedt (1972) found that the normally high fibrinolytic activity in the blood in response to venous occlusion progressively diminished and was barely detectable at term. The placenta was shown to contain inhibitors which block urokinase-induced fibrinolysis (Kawano, Morimoto & Uemura, 1968; Uazynski & Abildgaard, 1971). The changes in the fibrinolytic activity may
be mediated by a direct or indirect effect of placental hormones on the synthesis of fibrinolytic activators in the vessel wall. Astedt (1972) showed that oestrogen & progesterone reduced the fibrinolytic activity of the blood.

Plasminogen activators in the blood is primarily responsible for fibrinolytic activity. Increased amount in the plasma can be detected after strenuous exercise, emotional stress, surgical operation & trauma. It is interesting to note that no increase in the fibrinolytic activity is found during labour until after the placenta is delivered. With the exception of placenta most human tissues contain activator.

It is possible, however, that as a result of the depression of fibrinolysis in pregnancy, extensive fibrin deposition can occur in the uteroplacental vasculature without any marked increase of fibrinogen degradation product (FDP) in circulation.

There is now good evidence that during late pregnancy physiological intravascular coagulation occurs in the uteroplacental circulation and this chronic process is the most likely explanation for the elevation of blood coagulation factors in normal pregnancy.

It is possible that deportation of thromboplastin rich trophoblasts or the leakage of amniotic fluid in maternal circulation may initiate these changes.

In preeclampsia-eclampsia syndrome, exaggerated trophoblastic deportation has been observed (Jaamari, 1965). A greater depression of plasma fibrinolytic activity (euglobulin lysis time)
than in normal pregnancy, a higher level of inhibitor to urokinase induced lysis and increased level of serum fibrin degradation products have also been found in preeclampsia-eclampsia (Bonnar 1971).

It is widely believed that there occurs a generalised Shwartzman reaction which denoted disseminated intravascular coagulation in preeclampsia-eclampsia (McKay et al, 1953, McKay 1965, Henderson 1970, Bonnar 1971, Birmingham eclampsia study group 1971, Page 1972). It is further suggested that in eclampsia the rate of intravascular coagulation is much more rapid and in preeclampsia it is rather a chronic process (Page 1972).

The trigger mechanism is not yet known. Bonnar et al, 1976 remarked "whatever the mechanism may be in the uteroplacental circulation, an excessive generation of thrombin which is not neutralized by natural inhibitor mechanisms, will result in intravascular coagulation and will involve kidneys. The resulting fibrin deposition will aggravate uteroplacental ischaemia and generate a self-perpetuating process that is terminated abruptly by delivery of the baby".