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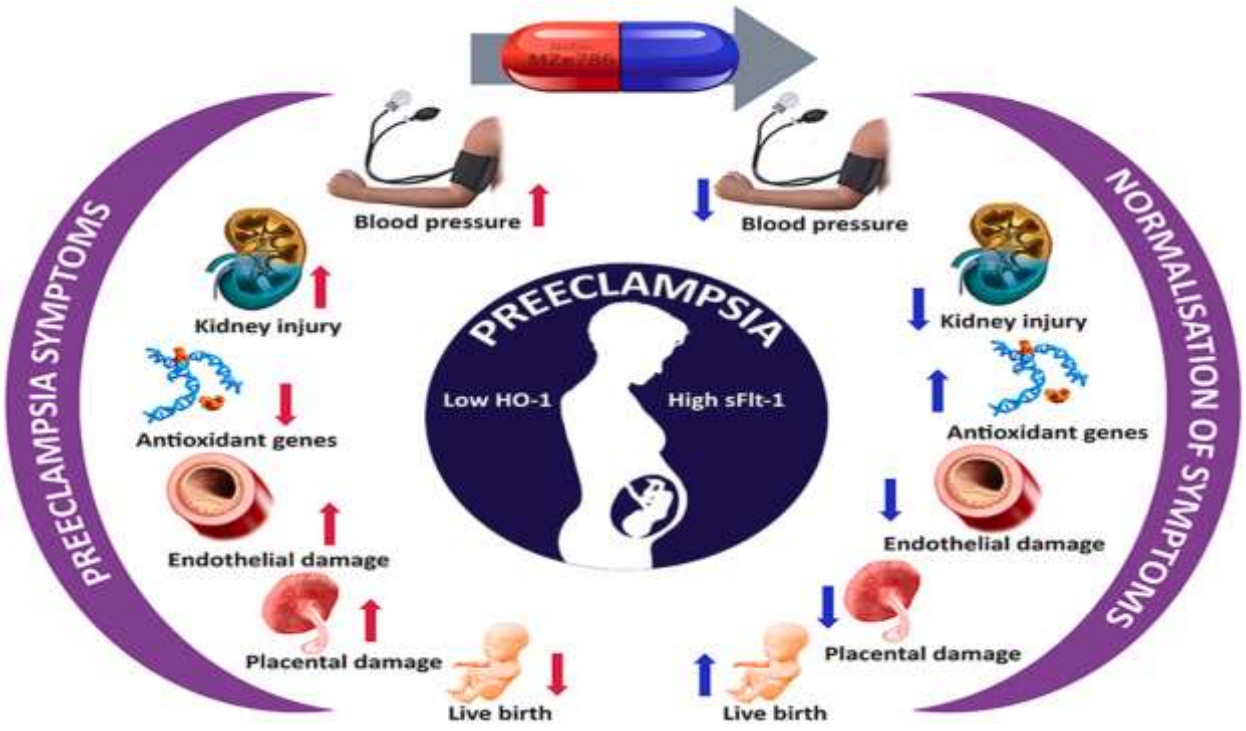
HYPERTENSIVE DISORDERS IN PREGNANCY

Methodical handbook for students of medical institutions, clinical residents and doctors



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Methodical handbook for 4-6 course students of medical institutions, clinical residents and doctors. Hypertensive disorders in pregnancy: gestational hypertension, chronic hypertension, preeclampsia, eclampsia, chronic hypertension with super imposed preeclampsia and eclampsia, HELLP syndrome.

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Abbreviations

APTT	Activated Partial thromboplastin time
AST	Aminotransferase
ALT	Alanine aminotransferase
ALA	Alpha-linoleic acid
ARDS	Adult respiratory distress syndrome
ARM	Artificial rupture of membranes
BP	Blood pressure
CT	Computer tomography
CAMM	clinical analysis of maternal mortality
CHD	Chronic hypertensive disease
CVP	Central venous pressure
DOC	Deoxycorticosterone
DHA	Docosahexaenoic acid
EEG	Electroencephalography
EPA	Eicosapentaenoic acid
FLAIR	Fluid-attenuated inversion recovery
HCG	Human chorionic gonadotropin
ICD	International Classification of Diseases
IL	Interleukins
IUFD	Intrauterine fetal distress
MAP	Mean arterial pressure
MRI	Magnetic Resonance Imaging
LVSWI	Left ventricular stroke work index.
NO	Nitric oxide
NICU	Neonatal intensive care unit
PAPP-A	Pregnancy-associated plasma protein A
PE	Pre-eclampsia
PI	Pulsatility index
PIH	Pregnancy-induced hypertension
PGI_2	Prostaglandin
PCWP	Pulmonary capillary wedge pressures
PRES	Posterior reversible encephalopathy syndrome
PlGF	Placental growth factor
RI	Resistive index
sFlt-1	Soluble Fms-like tyrosine kinase 1
sEng	Soluble endoglin
TXA_2	Thromboxane
TNF-a	Tumor necrosis factor
UOP	Urine output
VEGF	Vascular endothelial growth factor
VEGF	Vascular endothelial growth factor
WHO	World Health Organization

CONTENTS

ACTUALITY

Hypertension is one of the common medical complications of pregnancy and contributes significantly to maternal and perinatal morbidity and mortality. Hypertension is a sign of an underlying pathology which may be preexisting or appears for the first time during pregnancy. The identification of this clinical entity and effective management play a significant role in the outcome of pregnancy, both for the mother and the baby. In the developing countries with inadequately cared pregnancy, this entity on many occasions remains undetected till major complications supervene. (DC Dutta 9 edition).

How pregnancy incites or aggravates hypertension remains unsolved despite decades of intensive research. Indeed, hypertensive disorders remain among the most significant and intriguing unsolved problems in obstetrics.

Hypertensive disorders complicate 5 to 10 % of all pregnancies, and together they are one member of the deadly triad along with hemorrhage and infection – that contributes greatly to maternal morbidity and mortality. Of these disorders, the preeclampsia syndrome, either alone or superimposed on chronic hypertension, is the most dangerous. As subsequently discussed, new-onset hypertension during pregnancy – termed gestation hypertension – is followed by sings and symptoms of preeclampsia almost half the time, and preeclampsia is identified in 3.9 %t of all pregnancies.

Preeclampsia is one of the most complex and important problems of scientific and practical obstetrics. According to WHO, preeclampsia is diagnosed in 28 percent of pregnant women. Preeclampsia accounts for between 1.3 and 6.7 percent of all pregnancies and remains a leading cause of maternal and perinatal morbidity and mortality worldwide (Williams 24 edition).

The World Health Organization (WHO) systematically reviews maternal mortality worldwide, and in developed countries, 16 percent of maternal deaths were reported to be due to hypertensive disorders. (Williams 24 edition). Maternal

mortality due to hypertensive disorders is 7.1%, which is in the second place after postpartumhaemorrhagein the Kyrgyz Republic (National CRMS report (2014-2015.). In India, the incidence of preeclampsia is reported to be 8-10% among the pregnant women. According to a study, the prevalence of hypertensive disorders of pregnancy was 7.8 % with preeclampsia in 5.4% of the study population.

The purpose of the lesson:

To study etiologypathogenesis, pathophisiology, clinical manifestations, methods of diagnosis, differential diagnosis, management according to ICD-X, complications, prognosis and prevention of hypertensive disorders in pregnancy.

Learning objectives:

- Define mild and severe preeclampsia, eclampsia, gestational hypertension, chronic hypertension, HELLP syndrome;
- Understand the pathophysiology of preeclampsia, eclampsia;
- Identify patients at risk of preeclampsia and discuss prevention strategies;
- Recognize and explain possible maternal consequences of preeclampsia, eclampsia, HELLP syndrome;
- Explain and discuss the management of preeclampsia. Including:
    - Assessment of maternal condition;
    - Assessment of fetal condition;
    - Delivery considerations, including timing and mode of delivery;
    - Medical considerations, including antihypertensive drugs, analgesics, MgSO4, drug availability and preparing and mixing drugs;
    - Discuss delivery considerations in preeclampsia;
    - Discuss investigations to come to evidence based medicine guidelines for low- and middle income country setting;
    - Counsel patients on the risk for recurrence in future pregnancy and long term health consequences;
    - Understand importance of family planning after event of hypertensive

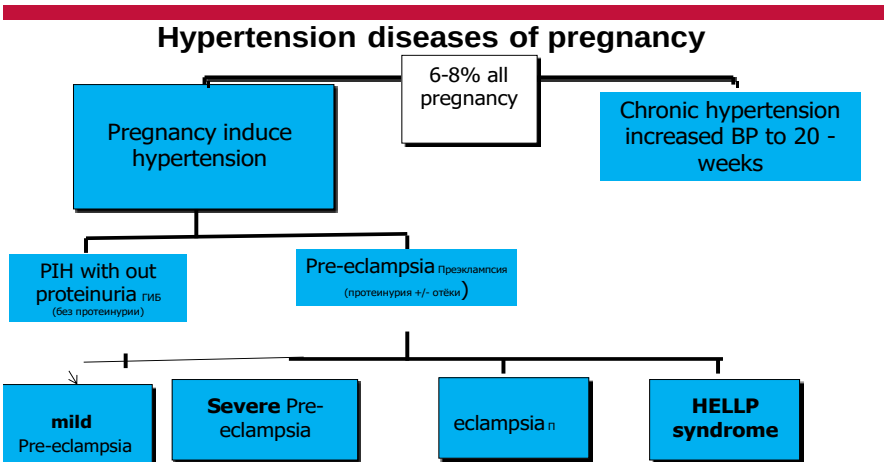
disorder in pregnancy;

- Differentiate gestational hypertension, chronic hypertension, preeclampsia, eclampsia, HELLP syndrome.

PREGNANCY-INDUCED HYPERTENSION

Pregnancy-induced hypertension (PIH) - hypertension that develops as a direct result of the gravid state. It includes—(i) gestational hypertension, (ii) pre-eclampsia, and (iii) eclampsia

Classification by ICD-X



Classification of hypertension in pregnancy			
Hypertension	BP >140/90 mm Hg measured 2 times with at least a 6-hour interval	*Chronic hypertension with super imposed pre-eclampsia and eclampsia*	• The common causes of chronic hypertension: • Essential hypertension • Chronic renal disease (reno vascular) • Coarctation of aorta • Endocrine disorders (diabetes mel- litus, pheochromocytoma, thyrotoxicosis • Connective tissue diseases (Lupus erythematosus). • The criteria for diagnosis of super imposed pre-eclampsia: • New onset of proteinuria >0.5 gm/24 hours specimen.
Proteinuria	Urinary excretion of > 0.3 gm protein/24 hours specimen or 0.1 gm/L		
Gestational hypertension	BP >140/90 mm Hg for the first time in pregnancy after 20 weeks, without proteinuria		
Pre-eclampsia	Gestational hypertension with proteinuria		

			• Aggravation of hypertension. • Thrombocytopenia or • Raise of liver enzymes
Eclampsia	Women with pre-eclampsia complicated with convulsions and/ or coma		
Chronic hypertension	Known hypertension before pregnancy or hypertension diagnosed first time before 20 weeks of pregnancy		
Superimposed pre-eclampsia or eclampsia	Occurrence of new onset of proteinuria in women with chronic hypertension		

PREECLAMPSIA

DEFINITION: Preeclampsia is a multisystem disorder of unknown etiology characterized by development of hypertension to the extent of 140/90 mm Hg or more with proteinuria (≥ 0,3 g/day) after the 20th week in a previously normotensive and nonproteinuric woman. Some amount of edema is common in a normal pregnancy. Edema has been excluded from the diagnostic criteria unless it is pathological. The preeclamptic features may appear even before the 20th week as in cases of hydatidiform mole and acute polyhydramnios.

Preeclampsia is a polysystemic syndrome that reflects the inability of the adaptation mechanisms of the maternal organism to adequately provide requirements of the growing fetus, expressed by increased blood pressure and proteinuria.

RISK FACTORS FOR PRE-ECLAMPSIA

1. Clinical and anamnestic risk factors for the development of PE:

- primigravidae;
- multigravida (last interval more than 10 years);
- family history (PE in mother or sister);

- elder age of women (more than 35 years);
- multiple pregnancy;
- extragenital diseases (chronic hypertension, kidney diseases, liver, connective tissue, vascular diseases, diabetes);
- pre-existing vascular disease: thrombophilias (antiphospholipid syndrome, protein Cdeficiency);
- obesity: BMI >35 kg/M^2, Insulin resistance, metabolic syndrome;
- diastolic blood pressure-80 mm Hg and higher;
- pathological weight gain during pregnancy;
- proteinuria during pregnancy (more than one + with double test or ≥ 300 mg/per day);
- oligouria (900 ml or less) and nikturia (> 75 ml);
- placental abnormalities: hyperplacentosis: excessive exposure to chorionic villi — (molar pregnancy twins, diabetes), placental ischemia.

2. Hemodynamic risk factors for development of PE:

- unstable of blood pressure in the first trimester of pregnancy;
- increase in diastolic blood pressure at night according to daily monitoring;
- detection of asymmetry in blood pressure on both hands more than 10 mm Hg, decrease pulse pressure varation to 30 mm Hg and lower (the N - is 40-50 mm Hg), and increase blood pressure more than 10-20 mm Hg;
- increasing Resistive index (RI) or pulsatility index (PI) in the uterine arteries according to the doppler velocimetry of uterine arteryat 7-15 weeks of pregnancy.

3. Biochemical risk factors of development of PE:

- hypercoagulation (thrombocytopenia less than 160 × 109/l, increased platelet aggregation up to 76 %, decreased APTT (< 20 s), hyperfibrinogenemia 4-5 g / l or more, increased hematocritlevel more than 0.46);

- reducing the level of anticoagulants: endogenous heparin and antithrombin III;
- hypoproteinemia (60 g / l or less); dysproteinemia with a decrease albumin-globulin ratio (< 0.5);
- decrease in the first trimester of pregnancy-associated plasma protein A (PAPP-A) < 5th percentile;
- unexplained increase in the second trimester pregnancy alpha-fetoprotein (> 2.5 MoM multiple of median);
- increase in the second trimester human chorionic gonadotropin (HCG) (> 3 mIU/mL);
- increase in the I or II trimester of inhibin A (> 2 mIU/mL).

ETIOLOGY OF PRE-ECLAMPSIA

There are an imposing number of mechanisms have been proposed to explain its cause:

1. Placental implantation with abnormal trophoblastic invasion of uterine vessels
2. Immunological maladaptive tolerance between maternal, paternal (placental), fetal tissues
3. Maternal maladaptation to cardiovascular or inflammatory changes of normal pregnancy
4. Genetic factors including inherited predisposing genes and epigenetic influences.

Abnormal trophoblastic invasion. Normal implantation is characterized by extensive remodeling of the spiral arterioles within the decidua basalis. Endovascular trophoblasts replace the vascular endothelial and muscular linings to enlarge the vessel diameter, veins invased superficially. In some cases of preeclampsia, there may be incomplete trophoblastic invasion. With this, decidual vessels, but not myometrial vessels, become lined with endovascular trophoblasts.

Deeper myometrial arterioles do not lose their endothelial lining and musculoelastic tissues, and mean external diameter is only half that of corresponding vessels in normal placentas. In general, the magnitude of defective trophoblastic invasion is thought to correlate with severity of the hypertensive disorder.

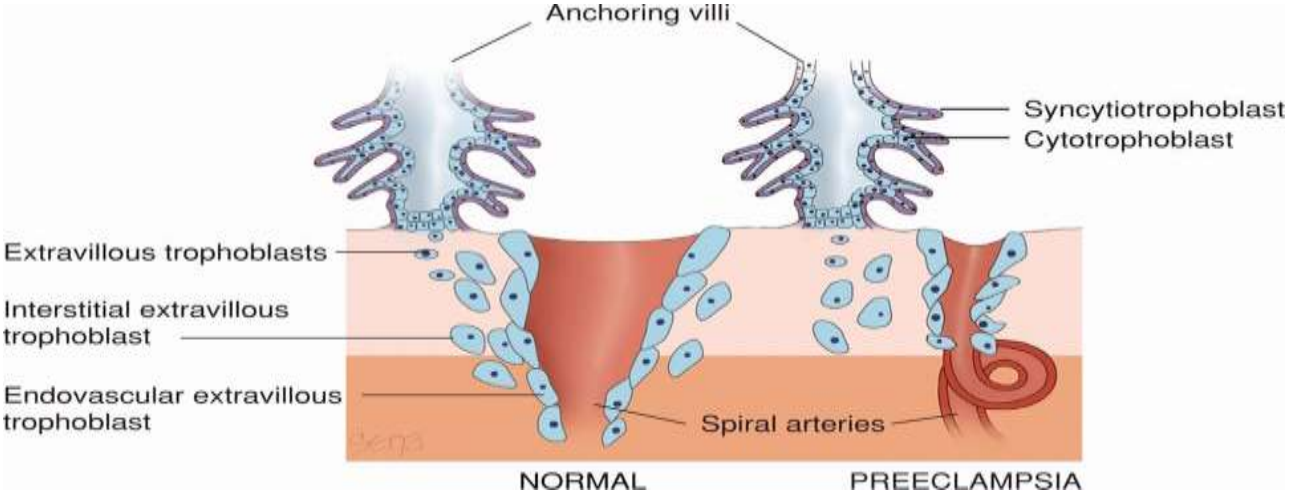


Fig. 1. Schematic representation of normal placental implantation shows proliferation of extravilluos trophoblasts from an anchoring villus. These trophoblasts invade the deciduas and extend into the walls of the spiral arteriole to replace the endothelium and muscular wall to create a dilated low-resistance vessel. With preeclampsia, there is defective implantation characterized by incomplete invasion of the spiral arteriolar wall by extravillous trophoblasts.This results in a small-caliber vessel with high resistance to flow.

Defective placentation is posited to further cause the susceptible (pregnant) woman to develop gestational hypertension, the preeclampsia syndrome, preterm delivery, a growth restricted fetus, and/or placental abruption. Acute atherosis is identifesa group of women at increased risk for later atherosclerosis and cardiovascular disease.

Trophoblast invasion and uterine vascular changes. Normally, there is invasion of the endovascular trophoblasts into the walls of the the spiral arterioles of the uteroplacental bed. In the first trimester (10-12 weeks) endovascular trophoblasts invades up to decidual segments and in the second trimester (16-18 weeks) another wave of trophoblasts invades upto the myometrial segments (Fig. 2). This process replaces the endothelial lining and the muscular arterial wall by fibrinoid formation. The spiral arterioles thereby become distended, tortuous, and

funnel-shaped. This physiological change transforms the spiral arterioles into a low resistance, low pressure, high flow system. In pre-eclampsia, there is failure of the second wave of endovascular trophoblast migration and there is reduction of blood supply to the fetoplacental unit.

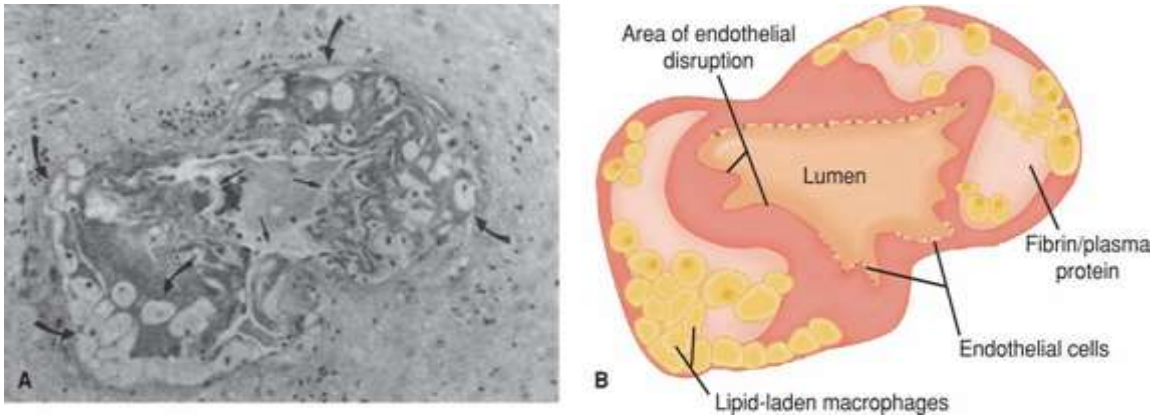


Fig. 2. Atherosis in a blood vessel from a placental bed. A. Photomicrograph shows disruption of the endothelium that results in a narrowed lumen because of subendotelial accumulation of plasma proteins and foamy macrophages. Some of the foamy macrophages are shown by curved arrows, and straight arrows highlight areas of endothelial disruption. B. Schematic diagram of the photomicrograph.

In normal pregnancy:

1. Angiotensin-II (part of a_2 globulin) is destroyed by angiotensinase, which is liberated from the placenta. Thus, the blood pressure is stabilized.
2. The vascular system becomes refractory, selectively to pressor agent angiotensin-II. This is probably brought out by vascular synthesis of prostaglandin I_2 and nitric oxide (NO) which have got vasodilator effect. The interaction between the two systems stabilises the blood pressure in normal pregnancy. Vascular endothelial growth factor (a mitogenic glycoprotein) — increased VEGF restores the uteroplacental blood flow to normal level.

In pre-eclampsia:

There is an imbalance in different components of prostaglandins—relative orabsolute deficiency of vasodilator prostaglandin (PGI_2) from vascular endothelium and increased synthesis of thromboxane (TXA_2), a potent vasoconstrictor in platelets.

There is increased vascular sensitivity to the pressor agent angiotensin-II.

Angiotensinase activity is depressed, following proteinuria with elimination of a_2 globulin (see scheme for pathophysiology).

1. Nitric oxide (NO): It is synthesized in the vascular endothelium and syncytiotrophoblast from L-arginine. It significantly relaxes vascular smooth muscle, inhibits platelet aggregation and prevents intervillous thrombosis. Deficiency of nitric oxide contributes to the development of hypertension.
2. Endothelin-1 is synthesized by endothelial cells, and it is a potent vasoconstrictor compared to angiotensin-II. Endothelin-1 also contributes to the cause of hypertension.
3. Inflammatory mediators: *Cytokines* [tumor necrosis factor (TNF-a), interleukins (IL-6) and others] derived from activated leukocytes cause endothelial injury
4. Abnormal lipid metabolism—results in more oxidative stress. *Lipid peroxides, reactive oxygen species (ROS) and superoxide anion radicals* — cause endothelial injury and dysfunction. Platelet and neutrophil activation, cytokines, superoxide radical production and endothelial damage are in a vicious cycle.
5. Others—mutation of factor V Leiden increases the risk.
6. Hence pre-eclampsia is characterized by endothelial dysfunction and vasospasm. Endothelial dysfunction is due to oxidative stress and the inflammatory mediators. Vasospasm results from the imbalance of vasodilators (PGI_2, NO) and vasoconstrictors (Angiotensin-II, TXA_2, Endothelin-1). Both are in a vicious cycle.

Immunological factors. Loss of materal immune tolerance, or perhaps its dysregulation, is another theory cited to account for preeclampsia. Certainly, the histological changes at the maternal-placental interface are suggestive of acute graft rejection. The risk of preeclampsia is appreciably enhanced in circumstances in which formation of blocking antibodies to placental antigenic sites might be impared. In this scenario, the first pregnancy would carry a higher risk. Tolerance dysregulation might also explain an increased risk when the paternal antigenic load is increased, that is, with two sets of paternal chromosomes - a “double dose”. Namely, women with molar pregnancies have a high incidence of early-onset

preeclampsia. Women with a trisomy 13 fetus also have a 30 percentincidence of preeclamsia. These women have elevated serum levels of antiangiogenic factors, and the gene for one of these factors, sFlt-1, is on chromosome 13. Conversely, women previously exposed to paternal antigens, such as a prior pregnancy with the same partner, are “immunized” against preeclampsia This phenomenon is not as apparent in women with a prior abortion. There is may be possible role of immune maladaptation in preeclampsia pathophisiology. In womn destined to be preeclamptic, extravillous trophoblasts early in pregnancy express reduced amounts of immunosuppressive nonclassic HLA G.

Endothelial cell activation. Inflamatory changes are believed to be a continuation of the stage 1 changes caused by defective placentation. In response to placental factors released by ischemic changes or by any other inciting cause, a cascade of events begins. Thus antiangiogenic and metabolic factors and other inflammatory mediators are thought to provoke endothelial cell injury.

Endothelial cell dysfunction may result from an extreme activated state of leukocytes in the maternal circulation. Briefly, cytokines such as tumor necrosis factor-a (TNF-a) and the interleukins (IL) may contribute to the oxidative stress associated with preeclampsia. This is characterized by reactive oxygen species and free radicals that lead to formation of self –propagating lipid peroxides. These in turn generate highly toxic radicals that injure endothelial cells, modify their nitric oxide production, and interfere with prostaglandin balance. Other consequences of oxidative stress include production of the lipid-laden macrophage foam cells seen in atherosis and shown in Table 1; activation of microvascular coagulation manifest by edema and proteinuria.

These observations on the effects of oxidative stress in preeclampsia have given rise increased interest in the potential benefit of antioxidants to prevent preeclampsia. Unfortunately, dietary supplementation with vitamins E (a-tocopherol) and C (acosbic acid) to prevent preeclampsiahas thus far proven unsuccessful.

Nutritional factors. A diet high in fruits and vegetables with antioxidant activity is associated with decreased blood pressure. Calcium supplementation in populations with a low dietary calcium intake had a small effect to lower perinatal mortality rates but no effect on preeclampsia incidence.

Genetic factors. From a hereditary viewpoint, PE is a multifactorial, polygenic disorder. An incident risk for PE of 20 to 40 percent for daughters of preeclamptic mothers, 11 to 37 percent for sisters of preeclamptic women; and 22 to 47 percent for twins; 60 percent concordance in monozygotic female twin pairs. Hereditary predisposition for preeclampsia likely is the result of interactions of literally hundreds of inherited genes-both maternal and paternal – that control myriad enzymatic and metabolic functions throughout every organ system. Phenotype expression will differ among similar genotypes depending o n interaction with environmental factors.

Table 1. Genes with possible associations with preeclampsia.

Gene (Polymorphism)	Function Affected
MTHFR (C677T)	Methylene tetrahydrofolate reductase
F5 (Leiden)	Factor V_{Leiden}
AGT (M235T)	Angiotensinogen
HLA (Various)	Human leukocyte antigens
NOS3 (Glu 298 Asp)	Endothelial nitric oxide
F2 (G20210A)	Prothrombin (factor II)
ACE (I/D[at]Intron 16)	Angiotensin-converting enzyme
CTLA4	Cytotoxic T-lymphocyte-associated protein
LPL	Lipoprotein lipase
SERPINE1	Serine peptidase inhibitor

Data from Buurma, 2013; Staines-Urias, 2012; Ward, 2014.

PATHOGENESIS OF PRE-ECLAMPSIA

Vasospasm. Endothelial activation causes vascular constriction with increased resistance and subsequent hypertension. At the same time, endothelial cell damage causes interstitial leakage through which blood constituents, including platelets and fibrinogen, are deposited subendothelially. Ultrastructural changes in

the subendothelial region of resistance arteries in preeclamptic women. Thus, much larger venous circuit is similarly, involved, and with diminished blood flow because of maldistribution, ischemia of the surrounding tissues can lead to necrosis, hemorrhage, and other end-organ disturbances characteristic of the syndrome. One important clinical correlate in the markedly, attenuated blood volume seen in women with severe preeclampsia.

Endothelial cell injury. Protein factors – likely placental - are secreted into the maternal circulation and provoke activation and and dysfunction of the vascular endothelium. Intact endothelium has anticoagulant properties, and endothelial cells blunt the response of vascular smooth muscle to agonists by releasing nitric oxide. Damaged or activated endothelial cells may produce less nitric oxide and secrete substances that promote coagulation and increase sensitivity to vasopressors. Further evidence of endothelial activation includes the characteristic changes in glomerular capillary endothelial morphology, increased capillary permeability, and elevated blood concentrations of substances associated with endothelial activation. These latter substances are transferable, and serum from women with preeclampsia stimulates some of these substances in greater amounts. It seems likely that multiple factors in plasma of preeclamptic women combine to have these vasoactive effects.

Increased pressor responses. Pregnant women normally develop refractoriness to infused vasopressors. Women with early preeclampsia, however, have increased vascular reactivity to infused nonepinephrine and angiotensin II. Morever, increased sensitivity to angiotensin II clearly precedes the onset of gestational hypertension.

Prostaglandins. Several proteinoids are thought to be central to preeclampsia syndrome pathophisiology. Specifically, the blunted pressor response seen in normal pregnancy is at least partially due to decreased vascular responsiveness mediated by endothelial prostaglandin synthesis. For example, compared with normal pregnancy, endothelial prostacyclin (PGI 2) production is decreased in

preeclampsia This action appears to be mediated by phospholipase A2. At the same time tromboxane A2 secretion by platelets is increased, and the prostacyclin: tromboxane A2 ratio decreases This result favors increased sensitivity to infused angiotensin II and, ultimately, vasoconstriction. These changes are apparent as early as 22 weeks in women who later develop preeclampsia.

Nitric oxide. This is potent vasodilator is synthesized from L-arginine by endothelial cells. Inhibition of nitric oxide synthesis increases mean arterial pressure, decreases heart rate, and reverses the pregnancy-induced refractoriness to vasopressors. It is maintain the normal low-pressure vasodilated state characteristic of fetoplacental perfusion. It is also produced by fetal endothelium, and here it response to preeclampsia, diabetes, and sepsis.

Endothelins. These 21-amino acid peptides are potent vasoconstrictors, and endothelin-1 (ET-1) is the primary isoform is produsedby human endothelium. Plasma ET-1 levels are increased in normotensive pregnant women, but women with preeclampsia have even higher levels. Interestingly, treatment of preeclamptic women with magnesium sulfate lowers ET-1 concentrations.

Angiogenic and antiangiogenic proteins. Placental vasculogenesis is evident by 21 days after conception. There is an ever-expanding list of pro- and antiangiogenic substances involved in placental vascular endothelial growth factor and angiprotein are most extensively studied. *Angiogenic imbalance* is used to describeexcessive amounts of angiogenic factors that are hypothesized to be stimulated by worsening hypoxia at the uteroplacental interface. Trophoblast of women destined to develop preeclampsia overproduces at least two antoangiogenic peptides that enter the maternal circulation:

1. Soluble Fms-like tyrosine kinase 1 (sFlt-1)
2. Soluble endoglin (sEng)

These proteins cause of placental overproduction of antiangiogenic proteins remains an enigma. Concentrations of soluble forms are not increased in the fetal circulation or amnionic fluids, and their levels in maternal blood dissipate after

delivery.

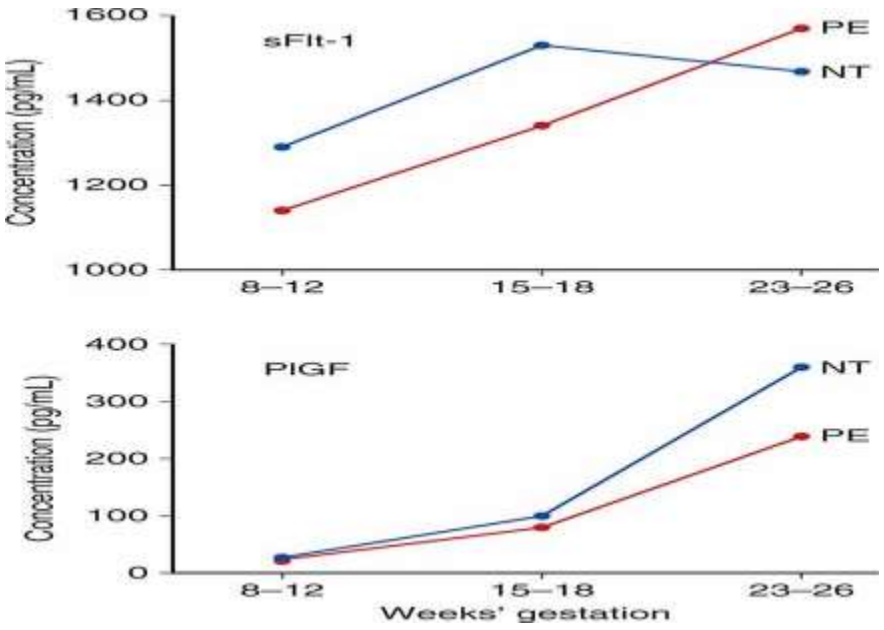


Fig. 3. Angiogenic and antiangiogenic factors in normotensive (NT) and preeclamptic (PE) women across pregnancy. Both pairs of factors are significantly divergent by 23 to 26 weeks sFlt – soluble Fms-like tyrosine kinase 1, PIGF – placental growth factor.

PATHOPHYSIOLOGY OF PRE-ECLAMPSIA

Although the cause of preeclampsia remains unknown, evidence for its manifestation begins early in pregnancy with covert pathophysiological changes that gain momentum across gestation and eventually become clinically apparent. Unless delivery supervenes, these changes ultimately result in multiorgan involvement with a clinical spectrum ranging from an attenuated manifestation to one of cataclysmic deterioration that is life threatening for both mother and fetus. Although the many maternal consequences of the preeclampsia syndrome are usually described in terms of individual organ systems, they frequently are multiple, and they overlap clinically.

Cardiovascular system

Severe disturbances of normal cardiovascular function are common with preeclampsia syndrome. These are related to:

1. increased cardiac afterload caused by hypertension;

2. cardiac preload, which is affected negatively by pathologically diminished hypervolemia of pregnancy and is increased by intravenous crystalloid or oncotic solutions;
3. endothelial activation with interendothelial extravasation of intravascular fluid into the extracellular space and importantly, into the lungs.

Hemodynamic changes and cardiac function

Cardiovascular aberrations of pregnancy-related hypertensive disorders vary depending on several modifiers. These factors include hypertension severity, underlying chronic disease, preeclampsia severity, and in which part of the clinical spectrum these are studied. In some women these cardiovascular changes may precede hypertension onset. Nevertheless, with the clinical onset of preeclampsia, cardiac output declines, due at least in part to increased to peripheral resistance. When assessing cardiac function in preeclampsia, consideration is given to echocardiographic measures of *myocardial function* and to clinically relevant *ventricular function*.

Myocardial function. Serial echocardiographic studies have documented in preeclampsia evidence for ventricular remodeling that is accompanied by diastolic dysfunction 40 percent of women. In some of these women, functional differences persisted up to 16 months after delivery. Ventricular remodeling was judged to be an adaptive response to maintain normal contractility with the increased afterload of preeclampsia. In the otherwise healthy pregnant woman, these changes are usually clinically inconsequential. But when combined with underlying ventricular dysfunction – for example, concentric ventricular hypetrophy from chronic hypertension - further diastolic dysfunction may cause cardiogenic pulmonary edema.

Ventricular function. Despite the relatively high frequency of diastolic dysfunction with preeclampsia, in most women clinical cardiac function is appropriate. Importantly, both normally pregnant women and those with preeclampsia syndrome can have normal or slightly hyperdynamic ventricular

function in Figure 4. Thus, both have a cardiac output that is appropriate for left-sided filling pressures. Ventricular function studies of preeclamptic women from several investigations are shown in Figure 5. Although cardiac function was hyperdinamic in all women, filling pressures were dependent on the volume of intravenous fluids. Specifically, aggressive hydration resulted in overtly hyperdynamic ventricular function in most women. However, this was accompanied by elevated pulmonary capillary wedge pressures. In some of these women, pulmonary edema may develop despite normal ventricular function because of an alveolar endothelial leak. This is compounded by decreased oncotic pressure from a low serum albumin concertration.

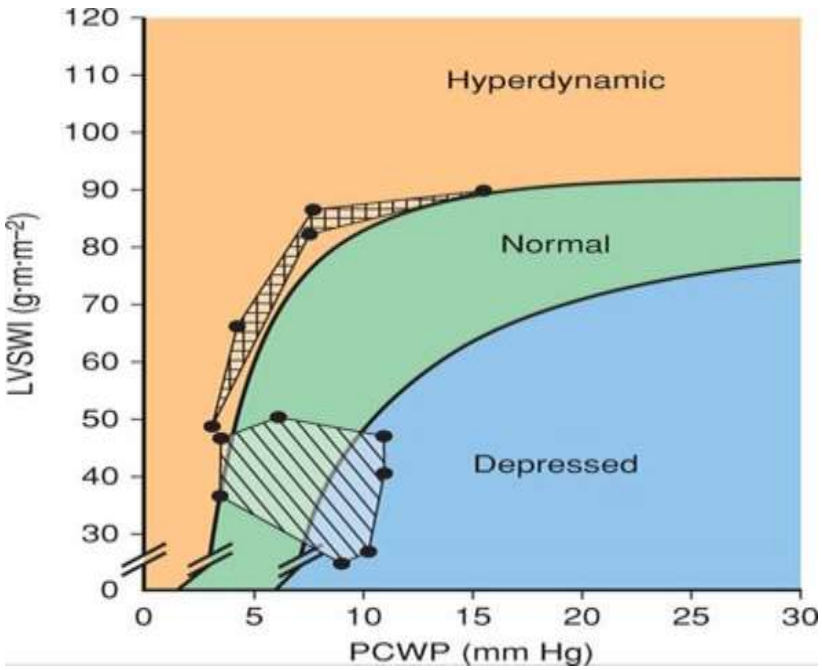


Fig. 4. Ventricular function in normally pregnant women (stripped area) and in women with eclampsia (boxed area) is plotted on a Braunwald ventricular function curve. LVSWI = left ventricular stroke work index; PCWP =pulmonary capillary wedge pressure.

Thus, increased cardiac output and hyperdynamic ventricular function is largely a result of low wedge pressures and not a result of augmented myocardial contractility. By comparison, women given appreciably larger volumes of fluid commonly had filling pressures that exceeded normal, but their ventricular function remanded hyperdynamic because of concomitantly increased cardiac

output.

From these studies, it is reasonable to conclude that aggressive fluid administration to otherwise normal women with severe preeclampsia to otherwise normal women with severe preeclampsia substantially elevates normal left-sided filling pressures and increases a physiologically normal cardiac output to hyperdynamic levels.

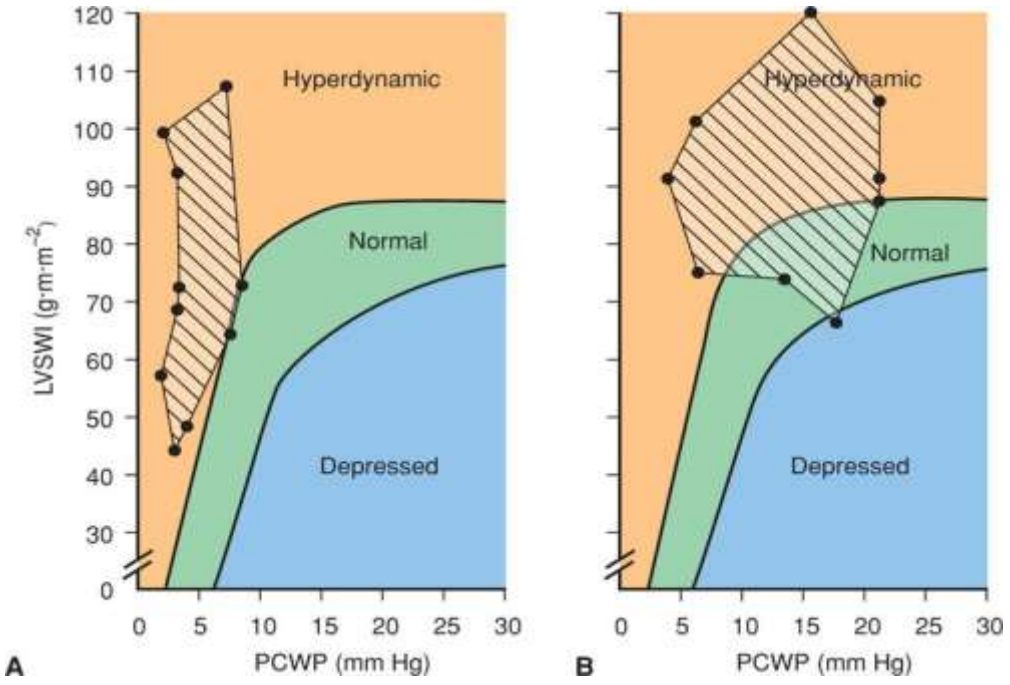


Fig. 5. Venticular function in women with severe preeclampsia-eclampsi plotted on the Braunwald ventricular function curve. The pulmonary capillary wedge pressures (PCWP) are lower in those managed with restricted fluid administration (stripped area in A) compared with women managed with aggressive fluid therapy (stripped area in B). In those managed with aggressive fluid infusions, eight developed pulmonary edema despite normal to hyperdynamic ventricular function in all but one. LVSWI = left ventricular stroke work index.

Blood volume

Eclamptic women that the normally expected hypervolemia is severely curtailed (Figure 5). Women of average size should have a blood volume of nearly 4500 ml during the last several weeks of a normal pregnancy. In nonpregnant women, this volume approximates only 3000ml. With eclampsia, however, much or all of the anticipated normal excess 1500 ml lost. Such hemoconcentration results from generalized vasoconstriction that follows endothelial activation and leakage of plasma into the interstitial space because of increased permeability. In

women with preeclampsia and depending on its severity, hemoconcentration is usually not as marked. Women with gestational hypertension, but without preeclampsia, usually have a normal blood volume.

For women with severe hemoconcentration, it was once taught that in acute fall in hematocrit suggested resolution of preeclampsia. In this scenario, hemodilution follows endothelial healing with return of interstitial fluid into the intravascular space. Although, this is somewhat correct, it is important to recognize a substantive cause of this fall in hematocrit is usually the consequence of blood loss at delivery. Vasospasm and endothelial leakage of plasma may persist for a variable time after delivery as the endothelium is restored to normally. As this takes place, vasoconstriction reverses, and as the blood volume increases, the hematocrit is usually falls. Thus, women with eclampsia:

- Are unduly sensitive to vigorous fluid therapy administered in an attempted to expand the contracted blood volume to normal pregnancy levels.
- Are sensitive to amounts of blood loss at delivery that are considered normal for a normotensive woman.

Hematological changes

Several hematological abnormalities are associated with the preeclampsia syndrome. Among those commonly identified is thrombocytopenia, which at times may become severe enough to be life threatening. Occasionally, the levels of some plasma clotting factors may be decreased, and erythrocytes display abnormal morphology and undergo rapid hemolysis.

Thrombocytopenia

The frequency and intensity of thrombocytopenia vary and are dependent on the severity and duration of the preeclampsia syndrome and the frequency with which platelet counts are performed. Overt thrombocytopenia - defined by a platelet count < 100, 000 ML – indicates severe disease. In general, the lower the platelet count, the higher the rates of maternal and fetal morbidity and mortality. In most cases, delivery is advisable because thrombocytopenia usually continues to worsen.

After delivery the platelet count may continue to decline for the first day. It then usually increases progressively to reach a normal level within 3 to 5 days.

Hemolysis

Severe preeclampsia is frequently accompanied by evidence of hemolysis as manifestby elevated serum lactate dehydrogenase levels and decreased haptoglobin levels and decreased haptoglobin levels. Other evidence comes from schizocytosis, and sphrecytosis, and reticulocytosis in peripheral blood. This dearrangments result in part from microangipatic hemolysis caused by endothelial disruption with platelet adherence and fibrin deposition. Erythrocyte membrane changes, increased adhesiveness, and aggregation may also promote a hypercoagulable state.

Coagulation changes

Subtle changes consistent with intravascular coagulation, and less often erythrocyte destruction, commonly are found with preeclampsia and especially eclampsia. Some of these changes include increased factor VIII consumption, increased levels of fibrinopeptides A and B and of D-dimers, and decreased levels of regulatory proteins – antithrombin III and protein C and S. Except for thrombocytopenia discussed above, coagulation aberrations generally are mild and are seldom clinically significant. Unless there is associated placental abrubtion, plasma fibrinogen levels found in normal pregnancy. Fibrin degradation products such as a-dimers are elevated only occasionally *Fibronectin*, a glycoprotein associated with a vascular endothelial cell basement membrane, is elevated in women with preeclampsia. As preeclampsia worsens, so do abnormal findings with thromboelastography. Despite these changes, routine laboratory assessments of coagulation, including prothrombin time, activated partial thromboplastin time, and plasma fibrinogen level, were found to be unnecessary in the management of pregnancy associated hypertensive disorders.

Volume homeostasis

Normal pregnancy- induced extra- and intravascular volume increases that are accompanied by vasodilatation undergo further complex shifts with the

preeclampsia syndrome. In addition to blood volume changes shown in Fig. 6, there are many hormonal, fluid, and electrolyte aberrations.

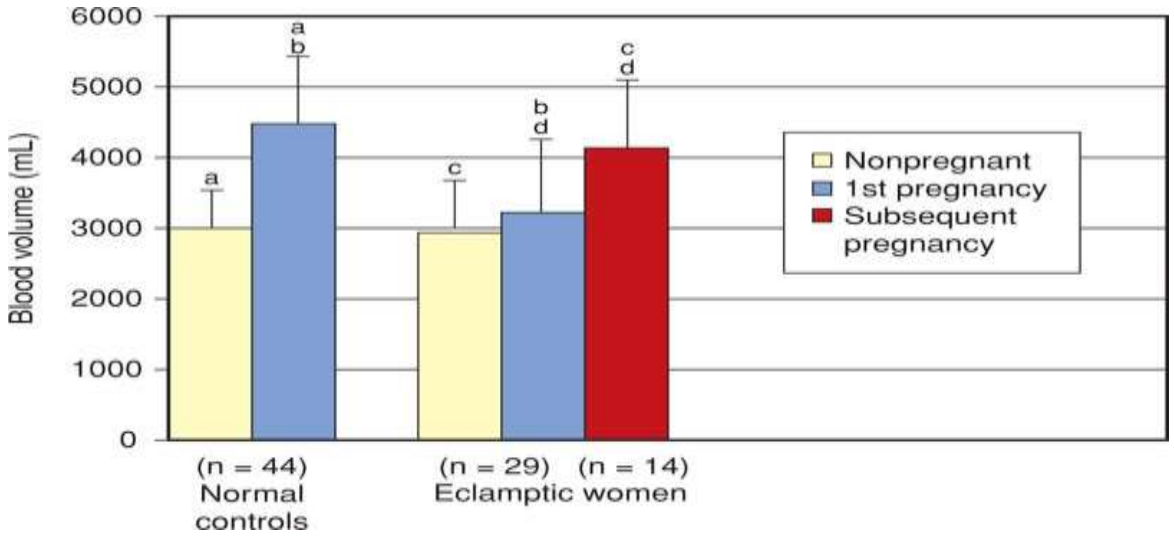


Fig. 6. The two bar graphs on the left compare mean blood volumes in nonpregnant and term normally pregnant women. On the right, graphs display values for a group of 29 women with eclampsia and their nonpregnant values. The red bar reflects values for a subset of 14 who had a subsequent normotensive pregnancy. Extensions above bars represent one standart deviation. Comparison between valueswith identical lowercase letters, that is a-a,b-b, c-c, d-d, are significant p> 001

Endocrine changes

Plasma levels of rennin, angiotensin II, angiotensin 1-7, aldosterone, and atrial natrietic peptide are substantively increased during normal pregnancy. Deoxycorticosterone (DOC) is a potent mineralocorticoid that is also increased remarkably in normal pregnancy. This compound results from conversion of plasma progesterone to DOC rather than increased maternal adrenal secretion. Because of this, DOC secretion is not reduced by sodium retention or hypertension. This may explain why women with preeclampsia retain sodium. In pregnancy, the mineralocorticoid receptor becomes less sensitive to aldosterone.

Vasopressin levels are similar in nonpregnant, normally pregnant, and preeclamptic women even though the metabolic clearance is increased in the latter two.

Atrial natriuretic peptide is released during atrial wall stretching from blood volume expansion, and is responds to cardiac contractility. Serum levels rise in

pregnancy, and its secretion is further increased in women with preeclampsia. Levels of its precursor-proatrial natriuretic peptide – are also increased in preeclampsia.

Fluid and electrolyte changes

In women with severe preeclampsia, the volume of extracellular fluid manifest as edema, is usually much greater than that in normal pregnant women. This mechanism responsible for pathological fluid retention is thought to be endothelial injury. In addition to generalized edema and proteinuria, these women have reduced plasma oncotic pressure. This reduction creates a filtration imbalance and further displaces intravascular fluid into the surrounding interstitium.

Electrolyte concentrations do not differ appreciably in women with preeclampsia compared with those of normal pregnant women. This is may not be the case if there has been vigorous diuretic therapy, sodium restriction, or administration of free water with sufficient oxytocin to produce antidiuresis.

Following an eclamptic convulsion, the serum pH and bicarbonate concentration are lowered due to lactic acidosis and compensatory respiratory loss of carbon dioxide. This intensity of acidosis relates to the amount of lactic acid produced metabolic acidosis – and the rate at which carbon dioxide is exhaled – respiratory acidosis.

Kidney

During normal pregnancy, renal blood flow and glomerular filtration rate are increased appreciably. With development of preeclampsia, there may be a number of reversible anatomical and pathophysiological changes. Of clinical importance, renal perfusion and glomerular filtration are reduced. Levels that are much less than normal nonpregnant values are infrequent and are the consequence of severe disease. A small degree of decreased glomerular filtration may result from reduced plasma volume. There is also morphological changes characterized by glomerular endotheliosis blocking the filtration barrier. Diminished filtration causes serum creatinine levels to rise to values seen in nonpregnant individuals that is 1 mg/ml,

sometime even higher. Abnormal values usually begin to normalize 10 days or later after delivery.

In most preeclamptic women, urine sodium concentration is elevated. Urine osmolality, urine plasma creatinine ratio, and fractional excretion of sodium also indicate that a prerenal mechanism is involved.

Plasma uric acid concentration is typically elevated in preeclampsia. Elevation exceeds the reduction in glomerular filtration rate and likely is also due to enhanced tubular reabsorption.

Proteinuria

Proteinuria may develop late and some women may already be delivered or have had an eclamptic convulsion before it appears. Problematically, the optimal method of establishing abnormal levels of either urine protein or albumin remains to be defined. But dipstick qualitative determinations depend on urinary concentration and are not notorious for false-positive and –negative results. For a 24-hour quantitative specimen, the "consensus" threshold value used is > 300 mg/24 hours. Determination of urinary protein: creatinine ratio may supplant the cumbersome 24-hour quantification. There are several methods used to measure proteinuria, and none detect all of the various proteins normally excreted. A more accurate method involves measurement of albumin excretion. Albumin filtration exceeds that of larger globulins, and with glomerular disease such as preeclampsia, most of the protein in urine is albumin. There are test kits that permit rapid measurement of urinary albumin: creatinine ratios in an outpatient settings.

Anatomical changes

Glomeruli are enlarged by approximately 20 percent, they are "bloodless", and capillary loops variably are dilated and contracted. Endothelial cells are swollen – termed glomerular term capillary lumens (Fig. 7). Homogenous subendothelial deposis of proteins and fibrin-like material are seen.

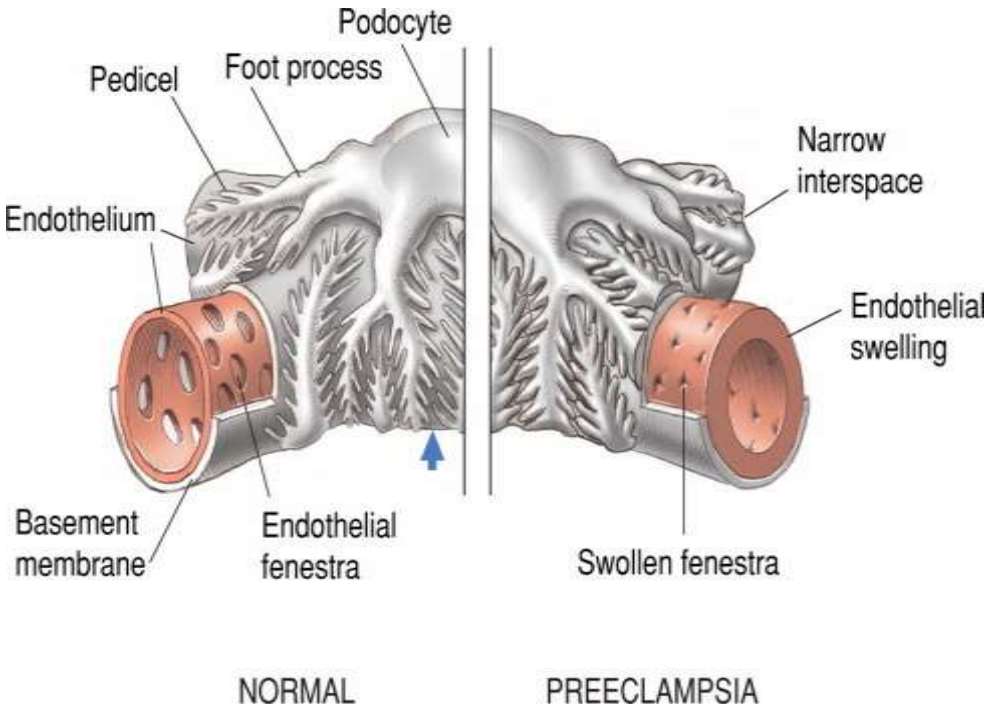


Fig. 7. Schematic showing glomerular capillary endotheliosis. The capillary of the normal glomerulus shown on the left has wide endothelial fenestrations, and the pedicels emanating from the podocytes are widely spaced (arrow). The illustration on the right is of a glomerulus with changes induced by the preeclampsia syndrome. The endothelial cells are swollen and their fenesrae narrowed, as are pedicels that now about each other.

Liver

Characteristic lesions were regions of periportal hemorrhage in liver periphery. In their elegant autopsy studies some degree of hepatic infarction accompanied hemorrhage. Along with the earlier observations by Pritchard and associates (1954) who described hemolysis and thrombocytopenia with eclampsia, this constellation of hemolysis, hepatocellular necrosis, and thrombocytopenia was later termed HELLP-syndrome by Weinstein (1985) to call attention to its seriousness.

First symptomatic involvement is considered a sign of severe disease. It typically manifests by moderate to severe right-upper quadrant or midepigastric pain and tenderness. In many cases such women also have elevated levels of serum aminotransferase (AST) or alanine aminotransferase (ALT). In some cases, however, the amount of hepatic tissue involved with infarction may be surprisingly extensive yet still clinically insignificant. In our experiences may be worsened by

hypotension from obstetrical hemorrhage, and it occasionally causes hepatic failure – so called shock liver.

Second asymptomatic elevations of serum hepatic transaminase levels – AST and ALT – are also considered markers for severe preeclampsia. Values seldom exceed 500 U/l., but have been reported to be greater than 2000 U/l in some women.

In a third example of liver involvement, hemorrhage infarction may extend to form a hepatic hematoma. This in turn may extend to form a subcapsular hematoma that may rupture. They can be identified using computed tomography (CT) scanning or magnetic resonance (MR) imaging as shown in Fig. 8.

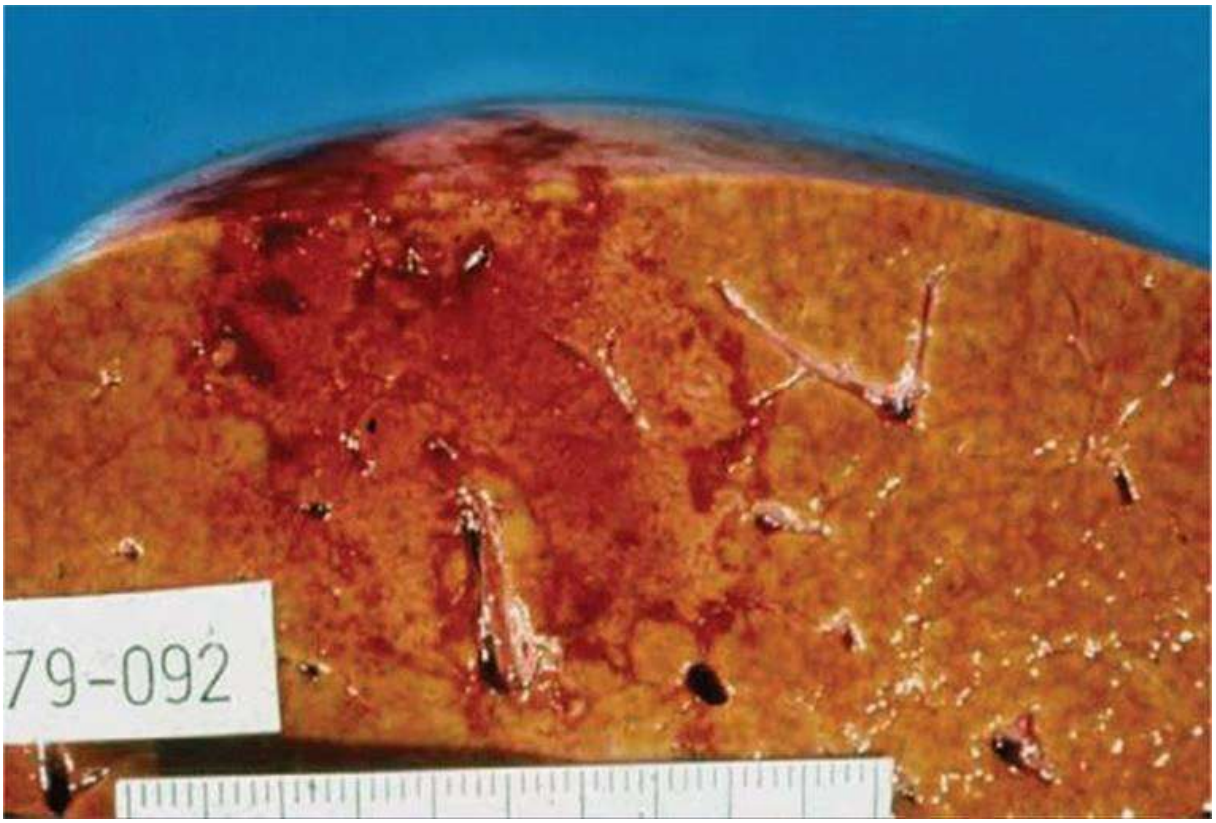


Fig. 8. Gross liver specimen from a woman with preeclampsia who died from aspiration pneumonitis. Periportal hemorrhagic necrosis was seen microscopically.

Pancreas

There are no convincing data that the pancreas has special involvement with preeclampsia syndrome. If so, the occasional case reports of concurrent hemorrhagic pancreatitis are likely unrelated. That said, severe hemoconcentration may

predispose to pancreatic inflammation.

Brain

Headaches and visual symptoms are common with severe preeclampsia, and associated convulsions define eclampsia. The earliest anatomical descriptions of brain involvement came from autopsy specimens, but CT- and MR-imaging and Doppler studies have added many important insights into cerebrovascular involvement.

Neuroanatomical Lesions

Most gross anatomical descriptions of the brain in eclamptic women are taken from eras when mortality rates were high. One consistent finding was that brain pathology accounted for only about a third of fatal cases such as the one shown in Figure 8. In fact, most deaths were from pulmonary edema, and brain lesions were coincidental. Thus, although gross intracerebral hemorrhage was seen in up to 60 percent of eclamptic women, it was fatal in only half of these. As shown in Figure 10, other principal lesions found at autopsy of eclamptic women were cortical and subcortical petechial hemorrhages. The classic microscopic vascular lesions consist of fibrinoid necrosis of the arterial wall and perivascular microinfarcts and hemorrhages. Other frequently described major lesions include subcortical edema, multiple nonhemorrhagic areas of “softening” throughout the brain, and hemorrhagic areas in the white matter. There also may be hemorrhage in the basal ganglia or pons, often with rupture into the ventricles.

Cerebrovascular pathophysiology

Clinical, pathological, and neuroimaging findings have lead to two general theories to explain cerebral abnormalities with eclampsia. Importantly, endothelial cell dysfunction that characterizes the preeclampsia syndrome likely plays a key role in both. The first theory suggests that in response to acute and severe hypertension, cerebrovascular overregulation leads to vasospasm. This presumption is based on the angiographic appearance of diffuse or multifocal segmental narrowing suggestive of vasospasm. In this scheme, diminished cerebral blood flow is hypothesized to result in ischemia, cytotoxic edema, and eventually tissue infarction.

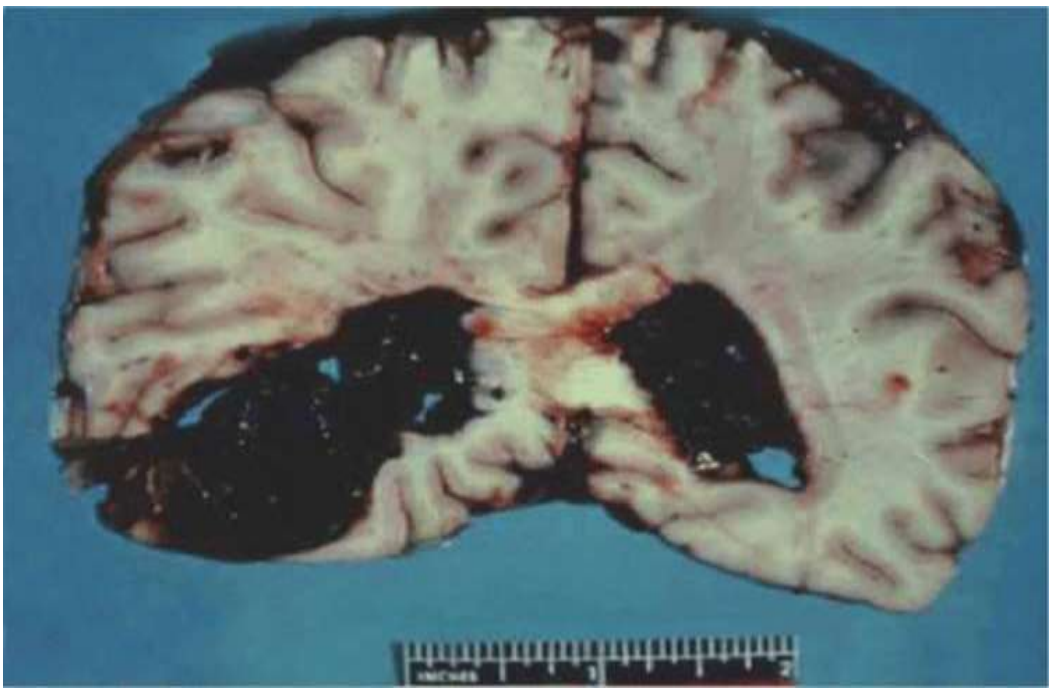


Fig. 9. This autopsy brain slice shows a fatal hypertensive hemorrhage in a primigravida with eclampsia.

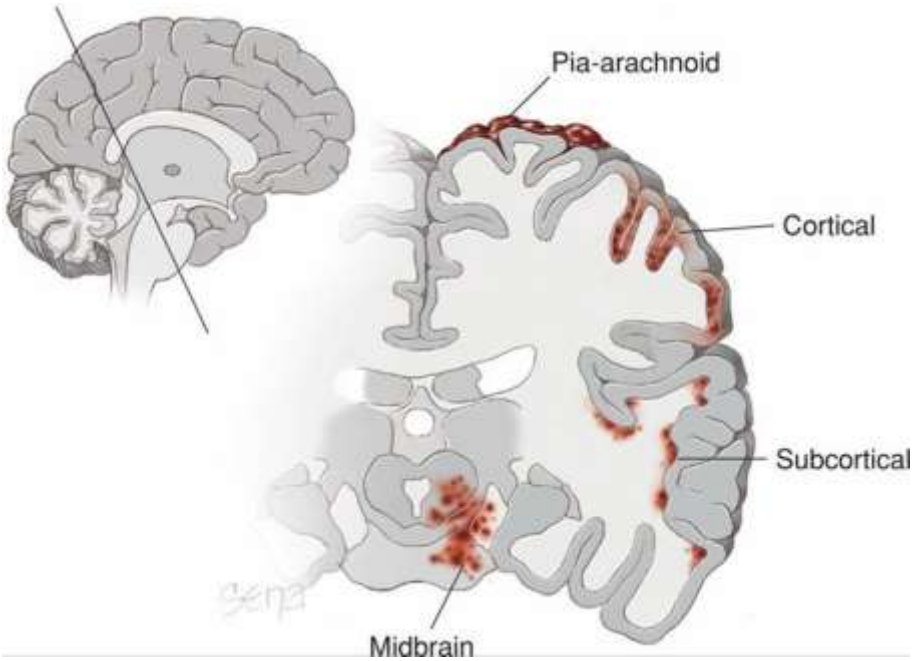


Fig. 10. Composite illustration showing location of cerebral hemorrhages and petechiae in women with eclampsia. Insert shows the level of the brain from which the main image was constructed.

Although this theory was widely embraced for many years, there is little objective evidence to support it.

The second theory is that sudden elevations in systemic blood pressure exceed the normal cerebrovascular autoregulatory capacity. Regions of forced vasodilation and vasoconstriction develop, especially in arterial boundary zones. At the capillary level, disruption of end-capillary pressure causes increased hydrostatic pressure, hyperperfusion, and extravasation of plasma and red cells through endothelial tight-junction openings. This leads to vasogenic edema. This theory is incomplete because very few eclamptic women have mean arterial pressures that exceed limits of autoregulation—approximately 160 mm Hg.

It seems reasonable to conclude that the most likely mechanism is a combination of the two. Thus, a preeclampsia-associated inter endothelial cell leak develops at blood pressure (hydraulic) levels much lower than those usually causing vasogenic edema and is coupled with a loss of upper-limit autoregulation. With imaging studies, these changes manifest as facets of the reversible posterior leukoencephalopathy syndrome. This subsequently became referred to as the posterior reversible encephalopathy syndrome—PRES. This term is misleading because although PRES lesions principally involve the posterior brain—the occipital and parietal cortices—in at least a third of cases, they also involve other brain areas. The most frequently affected region is the parietooccipital cortex—the boundary zone of the anterior, middle, and posterior cerebral arteries. Also, in most cases, these lesions are reversible.

Cerebral blood flow

Autoregulation is the mechanism by which cerebral blood flow remains relatively constant despite alterations in cerebral perfusion pressure. In nonpregnant individuals, this mechanism protects the brain from hyperperfusion when mean arterial pressures increase to as high as 160 mm Hg. These are pressures far greater than those seen in all but a very few women with eclampsia. Thus, to explain eclamptic seizures, it was theorized that autoregulation must be altered by pregnancy. Although species differences must be considered, autoregulation is

unchanged across pregnancy in rodents. That said, some, but not others, have provided evidence of impaired autoregulation in women with preeclampsia.

Cerebral blood flow during the first two trimesters of normal pregnancy is similar to nonpregnant values, but thereafter, it significantly decreases by 20 percent during the last trimester. These investigators also documented significantly increased cerebral blood flow in women with severe preeclampsia compared with that of normotensive pregnant women. Taken together, these findings suggest that eclampsia occurs when cerebral hyperperfusion forces capillary fluid interstitially because of endothelial damage, which leads to perivascular edema characteristic of the preeclampsia syndrome. In this regard, eclampsia is an example of the posterior reversible encephalopathy syndrome as previously discussed.

Neurological manifestations

There are several neurological manifestations of the preeclampsia syndrome. Each signifies severe involvement and requires immediate attention. First, headache and scotomata are thought to arise from cerebrovascular hyperperfusion that has a predilection for the occipital lobes. The headaches may be mild to severe and intermittent to constant. In our experiences, they are unique in that they do not usually respond to traditional analgesia, but they do improve after magnesium sulfate infusion is initiated.

Convulsions are a second potential manifestation and are diagnostic for eclampsia. These are caused by excessive release of excitatory neurotransmitters—especially glutamate; massive depolarization of network neurons; and bursts of action potentials (Meldrum, 2002). Clinical and experimental evidence suggest that extended seizures can cause significant brain injury and later brain dysfunction.

As a third manifestation, blindness is rare with preeclampsia alone, but it complicates eclamptic convulsions in up to 15 percent of women. Blindness has been reported to develop up to a week or more following delivery. There are at least two types of blindness as discussed subsequently.

Last, generalized cerebral edema may develop and is usually manifest by mental status changes that vary from confusion to coma. This situation is particularly

dangerous because fatal transtentorial herniation may result.

Neuroimaging studies

With CT imaging, localized hypodense lesions at the gray- and white-matter junction, primarily in the parietooccipital lobes, are typically found in eclampsia. Such lesions may also be seen in the frontal and inferior temporal lobes, the basal ganglia, and thalamus. The spectrum of brain involvement is wide, and increasing involvement can be identified with CT imaging. Edema of the occipital lobes or diffuse cerebral edema may cause symptoms such as blindness, lethargy, and confusion. In the latter cases, widespread edema shows as a marked compression or even obliteration of the cerebral ventricles. Such women may develop signs of impending life-threatening transtentorial herniation.

Several MR imaging acquisitions are used to study eclamptic women. Common findings are hyperintense T2 lesions—posterior reversible encephalopathy syndrome (PRES)—in the subcortical and cortical regions of the parietal and occipital lobes (Fig. 11). There is also relatively common involvement of the basal ganglia, brainstem, and cerebellum. Although these PRES lesions are almost universal in women with eclampsia, their incidence in women with preeclampsia is less frequent. They are more likely to be found in women who have severe disease and who have neurological symptoms. And although usually reversible, a fourth of these hyperintense lesions represent cerebral infarctions that have persistent findings.

Visual changes and blindness

Scotomata, blurred vision, or diplopia are common with severe preeclampsia and eclampsia. These usually improve with magnesium sulfate therapy and/or lowered blood pressure. Blindness is less common, is usually reversible, and may arise from three potential areas. These are the visual cortex of the occipital lobe, the lateral geniculate nuclei, and the retina. In the retina, pathological lesions may be ischemia, infarction, or detachment.

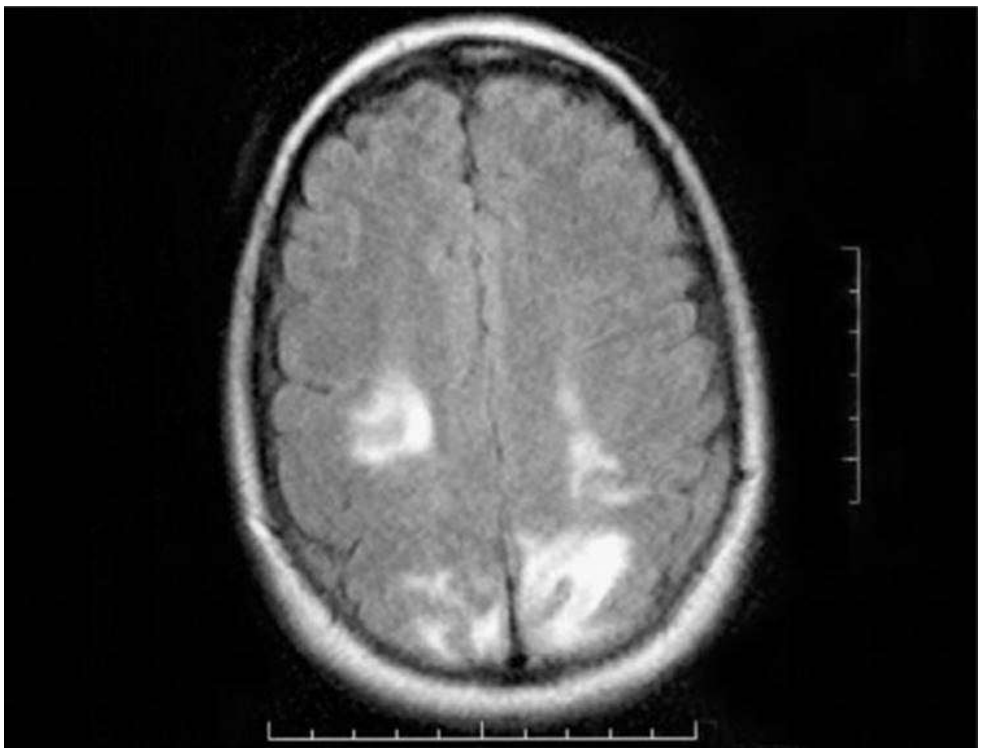


Fig. 11. Cranial magnetic resonance imaging in a nullipara with eclampsia. Multilobe T2-FLAIR high-signal lesions are apparent. FLAIR = fluid-attenuated inversion recovery.

Occipital blindness is also called amaurosis—from the Greek dimming. Affected women usually have evidence of extensive occipital lobe vasogenic edema on imaging studies. Of 15 women cared for at Parkland Hospital, occipital blindness lasted from 4 hours to 8 days, but it resolved completely in all cases. Rarely, extensive cerebral infarctions may result in total or partial visual defects (Fig. 12).

Blindness from retinal lesions is caused either by serous retinal detachment or rarely by retinal infarction, which is termed Purtscher retinopathy (Fig. 13). Serous retinal detachment is usually unilateral and seldom causes total visual loss. In fact, asymptomatic serous retinal detachment is relatively common. In most cases of eclampsia-associated blindness, visual acuity subsequently improves, but if caused by retinal artery occlusion, vision may be permanently impaired. In some women, these findings are additive.

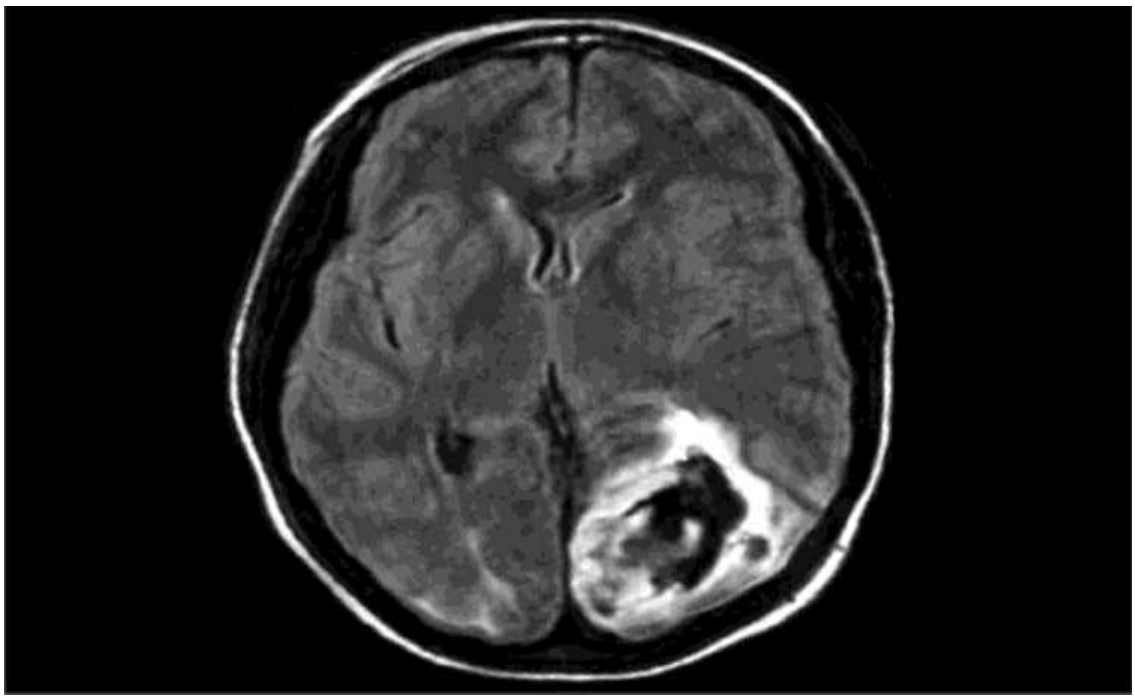


Fig. 12. Cranial magnetic resonance imaging performed 3 days postpartum in a woman with eclampsia and HELLP syndrome. Neurovisual defects persisted at 1 year, causing job disability.

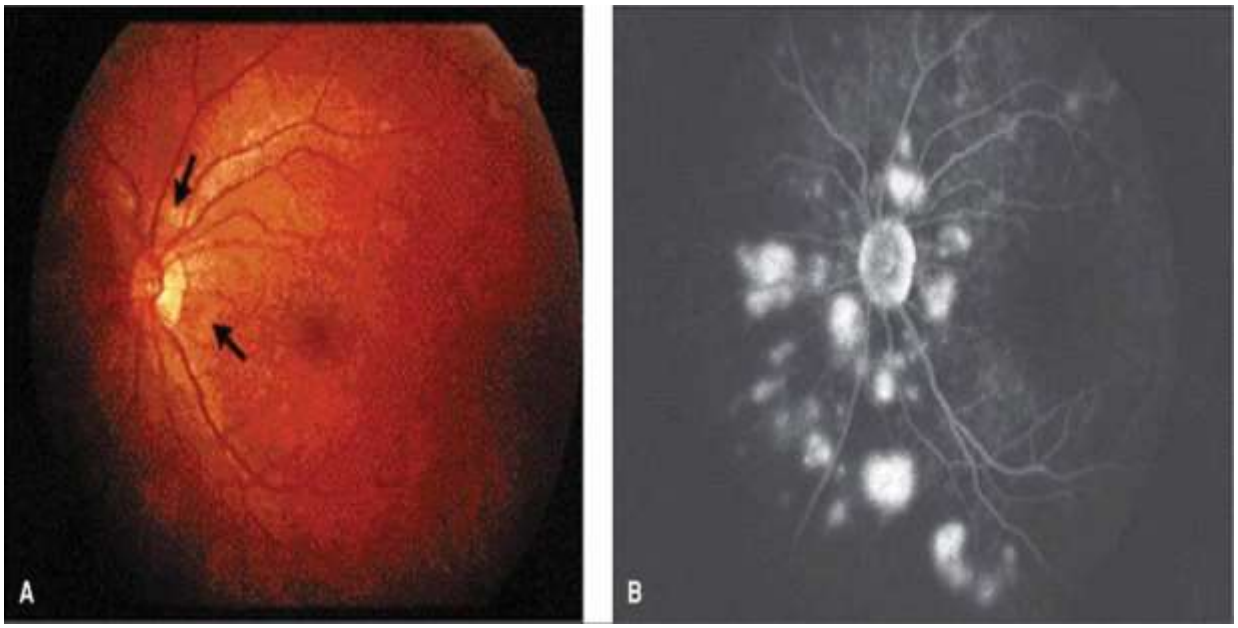


Fig. 13. Purtscher retinopathy caused by choroidal ischemia and infarction in preeclampsia syndrome. A. Ophthalmoscopy shows scattered yellowish, opaque lesions of the retina (arrows). B. The late phase of fluorescein angiography shows areas of intense hyperfluorescence representing pooling of extravasated dye.

Cerebral edema

Clinical manifestations suggesting widespread cerebral edema are worrisome.

Symptoms ranged from lethargy, confusion, and blurred vision to obtundation and coma. In most cases, symptoms waxed and waned. Mental status changes generally correlated with the degree of involvement seen with CT and MR imaging studies. These women are very susceptible to sudden and severe blood pressure elevations, which can acutely worsen the already widespread vasogenic edema. Thus, careful blood pressure control is essential. In the 10 women with generalized edema, three became comatose and had imaging findings of impending transtentorial herniation. One of these three died from herniation. Consideration is given for treatment with mannitol or dexamethasone.

Long-term neurocognitive sequelae

Women with eclampsia have been shown to have some cognitive decline when studied 5 to 10 years following an eclamptic pregnancy.

Uteroplacental perfusion

Defects in endovascular trophoblastic invasion and placentation germane to development of the preeclampsia syndrome and fetal-growth restriction. Of immense clinical importance, compromised uteroplacental perfusion is almost certainly a major culprit in the increased perinatal morbidity and mortality rates. Thus, measurement of uterine, intervillous, and placental blood flow would likely be informative. Attempts to assess these in humans have been hampered by several obstacles that include inaccessibility of the placenta, the complexity of its venous effluent, and the need for radioisotopes or invasive techniques.

Measurement of uterine artery blood flow velocity has been used to estimate resistance to uteroplacental blood flow. Vascular resistance is estimated by comparing arterial systolic and diastolic velocity waveforms. By the completion of placentation, impedance to uterine artery blood flow is markedly decreased, but with abnormal placentation, abnormally high resistance persists. Earlier studies were done to assess this by measuring peak systolic: diastolic velocity ratios from uterine and umbilical arteries in preeclamptic pregnancies. The results were interpreted as showing that in some cases, but certainly not all, there was increased resistance.

Another Doppler waveform—uterine artery “notching”—has been reported to

be associated with increased risks for preeclampsia or fetal-growth restriction. However, notching had a low predictive value except for early-onset severe disease. There are measured resistance in uterine spiral arteries. Impedance was higher in peripheral than in central vessels—a so-called ring-like distribution. Mean resistance was higher in all women with preeclampsia compared with that in normotensive controls. In MR imaging and other techniques to assess placental perfusion ex vivo in the myometrial arteries removed from women with preeclampsia or fetal-growth restriction. These investigators confirmed that in both conditions myometrial arteries exhibited endothelium-dependent vasodilatory response. Moreover, other pregnancy conditions are also associated with increased resistance.

Despite these findings, evidence for compromised uteroplacental circulation is found in only a few women who go on to develop preeclampsia. Indeed, when preeclampsia develops during the third trimester, only a third of women with severe disease have abnormal uterine artery velocimetry. In a study of 50 women with HELLP syndrome, only a third had abnormal uterine artery waveforms. In general, the extent of abnormal waveforms correlates with severity of fetal involvement.

DIAGNOSTIC CRITERIA OF PRE-ECLAMPSIA

Hypertension: An absolute rise of blood pressure of at least 140/90 mm Hg, if the previous blood pressure is not known or a rise in systolic pressure of at least 30 mm Hg, or a rise in diastolic pressure of at least 15 mm Hg over the previously known blood pressure is called *pregnancy induced hypertension*.

Calculation based on mean arterial pressure (MAP) as advocated by Page

Systolic pressure + (diastolic pressure x 2) MAP 3

A rise of 20 mm Hg MAP over the previous reading, or when the MAP is 105 mm Hg or more should be considered as significant.

The rise of blood pressure should be evident at least on two occasions at least 6 hours apart. The level is arbitrary and is based on the observation, that

complications are likely to be more beyond this level. Diastolic blood pressure is noted at the point of disappearance of sounds (Korotkoff - V).

Blood pressure is measured on the right arm, with the patient lying on her side at 45° to the horizontal. In the outpatient, sitting posture is preferred. In either case, the occluded brachial artery should be kept at the level of the heart. Blood pressure is measured at rest (after a 5-minute rest) 2 times with an interval of at least 1'.

Edema: Demonstration of pitting edema over the ankles after 12 hours bed rest or rapid gain in weight of more than 1 lb a week or more than 5 lb a month in the later months of pregnancy may be the earliest evidence of pre-eclampsia. However, some amount of edema is common (physiological) in a normal pregnancy.

Proteinuria: Presence of total protein in 24 hours urine of more than 0.3 gm or >2+ (1.0 gm/L) on at least two random clean-catch urine samples tested > 4 hours apart in the absence of urinary tract infection is considered significant. Test for protein in urine by multiple reagent strip (dipstick) as follows: Trace = 0.1 gm/L; 1+ = 0.3 gm/L; 2+ = 1.0 gm/L; 3+ = 3.0 gm/L; 4+ = 10.0 gm/L.

CLINICAL TYPES OF PRE-ECLAMPSIA

The clinical classification of pre-eclampsia is arbitrary and is principally dependent on the level of blood pressure for management purpose. But proteinuria is more significant than blood pressure to predict fetal outcome.

Mild: This includes cases of sustained rise of blood pressure of more than 140/90 mm Hg but less than 160 mm Hg systolic or 110 mm Hg diastolic without significant proteinuria.

Severe:

1. A persistent systolic blood pressure of >160 mm Hg or diastolic pressure of >110 mm Hg. (2) Protein excretion of >5 gm/24 hr.
2. Oliguria (<400 ml/24 hr).
3. Platelet count < 100,000/mm3.
4. HELLP syndrome.
5. Cerebral or visual disturbances.

6. Persistent severe epigastric pain.
7. Retinal hemorrhages, exudates or papilledema.
8. Intrauterine growth restriction of the fetus.
9. Pulmonary edema.

From the prognostic point of view, a diastolic rise of blood pressure is more important than the systolic rise. Moreover, convulsions may occur even with moderate rise of blood pressure; conversely, even with alarming high rise of pressure, the pregnancy may have an uneventful outcome. This calls for a strict vigilance whenever the blood pressure is raised to the pre-eclamptic level or even before that.

Table 2. Indicators of Severity of Gestational Hypertensive Disorders

Abnormality	Nonsevere[b]	Severe
Diastolic BP	< 110 mm Hg	≥ 110 mm Hg
Systolic BP	< 160 mm Hg	≥ 160 mm Hg
Proteinuria[c]	None to positive	None to positive
Headache	Absent	Present
Visual disturbances	Absent	Present
Upper abdominal pain	Absent	Present
Oliguria	Absent	Present
Convulsion (eclampsia)	Absent	Present
Serum creatinine	Normal	Elevated
Thrombocytopenia (< 100,000/μL)	Absent	Present
Serum transaminase elevation	Minimal	Marked
Fetal-growth restriction	Absent	Obvious
Pulmonary edema	Absent	Present

[a]Compare with criteria in Table 40-1.
[b]Includes "mild" and "moderate" hypertension not specifically defined.
[c]Most disregard degrees of proteinuria as being nonsevere or severe.
BP = blood pressure.

CLINICAL FEATURES OF PRE-ECLAMPSIA

Pre-eclampsia frequently occurs in primigravidae (70%). It is more often associated with obstetrical-medical complications such as multiple pregnancy, polyhydramnios, pre-existing hypertension, diabetes etc. The clinical manifestations appear usually after the 20th week.

ONSET: The onset is usually insidious and the syndrome runs a slow course. On rare occasion, however, the onset becomes acute and follows a rapid course.

SYMPTOMS: Pre-eclampsia is principally a syndrome of signs and when symptoms appear, it is usually late.

Mild symptoms: Slight swelling over the ankles which persists on rising from the bed in the morning or tightness of the ring on the finger is the early manifestation of pre-eclampsia edema. Gradually, the swelling may extend to the face, abdominal wall, vulva and even the whole body.

Alarming symptoms: The following are the ominous symptoms, which may be evident either singly or in combination. These are usually associated with acute onset of the syndrome.

1. Headache — either located over the occipital or frontal region
2. Disturbed sleep
3. Diminished urinary output—Urinary output of less than 400 ml in 24 hours is very ominous
4. Epigastric pain—acute pain in the epigastric region associated with vomiting, at times coffee color, is due to hemorrhagic gastritis or due to subcapsular hemorrhage in the liver
5. Eye symptoms—there may be blurring, scotomata, dimness of vision or at times complete blindness. Vision is usually regained within 4-6 weeks following delivery. The eye symptoms are due to spasm of retinal vessels (retinal infarction), occipital lobe damage (vasogenic edema) or retinal detachment. Reattachment of the retina occurs following subsidence of edema and normalization of blood pressure after delivery.

SIGNS

1. Abnormal weight gain: Abnormal weight gain within a short span of time probably appears even before the visible edema. A rapid gain in weight of more than 5 lb a month or more than 1 lb a week in later months of pregnancy is significant.
2. Rise of blood pressure: The rise of blood pressure is usually insidious but may be abrupt. The diastolic pressure usually tends to rise first followed by the systolic pressure
3. Edema: Visible edema over the ankles on rising from the bed in the morning is pathological. The edema may spread to other parts of the body in uncared cases. Sudden and generalized edema may indicate imminent eclampsia.
4. There is no manifestation of chronic cardiovascular or renal pathology.
5. Pulmonary edema — due to leaky capillaries and low oncotic pressure.
6. Abdominal examination may reveal evidences of chronic placental insufficiency, such as scanty liquor or growth retardation of the fetus.
7. Thus, the manifestations of pre-eclampsia usually appear in the following order—rapid gain in weight -> visible edema and/or hypertension -> proteinuria.

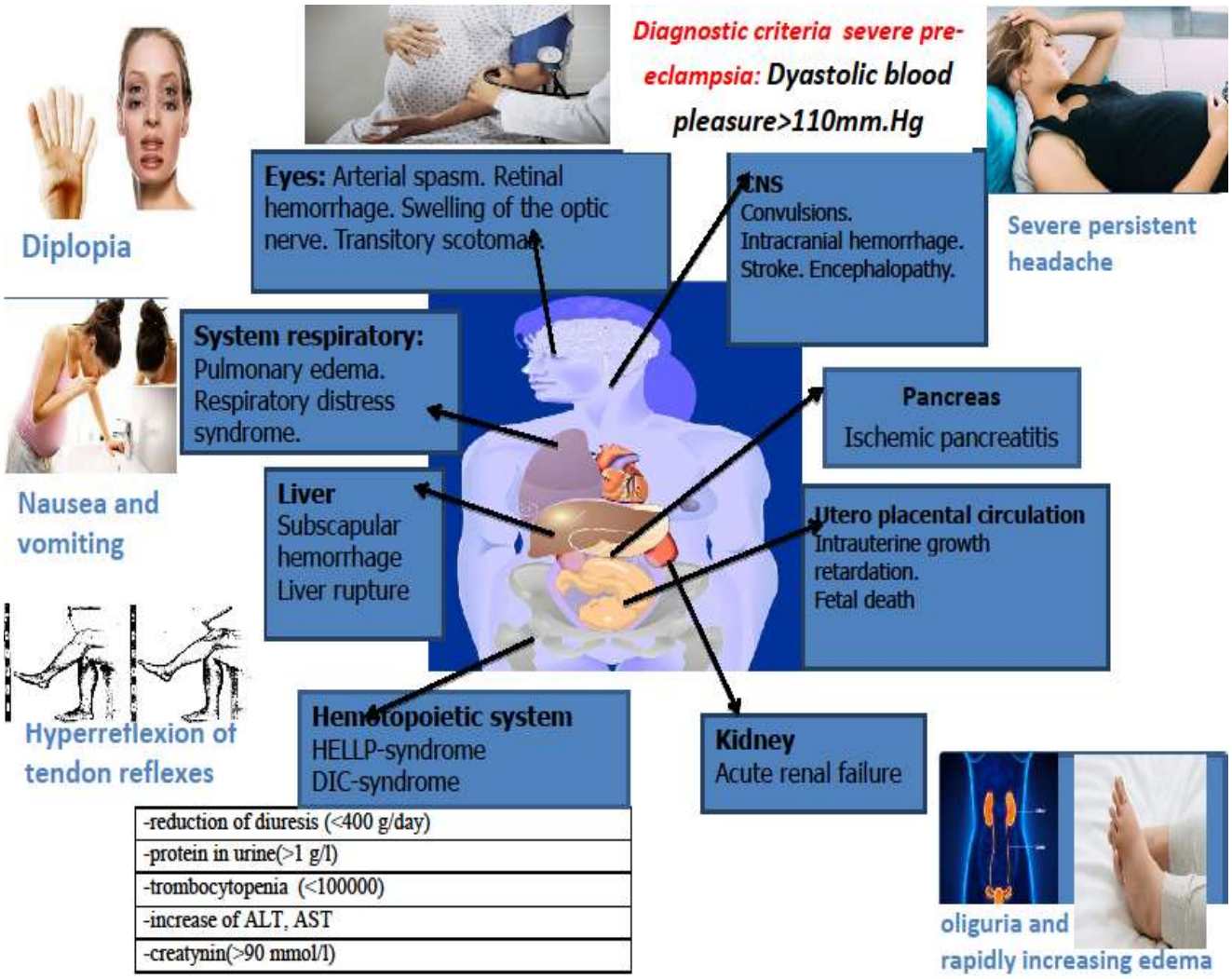
INVESTIGATIONS

Urine: Proteinuria is the last feature of pre-eclampsia to appear. It may be trace or at times copious so that urine becomes solid on boiling (10-15 gm/liter). There may be few hyaline casts, epithelial cells or even few red cells. 24 hours urine collection for protein measurement is done (see above).

Ophthalmoscopic examination: In severe cases there may be retinal edema, constriction of the arterioles, alteration of normal ratio of vein: arteriole diameter from 3 : 2 to 3 : 1 and nicking of the veins where crossed by the arterioles. There may be hemorrhage.

Blood values: The blood changes are not specific and often inconsistent. A serum uric acid level (biochemical marker of pre-eclampsia) of more than 4.5 mg/dL indicates the presence of pre-eclampsia.

Table 3. Diagnostic criteria of severe pre-eclampsia



Blood urea level remains normal or slightly raised. Serum creatinine level may be more than 1 mg/dL. There may be thrombocytopenia and abnormal coagulation profile of varying degrees. Hepatic enzyme levels may be increased.

Antenatal fetal monitoring: Antenatal fetal well being assessment is done by clinical examination, daily fetal kick count, ultrasonography for fetal growth and liquor pockets, cardiotocography, umbilical artery flow velocimetry and biophysical profile.

***Course of the disease*:** Pre-eclampsia is usually insidious in onset and runs a slow course. Rarely, the onset may be acute and follows a rapid course of events. The following course of events may occur:

If detected early: With prompt and effective treatment the pre-eclamptic features may subside completely.

If left untreated and uncared for:

a) The preeclamptic features remain stationary at varying degrees till delivery.
b) Aggravation of the preeclamptic features with appearance of symptoms of acute fulminating pre-eclampsia as mentioned earlier. This happens mostly in cases with acute onset.
c) Eclampsia - It may occur following acute fulminating pre-eclampsia or bypassing it. In fact, eclampsia can occur even with a blood pressure of 140/90 mm Hg.
d) Spontaneous remission of the preeclamptic features—a rare and fortunate event

PREDICTION AND PREVENTION OF PRE-ECLAMPSIA

Prediction

Measurement during early pregnancy—or across pregnancy—of various biological, biochemical, and biophysical markers implicated in preeclampsia syndrome pathophysiology has been proposed to predict its development. Attempts have been made to identify early markers of faulty placentation, impaired placental perfusion, endothelial cell activation and dysfunction, and activation of coagulation. For the most, these have resulted in testing strategies with poor sensitivity and with poor positive-predictive value for preeclampsia. Currently, no screening tests are predictably reliable, valid, and economical. There are, however, combinations of tests, some yet to be adequately evaluated, that may be promising

The list of predictive factors evaluated during the past three decades is legion. Although most have been evaluated in the first half of pregnancy, some have beentested as predictors of severity in the third trimester. Others have been used to forecast recurrent preeclampsia. Some of these tests are listed in Table 3, which is by no means all inclusive.

Provocative pressor tests. Three tests have been extensively evaluated to assess the blood pressure rise in response to a stimulus. The roll-over test measures

the hypertensive response in women at 28 to 32 weeks who are resting in the left lateral decubitus position and then roll over to the supine position. Increased blood pressure signifies a positive test. The isometric exercise test employs the same principle by squeezing a handball. The angiotensin II infusion test is performed by giving incrementally increasing doses intravenously, and the hypertensive response is quantified.

Uterine artery doppler velocimetry. Faulty trophoblastic invasion of the spiral arteries, which is depicted in Figure 1, results in diminished placental perfusion and upstream increased uterine artery resistance. Increased uterine artery

Table 4. Predictive tests for development of the preeclampsia syndrome

Testing Related To:	Examples
Placental perfusion/ vascular resistance	Roll-over test, isometric handgrip or cold pressor test, pressor response to aerobic exercise, angiotensin-II infusion, midtrimester mean arterial pressure, platelet angiotensin-II binding, renin, 24-hour ambulatory blood pressure monitoring, uterine artery or fetal transcranial Doppler velocimetry
Fetal-placental unit endocrine dysfunction	Human chorionic gonadotropin (hCG), alpha-fetoprotein (AFP), estriol, pregnancy-associated protein A (PAPP A), inhibin A, activin A, placental protein 13, corticotropin-releasing hormone, A disintegrin, ADAM-12, kisspeptin
Renal dysfunction	Serum uric acid, microalbuminuria, urinary calcium or kallikrein, microtransferrinuria, *N*-acetyl-β-glucosaminidase, cystatin C, podocyturia
Endothelial dysfunction/ oxidant stress	Platelet count and activation, fibronectin, endothelial adhesion molecules, prostaglandins, prostacyclin, MMP-9, thromboxane, C-reactive protein, cytokines, endothelin, neurokinin B, homocysteine, lipids, insulin resistance, antiphospholipid antibodies, plasminogen activator-inhibitor (PAI), leptin, p-selectin, angiogenic factors such as placental growth factor (PlGF), vascular endothelial growth factor (VEGF), fms-like tyrosine kinase receptor-1 (sFlt-1), endoglin
Others	Antithrombin-III(AT-3), atrial natriuretic peptide (ANP), β_2-microglobulin, haptoglobin, transferrin, ferritin, 25-hydroxyvitamin D, genetic markers, cell-free fetal DNA, serum and urine proteomics and metabolomic markers, hepatic aminotransferases

ADAM12 = ADAM metallopeptidase domain 12; MMP = matrix metalloproteinase.
Adapted from Conde-Agudelo, 2014.

velocimetry determined by Doppler ultrasound in the first two trimesters should provide indirect evidence of this process and thus serve as a predictive test for

preeclampsia. Increased flow resistance results in an abnormal waveform represented by an exaggerated diastolic notch. These have value for fetal-growth restriction but not preeclampsia. Several flow velocity waveforms—alone or in combination—have been investigated for preeclampsia prediction. In some of these, predictive values for early-onset preeclampsia were promising. At this time, however, none is suitable for clinical use.

Pulse wave analysis. Like the uterine artery, finger arterial pulse "stiffness" is an indicator of cardiovascular risk. Investigators have preliminarily evaluated its usefulness in preeclampsia prediction.

Fetal-placental unit endocrine function

Several serum analytes that have been proposed to help predict preeclampsia are shown in Table 3. Many of these gained widespread use in the 1980s to identify fetal malformations and were also found to be associated with other pregnancy abnormalities such as neural-tube defects and aneuploidy. Although touted for hypertension prediction, in general, none of these tests has been shown to be clinically beneficial for that purpose.

Tests of renal function

Serum uric acid. One of the earliest laboratory manifestations of preeclampsia is hyperuricemia.It likely results from reduced uric acid clearance from diminished glomerular filtration, increased tubular reabsorption, and decreased secretion.

Microalbuminuria. As a predictive test for preeclampsia, microalbuminuria has sensitivities ranging from 7 to 90 percent and specificities between 29 and 97 percent. There are found unacceptable sensitivity and specificity for urine albumin: creatinine ratios.

Endothelial dysfunction and oxidant stress

As discussed earlier, endothelial activation and inflammation are major participants in the pathophysiology of the preeclampsia syndrome. As a result, compounds such as those listed in Table 3 are found in circulating blood of affected women, and some have been assessed for their predictive value.

Fibronectins. These high-molecular-weight glycoproteins are released from endothelial cells and extracellular matrix following endothelial injury. More than 30 years ago, plasma concentrations were reported to be elevated in women with preeclampsia. Following their systematic review, however, neither cellular nor total fibronectin levels were clinically useful to predict preeclampsia.

Coagulation activation. Thrombocytopenia and platelet dysfunction are integral features of preeclampsia. Platelet activation causes increased destruction and decreased concentrations, and mean platelet volume rises because of platelet immaturity. Although markers of coagulation activation are increased, the substantive overlap with levels in normotensive pregnant women stultifies their predictive value.

Oxidative stress. Increased levels of lipid peroxides coupled with decreased antioxidant activity have raised the possibility that markers of oxidative stress might predict preeclampsia. For example, malondialdehyde is a marker of lipid peroxidation. Other markers are various prooxidants or their potentiators. These include iron, transferrin, and ferritin; blood lipids, including triglycerides, free fatty acids, and lipoproteins; and antioxidants such as ascorbic acid and vitamin E. These have not been found to be predictive, and treatment to prevent preeclampsia with some of them has been studied.

Hyperhomocysteinemia causes oxidative stress and endothelial cell dysfunction and is characteristic of preeclampsia. Although women with elevated serum homocysteine levels at midpregnancy had a three- to fourfold risk of preeclampsia, these tests have not been shown to be clinically useful predictors.

Angiogenic factors. Evidence has accrued that an imbalance between proangiogenic and antiangiogenic factors is related to preeclampsia pathogenesis. Serum levels of some proangiogenic factors—vascular endothelial growth factor (VEGF) and placental growth factor (PlGF)—begin to decrease before clinical preeclampsia develops. And, recall as shown in Figure 3 that at the same time levels of some antiangiogenic factors such as sFlt-1 and sEng become increased. In one study, these abnormalities were identified coincidentally with rising uterine artery

Doppler resistance.

Sensitivities for all cases of preeclampsia ranged from 30 to 50 percent, and specificity was about 90 percent. Their predictive accuracy was higher for early-onset preeclampsia. These preliminary results suggest a clinical role for preeclampsia prediction. However, until this role is better substantiated, their general clinical use is not currently recommended. Automated assays are being studied, and the World Health Organization (WHO) began a multicenter trial in 2008 to evaluate these factors.

Cell-free fetal DNA

Cell-free fetal DNA can be detected in maternal plasma. It has been reported that fetal-maternal cell trafficking is increased in pregnancies complicated by preeclampsia. It is hypothesized that cell-free DNA is released by accelerated apoptosis of cytotrophoblasts. Cell-free fetal DNA quantification is not yet useful for prediction purposes.

Proteomic, metabolomic, and transcriptomic markers

Methods to study serum and urinary proteins and cellular metabolites have opened a new vista for preeclampsia prediction. Preliminary studies indicate that these may become useful.

Prevention

Various strategies used to prevent or modify preeclampsia severity have been evaluated. Some are listed in Table 4. In general, none of these has been found to be convincingly and reproducibly effective.

Table 5. Some methods to prevent preeclampsia that have been evaluated in randomized trials

Dietary manipulation	Low-salt diet, calcium or fish oil supplementation
Exercise	Physical activity, stretching
Cardiovascular drugs	Diuretics, antihypertensive drugs
Antioxidants	Ascorbic acid (vitamin C), α-tocopherol (vitamin E), vitamin D

Antithrombotic drugs	Low-dose aspirin, aspirin/dipyridamole, aspirin + heparin, aspirin + ketanserin

Dietary and lifestyle modifications

A favorite of many theorists and faddists for centuries, dietary "treatment" for preeclampsia has produced some interesting abuses.

Low-salt diet. One of the earliest research efforts to prevent preeclampsia was salt restriction. This interdiction was followed by years of inappropriate diuretic therapy. Although these practices were discarded, it ironically was not until relatively recently that the first randomized trial was done and showed that a sodium-restricted diet was ineffective in preventing preeclampsia in 361 women.

Calcium supplementation. Women with low dietary calcium intake were at significantly increased risk for gestational hypertension. Increased calcium intake lowered the risk for preeclampsia in high-risk women. In aggregate, most of these trials have shown that unless women are calcium deficient, supplementation has no salutary effects (Staff, 2014).

Fish oil supplementation. Cardioprotective fatty acids found in some fatty fishes are plentiful in diets of Scandinavians and American Eskimos. The most common dietary sources are EPA—eicosapentaenoic acid, ALA—alpha-linoleic acid, and DHA—docosahexaenoic acid. With proclamations that supplementation with these fatty acids would prevent inflammatory-mediated atherogenesis, it was not a quantum leap to posit that they might also prevent preeclampsia. Unfortunately, randomized trials conducted thus far have shown no such benefits.

Exercise. There are a few studies done to assess the protective effects of physical activity on preeclampsia.

Antihypertensive drugs. Women given diuretics had a decreased incidence of edema and hypertension but not of preeclampsia. Because women with chronic hypertension are at high risk for preeclampsia, several randomized trials—only a few placebo-controlled—have been done to evaluate various antihypertensive drugs to reduce the incidence of superimposed preeclampsia. A critical analysis of these

trials by Staff and coworkers (2014) failed to demonstrate salutary effects.

Antioxidants. There are inferential data that an imbalance between oxidant and antioxidant activity may play an important role in the pathogenesis of preeclampsia. Thus, naturally occurring antioxidants—vitamins C, D, and E—might decrease such oxidation. Indeed, women who developed preeclampsia were found to have reduced plasma levels of these antioxidants. There have now been several randomized studies to evaluate vitamin supplementation for women at high risk for preeclampsia. None of these studies showed reduced preeclampsia rates in women given vitamins C and E compared with those given placebo. The recent metaanalysis showed no benefits of vitamin D supplementation.

The rationale for the use of statins to prevent preeclampsia is that they stimulate hemoxygenase-1 expression that inhibits sFlt-1 release. There are preliminary animal data that statins may prevent hypertensive disorders of pregnancy.

Antithrombotic agents. There are sound theoretical reasons that antithrombotic agents might reduce the incidence of preeclampsia. As discussed on page 734, the syndrome is characterized by vasospasm, endothelial cell dysfunction, and inflammation, as well as activation of platelets and the coagulation-hemostasis system. Moreover, prostaglandin imbalance(s) may be operative, and other sequelae include placental infarction and spiral artery thrombosis.

Low-dose aspirin. In oral doses of 50 to 150 mg daily, aspirin effectively inhibits platelet thromboxane A2 biosynthesis but has minimal effects on vascular prostacyclin production. However, clinical trials have shown limited benefits. For example, results in Table 5 are from the MFMU Network, and none of the outcomes shown were significantly improved. Some reports are more favorable. For women assigned to receive antiplatelet agents, the relative risk for development of preeclampsia, superimposed preeclampsia, preterm delivery, or any adverse pregnancy outcome was significantly decreased by 10 percent. Another review and metaanalysis reported marginal benefits for low-dose aspirin and severe preeclampsia. A recent small Finnish multicenter trial included 152 women at high

risk for preeclampsia. Although there were no benefits to low-dose aspirin, the accompanying metaanalysis reported a lowering of risk. The 2013 Task Force recommended the use of low-dose aspirin in some high-risk women to prevent preeclampsia.

Table 6. Maternal-fetal medicine units network trial of low-dose aspirin in women at high risk for preeclampsia

		Preeclampsia (%)[a]	
Risk Factors	No.	Aspirin	Placebo
Normotensive, no proteinuria	1613	14.5	17.7
Proteinuria plus hypertension	119	31.7	22.0
Proteinuria only	48	25.0	33.3
Hypertension only	723	24.8	25.0
Insulin-dependent diabetes	462	18.3	21.6
Chronic hypertension	763	26.0	24.6
Multifetal gestation	678	11.5	15.9
Previous preeclampsia	600	16.7	19.0

[a]No statistically significant difference for any comparison between groups.
Data from Caritis, 1998.

Low-dose aspirin plus heparin. In women with lupus anticoagulant, treatment with low-dose aspirin and heparin mitigates thrombotic sequelae. Because of the high prevalence of placental thrombotic lesions found with severe preeclampsia, observational trials have been done to evaluate such treatments for affected women. Reported that better pregnancy outcomes in women given low-molecular-weight heparin plus low-dose aspirin compared with those given low-dose aspirin alone. Similar findings were reported in a trial that included 139 women with thrombophilia and a history of early-onset preeclampsia. Despite these small trials, evidence is insufficient to recommend these regimens to prevent preeclampsia.

MANAGEMENT OF PRE-ECLAMPSIA

So long as the etiology of pre-eclampsia remains obscure, the treatment is mostly empirical and symptomatic. While measures are directed to relieve edema

and hypertension, there is no specific therapy for proteinuria which automatically subsides with the control of hypertension.

Objectives are:

1. To stabilize hypertension and to prevent its progression to severe pre-eclampsia;
2. To prevent the complications;
3. To prevent eclampsia;
4. Delivery of a healthy baby in optimal time;
5. Restoration of the health of the mother in puerperium.

Hospital or home treatment: Ideally, all patients of pre-eclampsia are to be admitted in the hospital for effective supervision and treatment. There is no place of domiciliary treatment in an established case of preeclampsia. However, in some centers cases of pre-eclampsia are managed in the day care unit. In the developing countries where the prevalence of pre-eclampsia is more and hospital facilities are meagre, there is no alternative but to put the uncomplicated mild pre-eclampsias in domiciliary treatment regime. Rest, high protein diet are prescribed and the patient is investigated and checked. If the treatment fails to improve the patient is to be admitted. It is essential that she should be warned against the ominous symptoms, such as headache, visual disturbances, vomiting, epigastric pain or scanty urine.

Home health care

Many clinicians believe that further hospitalization is not warranted if hypertension abates within a few days, and this has legitimized third-party payers to deny hospitalization reimbursement. Consequently, many women with mild to moderate hypertension are managed at home. Outpatient management may continue as long as preeclampsia syndrome does not worsen and fetal jeopardy is not suspected. Sedentary activity throughout the greater part of the day is recommended. These women are instructed in detail to report symptoms. Home blood pressure and urine protein monitoring or frequent evaluations by a visiting nurse may prove beneficial. Caution is exercised regarding use of certain automated home blood pressure monitors.

In an observational study by Barton and associates, 1182 nulliparas with mild

gestational hypertension—20 percent had proteinuria—were managed with home health care. Their mean gestational ages were 32 to 33 weeks at enrollment and 36 to 37 weeks at delivery. Severe preeclampsia developed in approximately 20 percent, about 3 percent developed HELLP syndrome, and two women had eclampsia. Perinatal outcomes were generally good. In approximately 20 percent, there was fetal-growth restriction, and the perinatal mortality rate was 4.2 per 1000.

Several prospective studies have been designed to compare continued hospitalization with either home health care or a day-care unit. In a pilot study from Parkland Hospital, Horsager and colleagues (1995) randomly assigned 72 nulliparas with new-onset hypertension from 27 to 37 weeks either to continued hospitalization or to outpatient care. In all of these women, proteinuria had receded to less than 500 mg per day when they were randomized. Outpatient management included daily blood pressure monitoring by the patient or her family. Weight and dipstick spot urine protein determinations were evaluated three times weekly. A home health nurse visited twice weekly, and the women were seen weekly in the clinic. Perinatal outcomes were similar in each group. The only significant difference was that women in the home care group developed severe preeclampsia significantly more frequently than hospitalized women—42 versus 25 percent.

After evaluation, half remained hospitalized, whereas the other half was managed as outpatients. As shown in Table 40-7, the mean duration of hospitalization was 22.2 days for women with inpatient management compared with only 6.5 days in the home-care group. Preterm delivery before 34 and before 37 weeks was increased twofold in the outpatient group, but maternal and infant outcomes otherwise were similar.

Day-care unit

Another approach, popular in European countries, is day care. This approach has been evaluated by several investigators. Progression to overt preeclampsia and labor inductions were significantly increased in the routine management group. Surprisingly, costs for either scheme were not significantly different. Perhaps not surprisingly, general satisfaction favored day care.

Summary of hospitalization versus outpatient management

From the above, either inpatient or close outpatient management is appropriate for a woman with mild de novo hypertension, including those with nonsevere preeclampsia. Most of these studies were carried out in academic centers with dedicated management teams. That said, the key to success is close follow-up and a conscientious patient with good home support.

HOSPITAL MANAGEMENT

Rest: Admission in hospital and rest is helpful for continued evaluation and treatment of the patient. While in bed patient should be in left-lateral position as much as possible, to lessen the effects of vena caval compression.

Rest — (1) increases the renal blood flow -> diuresis

(2) increases the uterine blood flow ^ improves the placental perfusion

(3) reduces the blood pressure.

Diet: The diet should contain adequate amount of daily protein (about 100 gm). Usual salt intake is permitted. Fluids need not be restricted. Total calorie approximate 1600 cal/day.

Diuretics: The diuretics should not be used injudiciously, as they cause harm to the baby by diminishing placental perfusion and by electrolyte imbalance. The compelling reasons for its use are—

1. Cardiac failure
2. Pulmonary edema
3. Along with selective antihypertensive drug therapy (diazoxide group) where blood pressure reduction is associated with fluid retention
4. Massive edema, not relieved by rest and producing discomfort to the patient. The most potent diuretic commonly used is frusemide (Lasix) 40 mg, given orally after breakfast for 5 days in a week.

BASIC THERAPY

1. Prevention and treatment of convulsions (anticonvulsant therapy);
2. Antihypertensive therapy and control of BP;

3. Delivery

Table 7. Prevention and treatment of convulsions (anticonvulsant therapy)

Magnesium sulfate (MgSO4)	1. This is the main drug for the prevention of convulsions. Its reduces risks for developing of eclampsia. 2. IT IS NOT ANTIHYPERTENSIVE DRUG!!!! Magnesium sulphate is not used as an antihypertensive therapy because it either does not reduce BP or causes a short-term reduction of BP; 3. IT IS AN ANTICONVULSANT DRUG, so it cannot be interrupted on the basis of reduced blood pressure; 4. Elective treatment with MgSO4 reduces the risk of development eclampsia!!!
	Before administrating magnesium, check the knee reflex and diuresis: - In the absence of a knee reflex, do not administer the drug (magnesium sulfate) - In anuria – only loading dose
Loading dose	5 g MgSO4 (20 ml 25% solution - 10 ml magnesia and 10 ml isotonic solution in two syringes) i/v, within 15 - 20 min.
Maintaining dose	- 1 g/h, preferably by infusomat, if absent – i/v drip; - If signs of convulsions appear increase the maintenance dose to 2 g/h
Algorithm of administration	1. Syringe pump: - Supply the syringe pump with magnesium sulfate 25% - 20 ml; - Enter at speed: • If the maintenance dose is 1g/h, set the injection rate of 4ml/h; • If the maintenance dose is 2g/h, set the injection rate to 8ml/h. 2. Infusion pump: - Prepare solution: • Magnesium sulfate 25% - 100ml + isotonic solution of sodium chloride 0.9% - 400ml; - Enter at speed: • If the maintenance dose is 1 g/h, set the injection rate to 20 ml/h; • If the maintenance dose is 2g/h, set the injection rate to 40 ml/h. 3. I/V drip - Prepare a solution: • Magnesium sulfate 25% - 100ml + isotonic solution of sodium chloride 0.9% - 400ml; - Enter at speed:

	• If the maintenance dose is 1 g/h, set the injection rate of 7 drops/min with 20 ml (20 ml/h); • If the maintenance dose is 2g/h, set a speed of 14 drops/min to be applied, for one hour must be recovered of 40 ml (40 ml/h).
Monitoring	1. Every hour: - Diuresis 2. Every 15 minutes for the first two hours of magnesium sulphate fusion: - Breathing rate - Knee reflex. 3. Further, every 30 minutes before the end of the magnesium sulphate infusion: - Breathing rate - Knee reflex. 4. Pulsoximetry
Actions in injudicious administration of magnesium sulfate	1. Diuresis: Diuresis < 30 ml/hour, but no other symptoms of magnesium toxicity: • Decraease the rate of administration (to 0.5 g/h); • Perform an analysis of the total assignment of magnesium; 2. Absence of knee reflex: • Immediately stop the magnesium sulphate infusion; • Resume when reflexes appear; 3. Respiratory distress: • Respiratory rate less than 10 - 12 per minute: • Immediately stop the magnesium sulphate infusion; • Start oxygen supply via oxygen mask, ready to provide artificial ventilation of lungs if necessary; • Monitoring of RR; • Only if respiratory distress (or apnea) increase, administer the antidote
Antidote	Calcium gluconate 10% - 10 ml (1 g): • Enter i/v slowly, within 3 minutes; • Administer only if respiratory distress are aggravated (RR less than 10 - 12/min or apnea)
Duration of magnesium therapy	1. At least 24 hours after birth, or at least 24 hours after last convulsions. 2. If necessary (risk of eclampsia) - 3. Apply magnesium sulphate for more than 24 hours 4. Criteria for withdrawal of magnesium therapy • Individual intolerance of the drug; • Emergence of drug overdose symptoms;

	5. Decision on prolongation of pregnancy

Antihypertensives: Antihypertensive drugs have limited value in controlling blood pressure due to preeclampsia. The indications are:

1. Persistent rise of blood pressure specially where the diastolic pressure is over 110 mm Hg. The use is more urgent if associated with proteinuria.
2. In severe pre-eclampsia to bring down the blood pressure during continued pregnancy and during the period of induction of labor.

Table 8. Emergency antihypertensive therapy during pregnancy

	EMERGENCY ANTIHYPERTENSIVE THERAPY DURING PREGNANCY	
Activities	Mild	Severe
	BP- 140/90 to 159/109 mm. Hg	More than 160/110 mm.Hg
Criteria to start antihypertensive treatment	BP more than 150/100 mm. Hg	Immediatly start hypotensive treatment
Antihypertensive drugs	1. Nifedipin shot term in capsules – 10 mg 2. Nifedipin prolonged in capsules – 10 mg	
Characteristics	1. Used as a primary treatment for rapid reduction of BP; 2. It's a drug for emergency obstetric care	
IMPORTANT!	1. Nifedipin apply only peros! 2. Do not recommend sub-lingual use due to risk of hypotension and stress - fetus!	
Onset of action	In 20 minutes 1. Therefore, time to absorb the effects of the drug should be tolerated; 1. If BP does not decrease after 20 minutes, repeat (10-20 mg depending on BP)	
The maximum total primary dose	1. If the BP does not decrease after 20 minutes of primary intake, the drug (10 mg) must be repeated; 2. Total PRIMARY dose scheme: 3. 10 (mg) + 10 + 10 every 20 minutes; 4. The total duration of immediate and mid-term primary nifedipine is 60 minutes (1 hour); 5. Attention!!! The total initial dose must not exceed 50 mg/hour 6. If BP in 1 hour does not decrease less than 160/110 mm. Hg. after taking the maximum total primary dose of nifedipine -	

	50 mg, other drugs have to be considered for the treatment of hypertension
Side effects	Tachycardia and severe headache
Magnesium therapy	Nifedipin and sulphate magnesium can be used simultaneously

Table 9. **Antihypertensive therapy**

Drug	Mode of action	Dose
Methyl-dopa	Central and peripheral anti-adrenergic	250-500 mg tid or qid
Labetalol	action Adrenoceptor antagonist (a and	100 mg tid or qid 10-20
Nifedipine	вblockers) Calcium channel blocker	mg bid 10-25 mg bid
Hydralazine	Vascular smooth muscle relaxant	

Hypertensive crisis: Any of the following drugs (Table 10) can be used when the BP is >160/110 mm Hg or the mean arterial pressure (MAP) is >125 mm Hg:

Table 10. Hypertensive crisis therapy

Drug	Onset of action	Dose schedule	Maximum dose	Maintenance dose
Labetalol *	5 min	10-20 mg IV every 10 m	300 mg IV	40 mg/hr 10 mg/hr
Hydralazine	10 min	5 mg IV every 30 min	30 mg IV	4-6 hours interval
Nifedipine	10 min	10-20 mg oral, can be	240 mg/24	
Nitroglycerin		Repeated in 30 min 5	Short-term therapy only when	
Sodium	0.5-5 min	g/min IV	the other drugs have failed	
nitroprusside		0.25-5 g/kg/min IV		
* To avoid labetalol in women having asthma or cardiac failure.				

Progress chart: The effect of treatment should be evaluated by maintaining a chart which records the following:

1. Daily clinical evaluation for any symptoms (e.g. headache, epigastric pain, visual disturbances, oliguria);
2. Blood pressure: at least four times a day;

3. State of edema and daily weight record;
4. Fluidintake and urinary output;
5. Urine examination for protein daily and if present, to estimate its amount in 24 hours urine;
6. Blood for hematocrit, platelet count, uric acid, creatinine and liver function tests at least once a week;
7. Ophthalmoscopic examination on admission and to be repeated, if necessary;
8. Fetal well-being assessment

Favorable signs: In favorable cases, there is fall of blood pressure and weight with subsidence of edema. Urinary ouput increases with diminishing proteinuria, if previously present.

DURATION OF TREATMENT: The definitive treatment of pre-eclampsia is termination of pregnancy (delivery). As such, the aim of the above treatment is to continue the pregnancy, if possible, without affecting the maternal prognosis until the fetus becomes mature enough to survive in extrauterine environment (>37 weeks). Thus, the duration of treatment depends on

1. severity of pre-eclampsia;
2. duration of pregnancy;
3. response to treatment;
4. condition of the cervix.

Depending on the response to the treatment, the patients are grouped into the following:

1. Pre-eclamptic features subside and hypertension is mild.
2. Partial control of the pre-eclamptic features but the blood pressure maintains a steady high level.
3. Persistently increasing BP to severe level, despite the use of antihypertensive and/or addition of grave features such as headache, epigastric pain, oliguria, blurring of vision or HELLP syndrome.

Complete remission of all signs and symptoms is uncommon until after

delivery and the underlying disease pathology persists.

Group A: If the duration of pregnancy is remote from term, the patient may be discharged with advice to attend the antenatal clinic after one week. These women are not cured as majority (90%) develop recurrence.

If the patient is near term, she should be kept for a few days till completion of 37th week. Thereafter, decision is to be taken either to deliver her or to wait for spontaneous onset of labor by the due date. It is not wise to allow the pregnancy to continue beyond the expected date.

Group B: If the pregnancy is beyond 37 completed weeks, delivery is to be considered without delay. If less than 37 weeks, expectant treatment may be extended judiciously at least up to 34 weeks. Careful maternal and fetal well-being are to be monitored during the period (see chapter 11).

Group C: The couple is counseled. Termination of pregnancy (delivery) is considered irrespective of duration of gestation. Seizure prophylaxis (magnesium sulfate) should be started. Steroid therapy is considered if the duration of pregnancy is < 34 weeks. It prevents neonatal RDS, IVH and maternal thrombocytopenia.

METHODS OF DELIVERY:

• Induction of labor • Cesarean section

Induction of labor

Indications: It is indeed difficult to lay down hard and fast rules for the indications for induction.

1. Aggravation of the preeclamptic features in spite of medical treatment and/or appearance of newer symptoms such as epigastric pain.
2. Hypertension persists in spite of medical treatment with pregnancy reaching 37 weeks or more.
3. Acute fulminating pre-eclampsia irrespective of the period of gestation
4. Tendency of pregnancy to overrun the expected date.

Methods*:* If the cervix is ripe, surgical induction by low rupture of the membranes is the method of choice. Oxytocin infusion may be added. If the cervix is unripe, prostaglandin gel 500 ig intracervical or 1-2 mg in the posterior fornix is

inserted to make the cervix ripe when low rupture of the membranes can be performed. In severe pre-eclampsia, antihypertensive drugs should be used during induction.

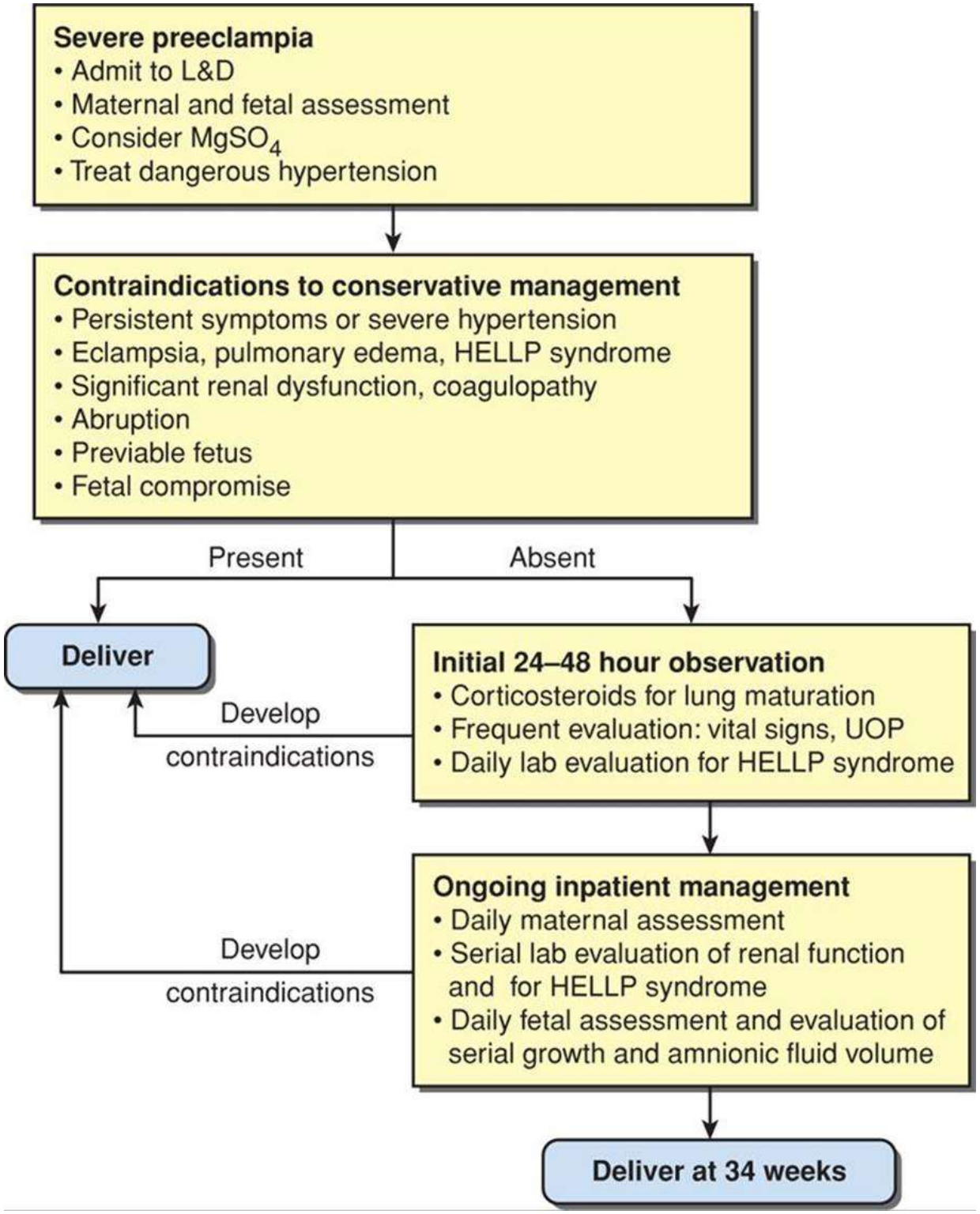


Fig. 14. Schematic clinical management algorithm for suspected severe preeclampsia at < 34 weeks. HELLP = hemolysis, elevated liver enzyme levels, low platelet count; L&D = labor and delivery; MgSO4 = magnesium sulfate; UOP = urine output.

Table 11. Indications for delivery in women < 34 weeks' gestation managed expectantly

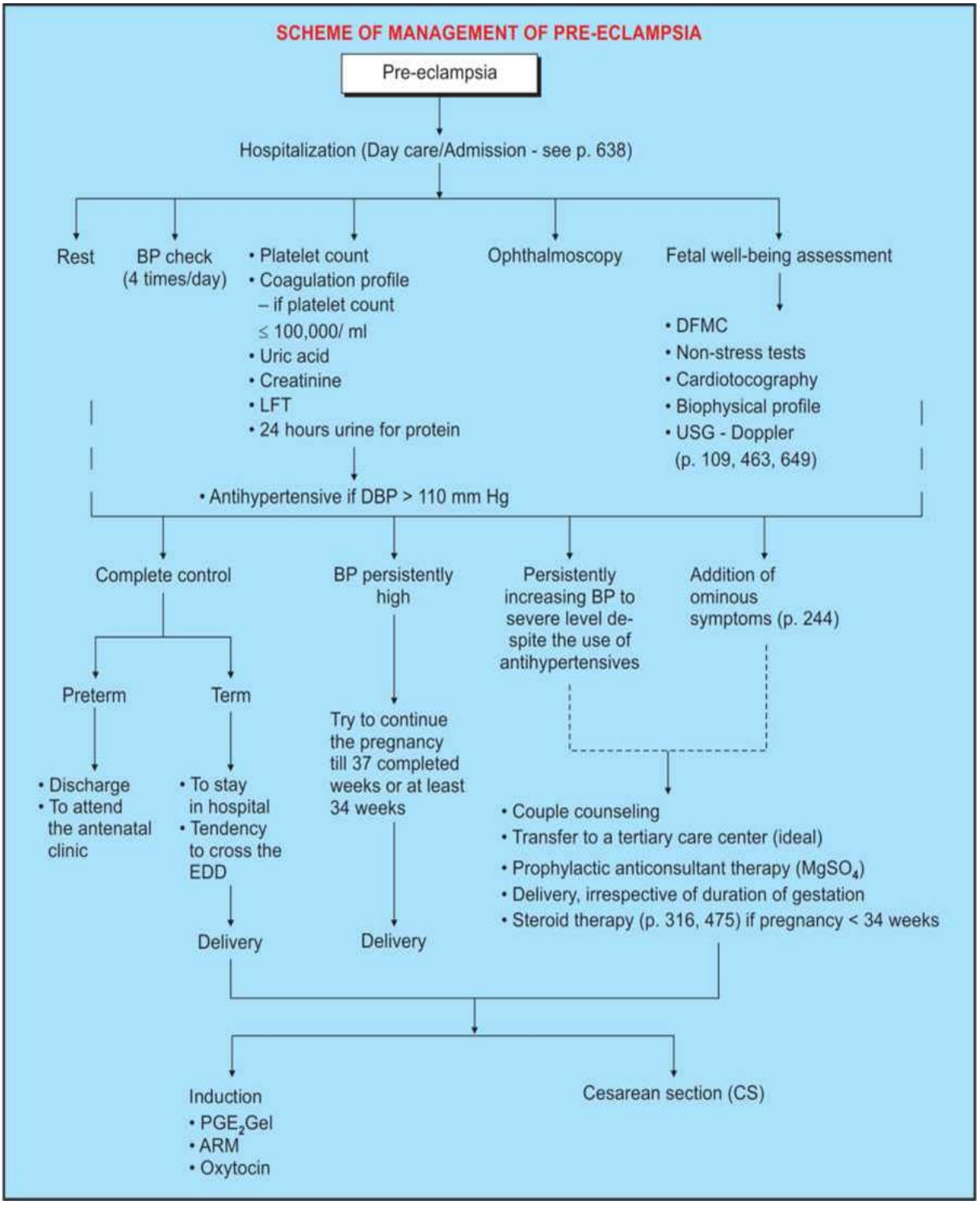
	Corticosteroid therapy for lung maturationa and delivery after maternal stabilization:
1	Uncontrolled severe hypertension
2	Eclampsia
3	Pulmonary edema
4	Placental abruption
5	Disseminated intravascular coagulation
6	Nonreassuring fetal status
7	Fetal demise
	Corticosteroid therapy for lung maturation—delay delivery 48 hr if possible:
1	Preterm ruptured membranes or labor
2	Thrombocytopenia < 100,000 /μL
3	Hepatic transaminase levels twice upper limit of normal
4	Fetal-growth restriction
5	Oligohydramnios
6	Reversed end-diastolic Doppler flow in umbilical artery
7	Worsening renal dysfunction
8	Initial dose only, do not delay delivery.

Cesarean section

Indications:

1. When an urgent termination is indicated and the cervix is unfavorable (unripe and closed);
2. Severe pre-eclampsia with a tendency to prolong the induction—delivery interval;
3. Associated complicating factors, such as elderly primigravidae, contracted pelvis, malpresentation;
4. The operation should be done by an experienced surgeon with the help of an expert anesthetist. Epidural anesthesia is preferred, unless there is coagulopathy.

Table 12. Scheme of management of pre-eclampsia



MANAGEMENT DURING LABOR:

Blood pressure tends to rise during labor and convulsions may occur (intrapartum eclampsia). The patient should be in bed. Antihypertensive drugs are

given if the blood pressure becomes high. Blood pressure and urinary output are to be noted frequently so as to detect imminent eclampsia. Prophylactic MgSO4 is started when systolic BP >160 diastolic >110, MAP >125 mm Hg. Careful monitoring of the fetal well-being is mandatory.

Labor duration is curtailed by low rupture of the membranes in the first stage; and forceps or ventouse insecond stage. Intravenous ergometrine following the delivery of the anterior shoulder is withheld as it maycause further rise of blood pressure. However, there is no contraindication of syntocinon IM or slow IV and to keep the patient under close observation for several hours.

To avoid maternal risks from cesarean delivery, steps to effect vaginal delivery are used initially in women with eclampsia. Following a seizure, labor often ensues spontaneously or can be induced successfully even in women remote from term. An immediate cure does not promptly follow delivery by any route, but serious morbidity is less common during the puerperium in women delivered vaginally.

Blood loss at delivery

Hemoconcentration or lack of normal pregnancy-induced hypervolemia is an almost predictable feature of severe preeclampsia-eclampsia shown in Figure 5. These women, who consequently lack normal pregnancy hypervolemia, are much less tolerant of even normal blood loss than are normotensive pregnant women. It is of great importance to recognize that an appreciable fall in blood pressure soon after delivery most often means excessive blood loss and not sudden resolution of vasospasm and endothelial damage. When oliguria follows delivery, the hematocrit should be evaluated frequently to help detect excessive blood loss. If identified, hemorrhage should be treated appropriately by careful crystalloid and blood transfusion.

Analgesia and anesthesia

During the past 20 years, the use of conduction analgesia for women with preeclampsia syndrome has proven ideal. Initial problems with this method included hypotension and diminished uterine perfusion caused by sympathetic blockade in these women with attenuated hypervolemia. But pulmonary edema was mitigated by

techniques that used slow induction of epidural analgesia with dilute solutions of anesthetic agents to counter the need for rapid infusion of large volumes of crystalloid or colloid to correct maternal hypotension. Moreover, epidural blockade avoids general anesthesia, in which the stimulation of tracheal intubation may cause sudden severe hypertension. Such blood pressure increases, in turn, can cause pulmonary edema, cerebral edema, or intracranial hemorrhage. Finally, tracheal intubation may be particularly difficult and thus hazardous in women with airway edema due to preeclampsia.

At least three randomized studies have been performed to evaluate these methods of analgesia and anesthesia. They had not been given labor epidural analgesia and were randomized to receive general anesthesia, epidural analgesia, or combined spinal-epidural analgesia. Their average preoperative blood pressures approximated 170/110 mm Hg, and all had proteinuria. Anesthetic and obstetrical management included antihypertensive drug therapy and limited intravenous fluids as previously described. Perinatal outcomes in each group were similar. Maternal hypotension resulting from regional analgesia was managed with judicious intravenous fluid administration. In women undergoing general anesthesia, maternal blood pressure was managed to avoid severe hypertension (Fig. 15). There were no serious maternal or fetal complications attributable to any of the three anesthetic methods. It was concluded that all three are acceptable for use in women with pregnancies complicated by severe preeclampsia if steps are taken to ensure a careful approach to the selected method.

Another randomized study included 70 women with severe preeclampsia receiving spinal analgesia versus general anesthesia. All had a nonreassuring fetal heart rate tracing as the indication for cesarean delivery, and outcomes were equivalent. Decreased mean arterial blood pressure induced by epidural blockade could be effectively counteracted by phenylephrine infusion to maintain cardiac output. A standardized protocol limited intravenous fluids to 100 mL/hr. More women—9 percent—from the group assigned to epidural analgesia required ephedrine for hypotension. As expected, pain relief was superior in the epidural

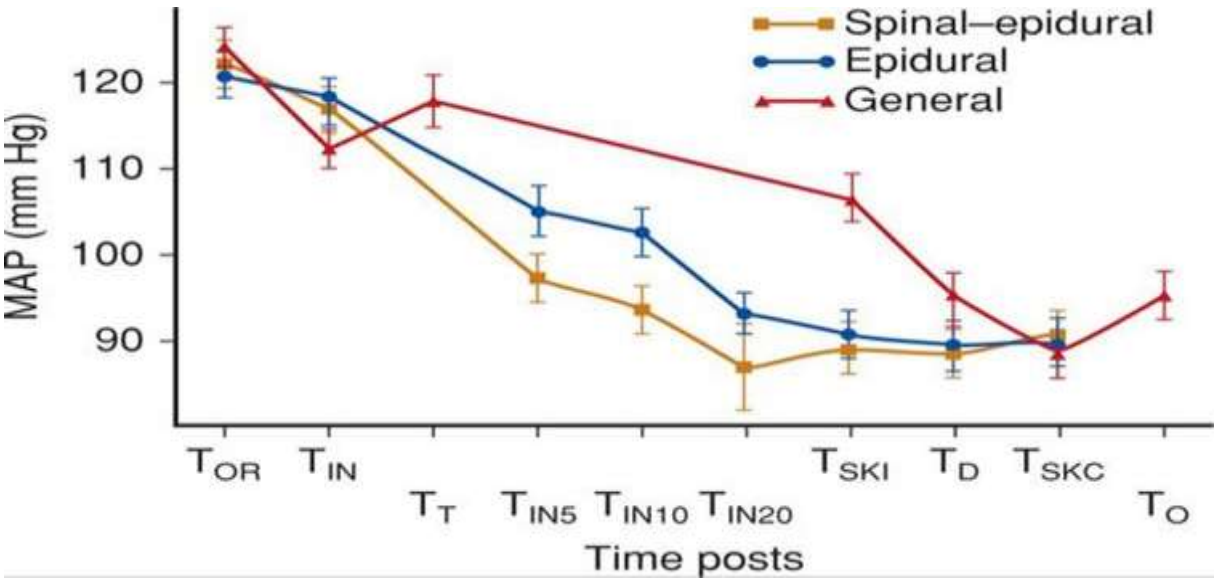


Fig. 15. Blood pressure effects of general anesthesia versus epidural or spinal–epidural analgesia for cesarean delivery in 80 women with severe preeclampsia. MAP = mean arterial pressure. Time posts (T): OR = operating room; IN = induction of anesthesia; T = tracheal intubation; IN5 = induction + 5 min; IN10 = induction + 10 min; IN20 = induction + 20 min; SKI = skin incision; D = delivery; SKC = skin closure; O = extubation. (From Wallace, 1995, with permission.)

group, but maternal and neonatal complications were similar between groups. One woman in each group developed pulmonary edema.

It is important to emphasize that epidural analgesia is not to be considered treatment of preeclampsia. Maternal and neonatal outcomes were similar in the two study groups. However, as shown in Table 40-17, epidural analgesia resulted in a greater decrement of mean maternal arterial pressure compared with meperidine, but it was not superior in preventing recurrent severe hypertension later in labor.

PUERPERIUM: The patient is to be watched closely for at least 48 hours, the period during which convulsions usually occur. Antihypertensive drug treatment should be continued if the BP is high (systolic >150 mm Hg or diastolic >100 mm Hg). Oral nifedipine 10 mg at every 6 hours is given until BP remains below the hypertensive levels for at least 48 hours. Oral frusemide 20 mg a day for 5 days is also found to improve recovery and to reduce the need of antihypertensive drugs in severe pre-eclampsia. Magnesium sulfate (for at least 24 hours) and antihypertensive drugs may be needed in women with severe hypertension and symptoms of acute fulminant pre-eclampsia during the postpartum period. The patient is to be kept in

the hospital, till the blood pressure is brought down to a safe level and proteinuria disappears.

Table 13. Comparison of cardiovascular effects of epidural versus patient-controlled meperidine analgesia during labor in women with gestational hypertension

Hemodynamic Change	Labor Analgesia		*p* value
	Epidural (n = 372)	Meperidine (n = 366)	
Mean arterial pressure change (mean)	−25 mm Hg	−15 mm Hg	< 0.001
Ephedrine for hypotension (%)	11%	0	< 0.001
Severe hypertension after analgesia (%) (BP ≥ 160/110 mm Hg)	< 1%	1%	NS

NS = not significant.
Data from Lucas, 2001.

Persistent severe postpartum hypertension

The potential problem of antihypertensive agents causing serious compromise of uteroplacental perfusion and thus of fetal well-being is obviated by delivery. Postpartum, if difficulty arises in controlling severe hypertension or if intravenous hydralazine or labetalol are being used repeatedly, then oral regimens can be given. Examples include labetalol or another β-blocker, nifedipine or another calcium-channel blocker, and possible addition of a thiazide diuretic. Persistent or refractory hypertension is likely due to mobilization of pathological interstitial fluid and redistribution into the intravenous compartment, underlying chronic hypertension, or usually both. In women with chronic hypertension and left-ventricular hypertrophy, severe postpartum hypertension can cause pulmonary edema from cardiac failure.

COUNSELING FOR FUTURE PREGNANCIES

Defective remodeling of the spiral arteries in some placentations has been posited as the cause of at least one preeclampsia phenotype. Lack of deep placentation has been associated with preeclampsia, placental abruption, fetal-

growth restriction, and preterm birth. With this type of "overlap syndrome," hypertensive disorders may serve as markers for subsequent preterm labor and fetal-growth restriction. For example, even in subsequent nonhypertensive pregnancies, women who had preterm preeclampsia are at increased risk for preterm birth. In addition, women who have had either gestational hypertension or preeclampsia are at higher risk to develop hypertension in future pregnancies. Generally, the earlier preeclampsia is diagnosed during the index pregnancy, the greater the likelihood of recurrence. Nulliparas diagnosed with preeclampsia before 30 weeks have a recurrence risk as high as 40 percent during a subsequent pregnancy. In a prospective study of 500 women previously delivered for preeclampsia at 37 weeks, the recurrence rate in a subsequent gestation was 23 percent. These investigators also found an increased risk during subsequent pregnancies for preterm delivery and fetal-growth restriction. Women whose first pregnancy was complicated by preeclampsia between 32 and 36 weeks had a significant twofold increased incidence of preeclampsia in their second pregnancy—25 versus 14 percent—compared with women who were normotensive during the first pregnancy. Analyzed from another view, they also found that preterm delivery and fetal-growth restriction in the first pregnancy significantly increased the risk for preeclampsia in the second pregnancy.

As probably expected, women with HELLP syndrome have a substantive risk for recurrence in subsequent pregnancies. In two studies the risk ranged from 5 to 26 percent, but the true recurrence risk likely lies between these two extremes. Even if HELLP syndrome does not recur with subsequent pregnancies, there is a high incidence of preterm delivery, fetal-growth restriction, placental abruption, and cesarean delivery.

LONG-TERM CONSEQUENCES

Over the past 20 years, evidence has accrued that preeclampsia, like fetal-growth disorders and preterm birth, is a marker for subsequent cardiovascular morbidity and mortality. Thus, women with hypertension identified during pregnancy should be evaluated during the first several months postpartum and

counseled regarding long-term risks. Hypertension attributable to pregnancy should resolve within 12 weeks of delivery. Persistence beyond this time is considered to be chronic hypertension. Importantly, even if hypertension does not persist in the short term, convincing evidence suggests that the risk for long-term cardiovascular morbidity is significantly increased in preeclamptic women.

ECLAMPSIA

In a woman with preclampsia, a convulsion that cannot be attributed to another cause is termed eclampsia. The seizures are generalized and may appear before, during, or after labor. The proportion who do not develop seizures until after 48 hours postpartum approximates 10 percent

ECLAMPSIA

The term eclampsia is derived from a Greek word, meaning "like a flash of lightening". It may occur quite abruptly, without any warning manifestations. In majority (over 80%); however, the disease is preceded by features of severe pre-eclampsia.

Pre-eclampsia when complicated with generalized tonic-clonic convulsions and/or coma is called eclampsia. Thus, it may occur in patients with pre-eclampsia or in patients who have pre-eclampsia superimposed on essential hypertension or chronic nephritis.

INCIDENCE: The incidence varies widely from country to country and even between different zones of the same country. While in the developed countries, its prevalence is far and few but in the developing ones, particularly in the rural areas, it is still high and contributes significantly to the maternal deaths. The hospital incidence in India ranges from 1 in 500 to 1 in 30. It is more common in primigravidae (75%), five times more common in twins than in singleton pregnancies and occurs between the 36th week and term in more than 50%.

PATHOPHYSIOLOGY: Since eclampsia is a severe form of pre-eclampsia,

the histopathological and biochemical changes are similar although intensified than those of pre-eclampsia as already described.

CAUSE OF CONVULSION: The cause of cerebral irritation leading to convulsion is not clear. The irritation may be provoked by:

1. Anoxia — spasm of the cerebral vessels ^ increased cerebral vascular resistance fall in cerebral oxygen consumption ^ anoxia,
2. Cerebral edema — may contribute to irritation,
3. Cerebral dysrhythmia — increases following anoxia or edema. There is excessive release of excitatory neurotransmitters (glutamate).

ONSET OF FITS: Fits occur more commonly in the third trimester (more than 50%). On rare occasions, convulsion may occur in early months as in hydatidiform mole.

- Antepartum (50%): Fits occur before the onset of labor. More often, labor starts soon after and at times, it is impossible to differentiate it from intrapartum ones.
- Intrapartum (30%): Fits occur for the first time during labor.
- Postpartum (20%): Fits occur for the first time in puerperium, usually within 48 hours of delivery. Fits occurring beyond 48 hours but less than 4 weeks after delivery is accepted as late postpartum eclampsia.
- Intercurrent (Antenatal): When the patient becomes conscious after recovery from convulsions and the pregnancy continues beyond 48 hours. The time limit is arbitrary as a period of 7-10 days has also been mentioned.

Cerebral pathology includes cortical or subcortical edema, infarction and hemorrhage. The neurological abnormalities are often due to hypoxia, ischemia or edema. Several neurodiagnostic tests e.g. EEG, CAT, cerebral Doppler Velocimetry, MRI, MRI angiography reveal presence of edema and infarction. Findings are similar to those as seen in hypertensive encephalopathy. Cerebral imaging is indicated when there is focal neurologic deficits, prolonged coma, or atypical presentation for eclampsia.

CLINICAL FEATURES OF ECLAMPSIA

Except on rare occasions, an eclamptic patient always shows previous

manifestations of acute fulminating pre-eclampsia — called premonitory symptoms (mentioned earlier).

Eclamptic convulsion or fit: The fits are epileptiform and consist of four stages.

- Premonitory stage: The patient becomes unconscious. There is twitching of the muscles of the face, tongue, and limbs. Eyeballs roll or are turned to one side and become fixed. This stage lasts for about 30 seconds.
- Tonic stage: The whole body goes into a tonic spasm — the trunk-opisthotonus, limbs are flexed and hands clenched. Respiration ceases and the tongue protrudes between the teeth. Cyanosis appears. Eyeballs become fixed. This stage lasts for about 30 seconds.
- Clonic stage: All the voluntary muscles undergo alternate contraction and relaxation. The twitchings start in the face then involve one side of the extremities and ultimately the whole body is involved in the convulsion. Biting of the tongue occurs. Breathing is stertorous and blood stained frothy secretions fill the mouth; cyanosis gradually disappears. This stage lasts for 1-4 minutes.
- Stage of coma: Following the fit, the patient passes on to the stage of coma. It may last for a brief period or in others deep coma persists till another convulsion. On occasion, the patient appears to be in a confused state following the fit and fails to remember the happenings. Rarely, the coma occurs without prior convulsion.
- The fits are usually multiple, recurring at varying intervals. When it occurs in quick succession, it is called status eclampticus. Following the convulsions, the temperature usually rises; pulse and respiration rates are increased and so also the blood pressure. The urinary output is markedly diminished; proteinuria is pronounced, and the blood uric acid is raised.

DIFFERENTIAL DIAGNOSIS: The diseases, which are associated with convulsions and/or coma are to be borne in mind while arriving at the diagnosis of eclampsia. Such diseases are: (1) Epilepsy, (2) Hysteria,

(3) Encephalitis, (4) Meningitis, (5) Puerperal cerebral thrombosis, (6) Poisoning, (7) Cerebral malaria in tropics, and (8) Intracranial tumors. Absence of previous

history of convulsion with presence of edema, hypertension and proteinuria along with fits or coma during pregnancy or soon after, points to the diagnosis of eclampsia. In doubtful cases, it is desirable to place the patient in the obstetric unit for observation until the final diagnosis is made.

Table 14. Differential diagnosis

Cardiovascular	Hematological	Renal	Central nervous system	Hepatic
Generalized vasospasm Peripheral vascular resistance CVP Pulmonary wedge pressure	Plasma volume Hemoconcentration Coagulation disorder Blood viscosity	GFR Renal plasma flow Serum uric acid	Cerebral edema Cerebral hemorrhage Posterior (parietal and occipital lobe) reversible encephalopathy syndrome Basal ganglia brain stem lesion (rare)	Liver cell damage Periportal necrosis Subscapular hematoma

PROGNOSIS OF ECLAMPSIA

MATERNAL:

Immediate: Once the convulsion occurs, the prognosis becomes uncertain. Prognosis depends on many factors and the ominous features are:

1. Long interval between the onset of fit and commencement of treatment (late referral).
2. Antepartum eclampsia specially with long delivery interval.
3. Number of fits more than 10.
4. Coma in between fits.

5. Temperature over 102°F with pulse rate above 120/minute.
6. Blood pressure over 200 mm Hg systolic.
7. Oliguria (< 400 mL/24 hours) with proteinuria > 5 gm/24 hours.
8. Nonresponse to treatment.
9. Jaundice.

Mortality: Maternal mortality in eclampsia is very high in India and varies from 2-30%, much more in rural based hospital than in the urban counterpart. However, if treated early and adequately, the mortality should be even less than 2%.

Causes of maternal deaths:

1. Cardiac failure.
2. Pulmonary edema.
3. Aspiration and/or septic pneumonia.
4. Cerebral hemorrhage.
5. Acute renal failure.
6. Cardiopulmonary arrest.
7. Adult respiratory distress syndrome (ARDS).
8. Pulmonary embolism.
9. Postpartum shock.
10. Puerperal sepsis. Maternal complications are higher in antepartum eclampsia.

Remote*:* If the patient recovers from acute illness, she is likely to recover rapidly within 2-3 weeks. Recurrence of eclampsia in subsequent pregnancies is uncommon, although chance of pre-eclampsia is about 30%.

FETAL: The perinatal mortality is very high to the extent of about 30-50%. The causes are:

1. Prematurity —spontaneous or induced,
2. Intrauterine asphyxia due to placental insufficiency arising out of infarction, retroplacental hemorrhage and spasm of uteroplacental vasculature,
3. Effects of the drugs used to control convulsions,
4. Trauma during operative delivery.

MANAGEMENT OF ECLAMPSIA

Prediction and prevention: In majority of cases, eclampsia is preceded by severe pre-eclampsia. Thus the prevention of eclampsia rests on early detection and effective institutional treatment with judicious termination of pregnancy during pre-eclampsia. However, eclampsia can occur bypassing the preeclamptic state and as such, it is not always a preventable condition. Eclampsia may present in atypical ways; hence, it is at times difficult to predict. Use of antihypertensive drugs, prophylactic anticonvulsant therapy and timely delivery are important steps. Close monitoring during labor and 24 hours' postpartum, are also important in prevention of eclampsia. Magpie trial (2002) showed prophylactic use of magnesium sulfate lowers the risk of eclampsia. Unfortunately, 30-85 percent of cases of eclampsia remained unpreventable.

First aid treatment outside the hospital: The patient, either at home or in the peripheral health centers should be shifted urgently to the tertiary referral care hospitals. There is no place of continuing the treatment in such places. Transport of an eclamptic patient to a tertiary care center is important. Such a patient needs neonatal and obstetric intensive care management. Important steps in transport are:

- All maternal records and a detailed summary should be sent with the patient
- BP should be stabilized and convulsions should be arrested
- Magnesium sulfate (4 gm IV loading dose with 10 gm IM) is given. Labetalol 20 mg IV is given to control hypertension. Diuretic is given if there is pulmonary edema. Diazepam if used should be given 5 mg slowly over one minute period to avoid apnea or cardiac arrest
- One medical personnel or a trained midwife should accompany the patient in the ambulance equipped to prevent injury, recurrent fits and to clear air passage.

Hospital—the principles of management are:

- Maintain: airway, breathing & circulation
- Hemodynamic stabilization (control BP)

- Oxygen administration 8-10 L/min
- Arrest convulsions (see below)
- Ventilatory support (if needed)
- Prevention of injury
- Organize investigations
- Deliver by 6-8 hours
- Prevention of complications
- Postpartum care (intensive)

GENERAL MANAGEMENT (MEDICAL AND NURSING)

- Supportive care: (i) to prevent serious maternal injury from fall, (ii) prevent aspiration, (iii) to maintain airway and (iv) to ensure oxygenation.
- Patient is kept in a railed cot and a tongue blade is inserted between the teeth. She is kept in the lateral decubitus position to avoid aspiration. Vomitus and oral secretions are removed by frequent suctioning, oxygenation is maintained through a face mask (8-10 L/min) to prevent respiratory acidosis. Oxygenation is monitored using a transcutaneous pulse oximeter. Arterial blood gas analysis is needed when O2 saturation falls below 92 percent. Sodium bicarbonate is given when the pH is below 7.10. The patient should have a doctor or at least a trained midwife for constant supervision.
- Detailed history is to be taken from the relatives, relevant to the diagnosis of eclampsia, duration of pregnancy, number of fits and nature of medication administered outside.
- Examination: Once the patient is stabilized, a thorough but quick general, abdominal and vaginal examinations are made. A self retaining catheter is introduced and the urine is tested for protein. The continuous drainage facilitates measurement of the urinary output and periodic urine analysis.
- Monitoring: Half hourly pulse, respiration rates and blood pressure are recorded. Hourly urinary output is to be noted. If undelivered, the uterus should be palpated at regular intervals to detect the progress of labour and the fetal heart rate is to be monitored. Immediately after a convulsion, fetal bradycardia is common.

- Fluid balance: Crystalloid solution (Ringer's solution) is started as a first choice. Total fluids should not exceed the previous 24 hours urinary output plus 1000 ml (insensible loss through lungs and skin). Normally, it should not exceed 2 litres in 24 hours. Infusion of balanced salt solution should be at the rate of 1 ml/kg per hour. In pre-eclampsia-eclampsia although there is hypovolemia, the tissues are over loaded. An excess of dextrose or crystalline solutions should not be used as it will aggravate the tissue overload leading to pulmonary edema and adult respiratory distress syndrome. Colloids (albumin or hemaccel) remain in the vascular tree and they withdraw fluids from the interstitial space. Unless used carefully, they can lead to circulatory overload. CVP monitoring is needed for a patient with severe hypertension and reduced urine output. In pre-eclampsia, eclampsia, both the PCWP and CVP appear to be in the low to normal range. Invasive hemodynamic monitoring is rarely indicated.
- Antibiotic: To prevent infection, Ceftriaxone 1 gm IV twice daily is given.

SPECIFIC MANAGEMENT: Anticonvulsant and sedative regime: The aim is to control the fits and to prevent its recurrence. In areas where eclampsia is frequently encountered, it is obvious that the obstetric care is inadequate. In such circumstances any complicated regime is unlikely to give good result. Magnesium sulfate is the drug of choice. It acts as a membrane stabilizer and neuroprotector. It reduces motor endplate sensitivity to acetylcholine. Magnesium blocks neuronal calcium influx also. It induces cerebral vasodilatation, dilates uterine arteries, increases production of endothelial prostacyclin and inhibits platelet activation. It has no detrimental effects on the neonate within therapeutic level. It has got excellent result with maternal mortality of 3%. It does not control hypertension.

Table 15. Treatment of eclamptic convulsions (anticonvulsant therapy)

TREATMENT OF ECLAMPTIC CONVULSIONS (ANTICONVULSANT THERAPY)	
At the time of convulsions	Manipulations
At the time of the	Start the magnesium therapy:

convulsion, the patient had not yet received the magnesium therapy	1. Loading dose: 5 g (20 ml 25% solution - 10 ml magnesium sulfate and 10 ml isotonic solution in two syringes) i/v of 15-20 min; 2. Further a maintenance dose of 1 - 2 g/h (preferably by infusomate or i/v drip) with continuous monitoring (knee reflex, diuresis, RR)
At the time of the convulsion, the patient had already received a loading of magnesium sulfate, but the injection of a maintenance dose is still not started	1. Additionally inject 2 g of dry MgSO4 (8 ml 25% sulphate solution «+» 12 ml isotonic solution) i/v drip for 5 min; 2. Start maintenance magnesial therapy
At the time of the convulsions, the patient is already receiving a maintaining dose of magnesium sulfate	1. Introduce i/v 2 g MgSO4 (8 ml 25% solution «+» 12 ml isotonic solution) within 5 min; 2. Furthermore, if the maintenance dose before the convulsions was 1 g/h, increase it to 2 g/h, with continuous monitoring of the signs of overdose (knee reflex, diuresis, RR); 3. If the maintenance dose before the onset is 2 g/h but the drug was administered i/v drip (not infusomate): 4. If there is absent magnesium sulfate or if after delivery is individually intolerant, administrate diazepams: 10 mg i/v slowly, for more than 2 minutes; 4.2 Administration may be repeated every 10 minutes; 5. If the fits controlled, despite the available therapy: - Thiopental natrium 150 mg i/v; - Artificial ventilation

Table 16. Regimens of $MgSO_4$ for the management of severe pre-eclampsia and eclampsia

Regimens of $MgSO_4$ for the management of severe pre-eclampsia and eclampsia

Regimen	Loading dose	Maintenance dose
Intramuscular (Pritchard)	4 gm IV over 3-5 min followed by 10 gm deep IM (5 gm in each buttock)	5 gm IM 4 hourly in alternate buttock
Intravenous (Zuspan or Sibai)	4-6 gm IV over 15-20 min	1-2 gm/hr IV infusion

Repeat injections are given only if the knee jerks are present, urine output exceeds 30 mL/hour and the respiration rate is more than 12 per minute. The therapeutic level of serum magnesium is 4-7 mEQ/L. Magnesium sulfate is continued for 24 hours after the last seizure or delivery whichever is later. For recurrence of fits, further 2 gm IV bolus is given over 5 min in the above regimens. Other regimens are:

1. Lytic cocktail (Menon 1961) using chlorpromazine, promethazine and pethidine.
2. Diazepam (Lean)
3. Phenytoin. Compared to other regimes, magnesium sulfate has got the following benefits:

a. it controls fits effectively without any depression effect to the mother or the infant.
b. reduced risk of recurrent convulsions
c. significantly reduced maternal death rate (3%) and
d. reduced perinatal mortality rate.

Antihypertensives and diuretics: Inspite of anticonvulsant and sedative regime, if the blood pressure remains more than 160/110 mm Hg, antihypertensive drugs should be administered. Drugs commonly used are parenteral, hydralazine, labetalol, calcium channel blockers or nitroglycerin.

Presence of pulmonary edema requires diuretics. In such cases, the potent one (frusemide) should be administered in doses of 20-40 mg intravenously and to be repeated at intervals.

Management during fit:

a. In the premonitory stage, a mouth gag is placed in between the teeth to prevent tongue bite and should be removed after the clonic phase is over.
b. The air passage is to be cleared off the mucus with a mucus sucker. The patient's head is to be turned to one side and the pillow is taken off. Raising the footend of the bed, facilitates postural drainage of the upper respiratory tract.
c. Oxygen is given until cyanosis disappears.

Status eclampticus: Thiopentone sodium 0.5 gm dissolved in 20 mL of 5% dextrose is given intravenously very slowly. The procedure should be supervised by an expert anesthetist. If the procedure fails, use of complete anesthesia, muscle relaxant and assisted ventilation can be employed. In unresponsive cases, cesarean section in ideal surroundings may be a lifesaving attempt.

Treatment of complications: Prophylactic use of antibiotics markedly reduces the complications like pulmonary and puerperal infection.

Pulmonary edema: Frusemide 40 mg IV followed by 20 g. of mannitol IV reduces pulmonary edema and also prevents adult respiratory distress syndrome. Pulse oximeter is very useful to monitor such a patient. Aspiration of the mucus from the tracheobronchial tree by a suction apparatus is done.

Heart failure: inhalation, parenteral lasix and digitalis are used.

Anuria: The treatment should be in the line as formulated in the chapter of anuria. opamine infusion (1 l^g/kg) is given with oliguria when CVP is >8 mm Hg. It is often surprising that urine output returns to normal following delivery.

Hyperpyrexia: It is difficult to bring down the temperature as it is central in origin. However, cold sponging and antipyretics may be tried.

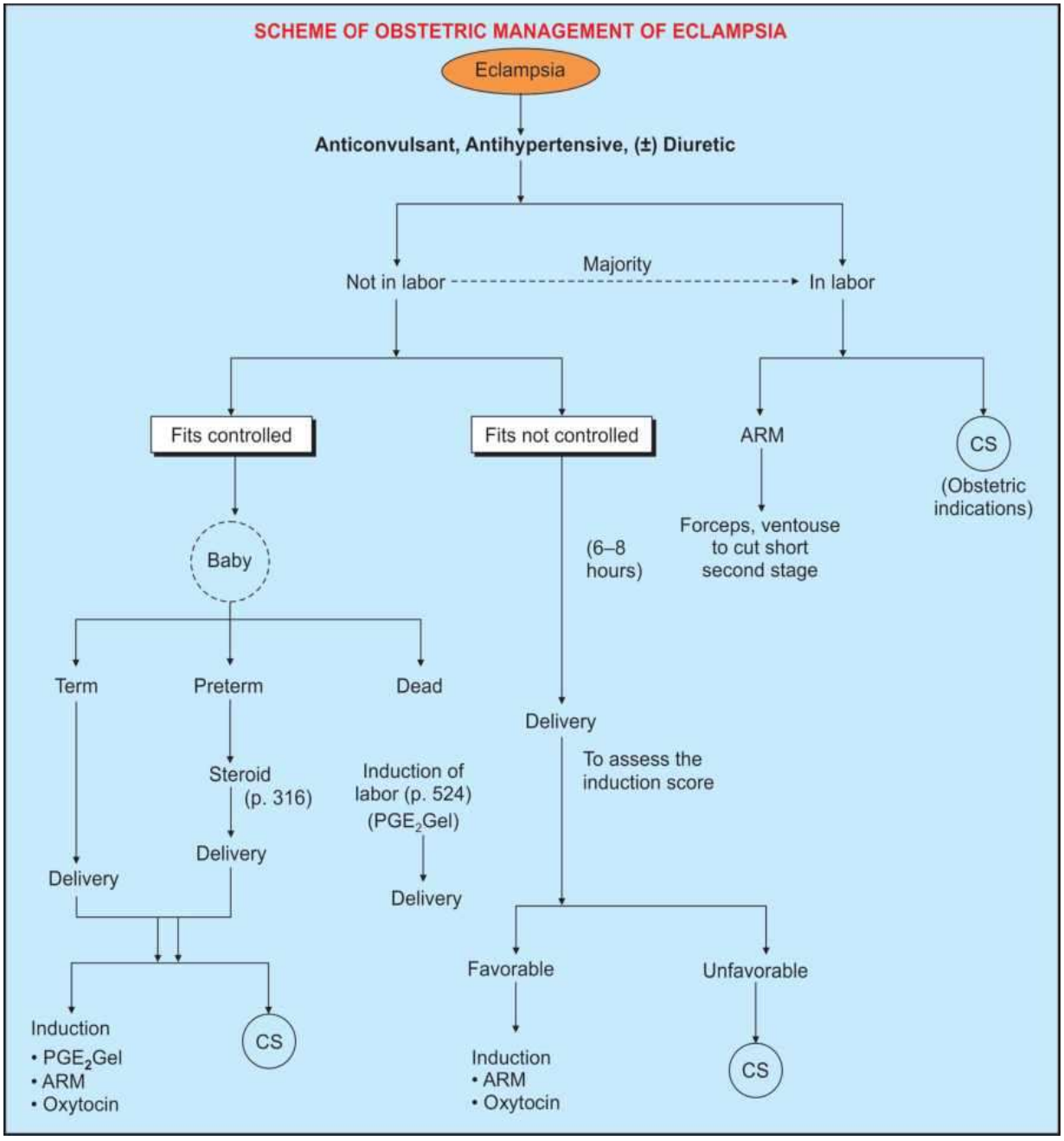
Psychosis: Chlorpromazine or Eskazine (trifluoperazine) is quite effective.

Intensive care monitoring: Patient with multiple medical problems needs to be admitted in an intensive care unit where she is looked after by a team consisting of an obstetrician, a physician and an expert anesthetist. Cardiac, renal or pulmonary complications are managed effectively. Use of blood gas analyzer (to detect hypoxia and acidosis), pulse oximeter and central venous pressure monitor should be done

depending on individual case. A deeply unconscious patient with raised intracranial pressure needs steroid and or diuretic therapy. CT scan or MRI may be needed for the diagnosis.

OBSTETRIC MANAGEMENT: During pregnancy: In majority of cases with antepartum eclampsia, labor start soon after convulsions. But when labor fails to start, the management depends on—(i) whether the fits are controlled or not and (ii) the maturity of the fetus. The decision to deliver is made once the woman is stable.

Table 17. Scheme of obstetric management of eclampsia.



- **Fits controlled:**

***Baby mature*:** Delivery should be done. (a) If the cervix is favorable and there is no contraindication of vaginal delivery, surgical induction by low rupture of the membranes is done. Oxytocin drip may be added, if needed. (b) When the cervix is unfavorable, cervical ripening with PGE2 gel or pessary could be achieved before ARM. (c) If the cervix is unfavorable and/or there is obstetric contraindication of vaginal delivery, cesarean section is done.

Baby premature (<37 weeks): Delivery is recommended in a set up with neonatal intensive care unit (NICU). The underlying disease process of pre-eclampsia eclampsia persists until the woman delivers. At times the disease process may flare up. Moreover, there lies the risk of recurrent convulsions and IUFD. Steroid therapy is given when pregnancy is less than 34 weeks. Conservative management at very early pregnancy may improve perinatal outcome but this must be carefully balanced with maternal well being (RCOG-2006).

APGAR SCORING SYSTEM

Evaluation on the Apgar scale is an objective method for quantifying the general condition of the body for ongoing resuscitation measures.

The Apgar rating use to determine the need for resuscitation, the types of resuscitation measures and the time they are taken.

Table 18. Apgar scoring system

	Sign	0	1	2
A	**Activity** (muscle tone)	No reaction	Grimace	Cough
P	**Pulse** (heart rate)	Absent	<100	> = 100
G	**Grimace**	Absent	Some flexion of the limbs	Active

	(reflex response to nasal catheter insertion)			
A	**Appearance** (skin color)	Cyanotic or pale	The body is pink, the limbs are blue	Pink
R	**Respiration** (breath)	Absent	Slow, irregular	Good scream

Baby dead: The preeclamptic process gradually subsides and eventually expulsion of the baby occurs. Otherwise medical method of induction is started.

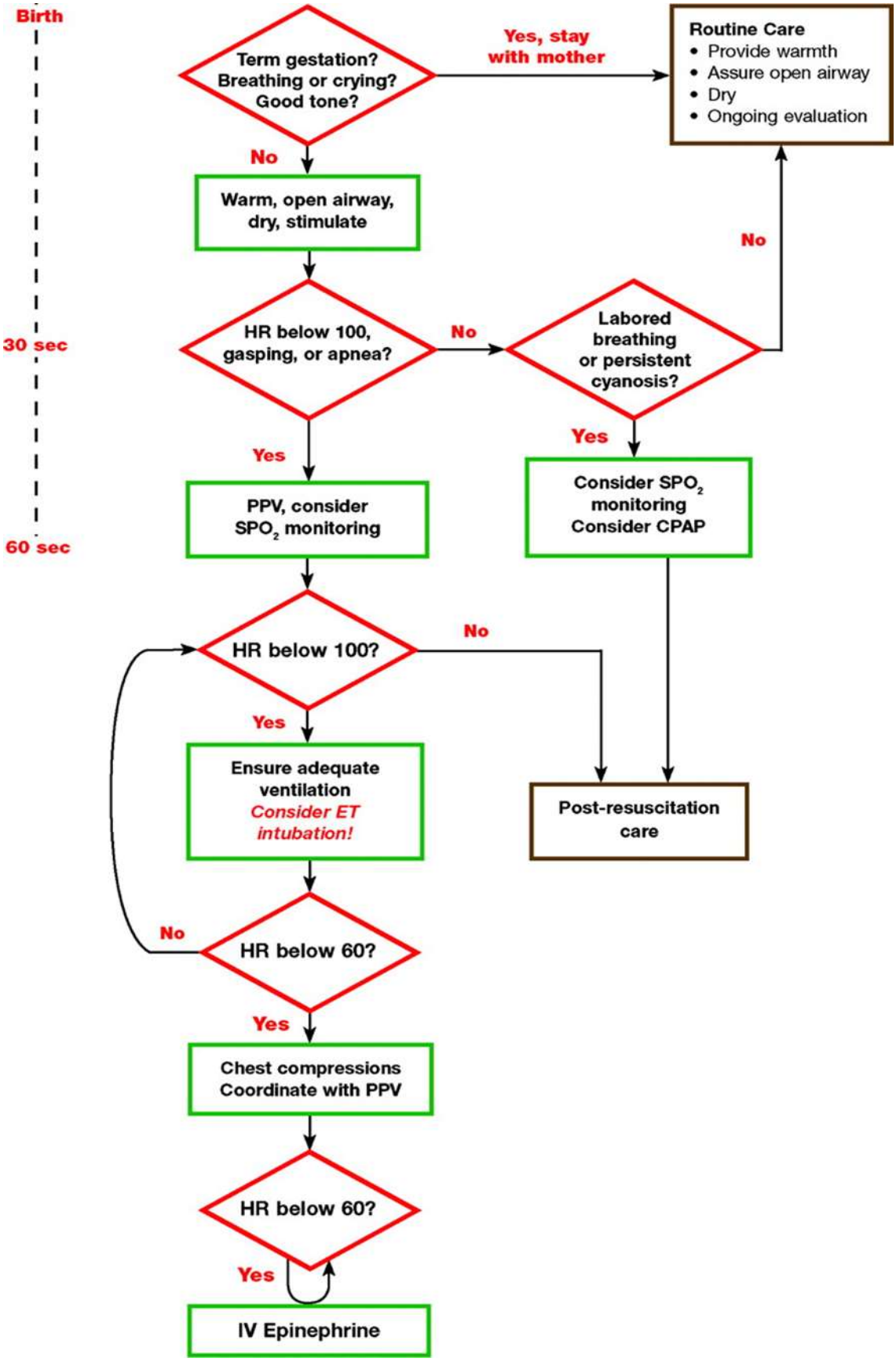
Fits not controlled: If the fits are not controlled with anticonvulsant within a reasonable period (6-8 hours), termination of pregnancy should be done. If vaginal examination indicates a quick response to induction, low rupture of the membranes is done. Oxytocin infusion may be added. The uterus responds well to oxytocin in such cases. In presence of unfavorable factors, cesarean section gives a quick response.

During labor: In the absence of any contraindication to vaginal delivery, as soon as the labor is well established, low rupture of the membranes is to be done to accelerate the labor. The dose schedule of antihypertensive and anticonvulsant drugs may be increased to quieten the patient. Second stage should be curtailed by forceps, ventouse or craniotomy, if the baby is dead. Prophylactic intravenous ergometrine or syntometrine following the delivery of the anterior shoulder should not be given as it may produce further rise of blood pressure. Instead, 10 units of oxytocin IM or IV slowly should be given. One should remain vigilant about postpartum hemorrhage and shock.

Indications of cesarean section:

1. Uncontrolled fits in spite of therapy.
2. Unconscious patient and poor prospect of vaginal delivery.
3. Obstetric indications (malpresentation).

THE ALGORITHM OF RESUSCITATION OF NEWBORNS



Follow up and prognosis*:* Patient should be followed up in the postnatal clinic by 6 weeks time. Persistence of hypertension, proteinuria and abnormal blood biochemistry necessitates further investigation and consultation with a physician. Further pregnancy should be deferred till they are controlled.

Recurrence risk varies between 2 and 25%. The risk of pre-eclampsia and eclampsia to the daughter of an eclampsia patient is about 25% and 3%, respectively.

Atypical eclampsia is defined when eclampsia occurs before 20th week of pregnancy or more than 48 hours postpartum. Patients are treated with parenteral magnesium sulfate.

GESTATIONAL HYPERTENSION

This diagnosis is made whose blood pressures reach 140/90 mm Hg or grater for the time after midpregnancy, but in whom proteinuria is not identified. Almost half of those women subsequently develop preeclampsia syndrome, which includes findings such as headaches or epigastric pain, proteinuria, and thrombocytopenia. Even so, when blood pressure increases appreciably, it is dangerous to both mother and fetus to ignore this rise only because proteinuria not developed.

GESTATIONAL HYPERTENSION

A sustained rise of blood pressure to 140/90 mm Hg or more on at least two occasions 4 or more hours apart beyond the 20th week of pregnancy or during the first 24 hours after delivery in a previously normotensive woman is called gestational hypertension. It is associated with a much higher incidence of essential hypertension in later life than pre-eclampsia. Both, thus appear to be two phases of the same disorder.

It should fulfill the following criteria:

1. Absence of any evidences for the underlying cause of hypertension
2. Unassociated with other evidences of pre-eclampsia (edema or proteinuria).
3. Majority of cases are > 37 weeks pregnancy.
4. Not associated with hemoconcentration, thrombocytopenia, raised serum uric

acid level or hepatic dysfunction.

5. The blood pressure should come down to normal within 6 weeks following delivery.

The hypertensive effect may be a stress response. Perinatal mortality remains unaffected. These patients are more likely to develop hypertension with the use of oral contraceptives or in subsequent pregnancies. Unless the woman develops severe hypertension and or pre-eclampsia, pregnancy may be continued to term.

Gestational edema is excessive accumulation of fluid with demonstrable pitting edema over the ankles greater than 1 + after 12 hours in bed or gain in weight of 2 kg or more in a week due to influence of pregnancy.

Gestational proteinuria is the presence of protein of more than 0.3 gm in the 24 hours urine during or under the influence of pregnancy in the absence of hypertension, edema or renal infection. It may be orthostatic proteinuria.

CHRONIC HYPERTENSION IN PREGNANCY

Chronic hypertensive disease (CHD) is defined as the presence of hypertension of any cause antedating or before the 20th week of pregnancy and its presence beyond the 12 weeks after delivery. The condition poses a difficult problem as regards the diagnosis and management when seen for the first time, beyond the 20th week of pregnancy. Overall incidence is 2-4% of which 90% are due to essential hypertension.

The high risk factors for CHD are: (i) Age (> 40 years), (ii) Duration of hypertension (>15 years), (iii) Level of BP (>160/110 mm of Hg), (iv) Presence of any medical disorder (renovascular), and (v) Presence of thrombophilias. Majority of women with CHD are low risk and have satisfactory maternal and fetal outcome without any antihypertensive therapy.

ESSENTIAL HYPERTENSION IN PREGNANCY

Apart from the specific hypertensive disorder in pregnancy (PIH), essential hypertension is the common hypertensive state in pregnancy. Its incidence varies

from 1-3%.

DIAGNOSIS: The diagnostic criteria are: (1) Rise of blood pressure to the extent of 140/90 mm Hg or more during pregnancy prior to the 20th week (molar pregnancy excluded), (2) Cardiac enlargement on chest radiograph and ECG, (3) Presence of medical disorders, and (4) Prospective follow up shows persistent rise of blood pressure even after 42 days following delivery. However, confusion in the diagnosis arises when the case is first seen in later months of pregnancy, specially when the pre-pregnant level of blood pressure remains unknown. Differential diagnosis with pre-eclampsia, gestational hypertension and essential hypertension are given below:

Table 20. Differential features of Pre-eclampsia with gestational and essential hypertension

Differential features of Pre-eclampsia with gestational and essential hypertension			
	Pre-eclampsia	Gestational hypertension	Essential hypertension
Age	Mostly young	Young	Usually elderly
Parity	Primigravidae — common	Primigravidae	Multipara — common
Past history	Pre-eclampsia in previous pregnancy	May be present	Pre-pregnant hypertension present
Family history	May be present	Unrelated	Often present
Onset of hypertension	After 20th week of pregnancy	Usually in third trimester	Before 20th week of pregnancy
Follow up BP following delivery	Subsides completely	Subsides completely	Persists even after 3 months
Proteinuria	Present	Absent	Usually absent
Eye changes	Usually none. Extreme cases— retinal edema, constriction of arterioles, nicking of the veins	None	Silver wiring of the arterioles. Hypertensive retinopathy
Specific blood values	· Hemoconcentration · Thrombocytopenia · Serum uric acid > 5	Absent	Not significant

	mg/dl · Raised liver enzymes		

EFFECTS OF PREGNANCY ON THE DISEASE:

1. There may be a mid-pregnancy fall of blood pressure in about 50%. However, the blood pressure tends to rise in the last trimester which may or may not reach its previous level
2. In 50%, the blood pressure tends to rise progressively as pregnancy advances
3. In about 20%, it is superimposed by pre-eclampsia evidenced by rise of blood pressure to the extent of 30 mm Hg systolic and 15 mm Hg diastolic associated with edema and/or proteinuria
4. Rarely, malignant hypertension supervenes
5. In 30%, there is permanent deterioration of the hypertension following delivery.

EFFECT OF THE DISEASE ON PREGNANCY: Maternal risk: In the milder form, the maternal risk remains unaltered but in the severe form or when superimposed by pre-eclampsia, the maternal risk is much increased.

Fetal risk: Due to chronic placental insufficiency, the babies are likely to be growth retarded. Preterm birth is high. In the milder form, with the blood pressure less than 160/100 mm Hg, the perinatal loss is about 10%. When the blood pressure exceeds 160/100 mm Hg, the perinatal loss doubles and when complicated by pre-eclampsia, it trebles. Risk of placental abruption is high (0.5-10%).

MANAGEMENT: The principles of management are: (1) To stabilize the blood pressure to below 160/100 mm Hg, (2) To prevent superimposition of pre-eclampsia, (3) To monitor the maternal and fetal well-being, (4) To terminate the pregnancy at the optimal time. Preconceptional evaluation and counseling is essential to assess the etiology, severity of hypertension and possible outcome of pregnancy.

GENERAL MANAGEMENT: In mild cases with blood pressure less than

160/100 mm Hg, adequate rest (physical and mental), low salt diet are all that are needed. The check up should be more frequent 1-2 weeks interval upto 28 weeks and thereafter weekly.

In severe cases or in cases of superimposed pre-eclampsia, the patients should be hospitalized and are placed in the treatmentprotocol as described under pre-eclampsia.

Antihypertensive drugs: Routine use of antihypertensive drug is not favored. It may lower the blood pressure and thereby benefit the mother but the diminished pressure may reduce the placental perfusion which may be detrimental to the fetus. Thus, antihypertensive drugs should be used only when the pressure is raised beyond 160/100 mm Hg. (see p. 506). To prevent target organ damage. In cases, where these drugs have been used before pregnancy, care should be taken to adjust the dose during pregnancy, specially, during mid-pregnancy when the blood pressure tends to fall.

OBSTETRIC MANAGEMENT: In mild cases, spontaneous labor is awaited. In severe or complicated cases, the aim is to try to continue the pregnancy to at least 34 weeks otherwise upto the 37th week to attain fetal maturity and then to terminate the pregnancy.

HELLP SYNDROME

HELLP syndrome - this is an acronym for Hemolysis (H), Elevated Liver enzymes (EL) and Low Platelet count (LP) (<100,000/mm3). This is a rare complication of pre-eclampsia (10-15%). HELLP syndrome may develop even without maternal hypertension.

Clinical features. This syndrome is manifested by nausea, vomiting, epigastric or right upper quadrant pain, along with biochemical, and hematological changes. Parenchymal necrosis of liver causes elevation in hepatic enzymes (AST and ALT >70 IU/L, LDH >600 IU/L) and bilirubin (>1.2 mg/dL). There may be subcapsular hematoma formation (which is diagnosed by CT scanning) and abnormal peripheral blood smear. Eventually liver may rupture to cause sudden

hypotension, due to hemoperitoneum

Management: Principles of management are same as that of pre-eclampsia and eclampsia. Antiseizure prophylaxis with magnesium sulphate is started. Careful assessment of maternal and fetal status followed by delivery is done. Administration of corticosteroids improves perinatal fetal pulmonary maturity, (IVH and necrotizing enterocolitis) and maternal (thrombocyte count, urinary output) outcome. Cesarean section is the common mode of delivery. Epidural anesthesia can be used safely if the platelet count is >1,00,000/mm3). Platelet transfusion should be given if the count is <50,000/mm3. Patient should be managed in an ICU until there is improvement in platelet count, urine output, BP and liver enzymes. Recurrence risk of HELLP syndrome is 3-19%.

Expectant management has been carried out selectively when pregnancy is < 34 weeks, with bed rest, plasma volume expansion (infusion of 5-25% albumin), antithrombotic agents (dipyridamole), immunosuppressive agents (steroids) and others (fresh frozen plasma). In HELLP syndrome perinatal mortality ranges between 5 and 60% and maternal mortality may be up to 25%.

SELF CONTROL

1. Which is not the risk factor for gestational hypertension

a. Obesity

b. Smoking

c. Primigravida

d. Factor V Leiden mutation

e. DM

2.What is the level of proteinuria to diagnose the lady to have severe preeclampsia

a. 20 mg

b. 200 mg

c. 300 mg

d. 3000 mg

e. 4000 mg

3. 39 weeks BP 150/99 mm.Hg. recorded on two occasions 8 hrs apart, previous base BP 120/70, proteinuria absent.

a. Eclampsia

b. Preeclampsia

c. Gestational hypertension

d. Essential hypertension

e. Superimposed preeclampsia

4. Clinically alarming sign of MgSO4 toxocity

a. Loss of knee jerk

b. Loss of superficial abdominal reflexes

c. Loss of proprioception

d. Loss of pin prick sensation

e. Decrease respiratory rate

5. Following are causes of death in hypertensive disorders in pregnancy except

a. Cardiac failure

b. Chronic renal failure

c. ARDS

d. Cerebral haemorrhage

e. Stroke

6. HELLP Syndrome all are criteria except

a. Hemolysis

b. Elevated liver enzymes

c. Low platelets< 25000

d. Retroperitoneal hemorrhages

e. Severe anemia

7. Definitive treatment of severe preeclampsia

a. MgSO4

b. Delivery of baby

c. Rest

d. A-HT

e. Corticosteroids

8. In case of preeclampsia Doppler USG will show

a. Reversed blood flow in Ductus venosus at 22 weeks

b. Diastolic notch in uterine artery at 22 weeks

c. Absent blood flow in umbilical artery at 22 weeks

d. Increase peak systolic flow velocity in middle cerebral artery

9. A female of 36 weeks gestation presents with hypertension, blurring of vision and headache. Her blood pressure reading was 180/120mm Hg and 174/110mm Hg after 20 minutes. How will you manage the patient?

a. Admit the patient and observe

b. Admit the patient, start anti-hypertensives and continue pregnancy till term

c. Admit the patient, start anti-hypertensives, MgSO4 and terminate the pregnancy

d. Give oral anti-hypertensives and follow up in out-patient department

e. Admit the patient and cesarean section

10. A 24-year-old primigravida presents at 37 weeks gestation with headache, a blood pressure of 170/102 mm Hg, and severe right upper quadrant pain. She is diagnosed with HELLP syndrome and undergoes an uncomplicated induction of labor. Her right upper quadrant pain persists, and a computed tomography scan of her abdomen/pelvis is completed with the findings as shown below. What is denoted by the asterisk?

a. Splenic infarction

b. Intrahepatic infarction

c. Subcapsular hematoma

d. Periporral hemorrhagic necrosis

e. Renal failure

11. Best regimen for eclampsia is

a. MgSO4

b. Lytic cocktail

c. Phenytoin

d. Diazepam

e. Labetolol

12. A lady in hospital at 37 weeks of pregnancy with history of previous LSCS with BP 150/100. On pelvic examination cervix is found to be soft with 50% effacement, station is-3, pelvis is adequate and cervical OS is closed. Most appropriate step at the moment would be?

a. Antihypertensive regimen and then wait for spontaneous labour

b. Prophylactic anti-seizure therapy

c. Induce labour

d. Do caesarean section

e. AROM

13. A pregnant lady with 32 weeks of gestation with BP 160/110 mm of Hg with proteinuria with retinal haemorrhage, management is:

a. Nifedipine

b. To prolong pregnancy

c.'Mgso4

d. Termination

e. Induce labor

14. In PIH impending sign of preeclampsia

a. Pedal edema

b. Severe proteinuria

c. Weight gain of 2lb per week

d. Visual disturbance

15. The drug of choice for preventing seizures in a patient with severe preeclampsia

a. Phenytoin

b. Diazepam

c. MgSO4

d. Nifedipine

16. The following changes may be seen in preeclampsia except

a. ↓Antithrombin III

b. Hemodilution

c. Uric acid

d. Thrombocytopenia

e. Anemia

17. A 21-year-old G1 at 36 weeks' gestation presents for her clinic visit and is noted to have a blood pressure of 148/88 mm Hg. A repeat blood pressure 30 minutes later is 146/92 mm Hg. Her blood pressures through out pregnancy have been below 140/90 mm Hg. She denies any complaints, and urinalysis is negative for proteinuria. What is the most likely diagnosis?

a. Delta hypertension

b. Chronic hypertension

c. Preeclampsia syndrome

d. Gestational hypertension

e. HELLP syndrome

18. A 28-year-old G1 at 38 weeks gestation presents with complaint of contractions. Her blood is noted to be 148/90 mm Hg and 152/96 m She has a urine protein:creatinine ratio of 04. a creatinine of 1.04 mg/dl. (baseline 0.48 mg/dl.).

normal AST and ALT, and platelet count of 110,000/µl. She denies any symptoms. What criteria for severe preeclampsia does this patient meet?

a. Proteinuria

b. Low platelets

c. Elevated creatinine

d. She does not meet criteria for severe preeclampia

e. ESR increased

19. Many conditions and factors are associated with an increased risk for preeclampsia. Which of the following factors results in the greatest relative risk for a diagnosis of preeclampsia in the current pregnancy?

a. Primigravida

b. Advanced maternal age

c. Systemic lupus erythematous

d. History of preeclampsia in a prior pregnancy

e. Essential hypertension

20. A 21-year-old primigravida presents at 36 weeks gestation with new-onset headache. Her blood pressure is 150/90 mm Hg, her serum creatinine is 0.8 mg/mL, AST is 32 U/L, and platelet count is 28,000/µL. Which of the following criteria for severe preeclampsia is met?

a. Hypertension

b. Liver dysfunction

c. Thrombocytopenia

d. Elevated serum creatinine

e. Stroke

1	B	**6**	D	**11**	A	**16**	**B**
2	D	**7**	B	**12**	D	**17**	**D**
3	C	**8**	B	**13**	C	**18**	**C**
4	A	**9**	C	**14**	D	**19**	**D**
5	B	**10**	C	**15**	B	**20**	**C**

Check list №1

Assessment of knowledge on the provision of assistance in severe pre-eclampsia/eclampsia

	Monitoring of the provision of assistance in severe pre-eclampsia/eclampsia (PE/E)		
	Task	**Yes**	**No**
	A pregnant woman BP 150/990 mm.Hg. recorded on two occasions 4 hrs apart, proteinuria present. (record the time of the onset of the complication).		
1	Get consent from the patient (or from her relatives, if she is unconscious)		
	EMERGENCY CARE		
2	Measure blood pressure, blood pressure>110 mmHg (record the time), (ECG, blood pressure, heart rate, RR, diuresis), fetal heart rate monitoring		
3	Urine test for protein: Proteinuria.		
4	To conduct an initial assessment upon admission with preeclampsia (the rule of ABCD): 1. A-airway-examination of the respiratory tract 2. B-breathing-assessment of respiration: Increasing of RR may be a sign of pulmonary edema. Auscultation eliminates pulmonary edema. 3. C-circulation-assessment of blood circulation: Turn to the left side, put the roller. Determine blood pressure, pulse, saturation. Peripheral vein catheterization with I/V canula 16-18G Blood sampling for laboratory testing Bladder catheterization, determination of protein in urine (daily proteinuria)		

	4. D-disability-assessment of consciousness: Headache, visual disturbances, seizures Determination of reflexes (knee) 5. Maintaining an intensive surveillance card 6. Assessment of the fetal condition of the fetus		
5	**To prevent seizures:** Introduce magnesium sulfate (Loading dose): Magnesia sulfate 25% - 20 ml (5 g of dry matter) dilute in 20 ml of isotonic solution in two syringes: 10 ml of magnesia and 10 ml of isotonic solution in each syringe I/V slowly for 15-20 minutes (record the time of the administration of drugs, the dose of the drug in grams).		
6	Maintenance dose. Preparation of a solution of 20 ml of 25% magnesia sulfate: dilute 5 g of dry matter in 200 ml of 0.9% isotonic sodium chloride solution. Enter at a rate of 1 g per hour (40-80 ml / h or 15-20 drops / min). If the blood pressure is higher - 160/110 mm. Hg. reduce to 140/90 mm.Hg.		
7	In case of Magnesia sulfate overdose: Introduce calcium gluconate. (record the time of administration, dose in mg, route of administration). Signs of overdose: 1. Absence of knee reflex (then the concentration of Mg in the blood is 3.5-5.0 mmol/l). 2. RR is less than 10-12 per minute (Mg in blood plasma is 5.0-6.5 mmol/l). 3. Diuresis is less than 100 ml in 4 hours. 4. Administering magnesia sulfate should be stopped if signs of overdose appear. The antidote to magnesium sulfate in overdose is calcium gluconate 10% -10 ml I/V		

	slowly.		
8	For stroke prevention: Nifedipine 10 mg - 1 tab., Dopegit 250 mg - 2-3 per day per os. (record the time and route of administration: per os, i / m, i / v) If a woman is unconscious, but high blood pressure, call an anesthesiologist for controlled hypotensive therapy.		
	Situation: Preeclampsia complicated with eclamptic convulsions.		
9	Position of the elevated head, on the either side, support of the lower jaw Insert an air duct if necessary Provide oxygen (it is possible through an oxygen bag, an Ambu bag, a nasal cannula or a facial mask at a speed of 8-10 l/min)		
10	Continue magnesia therapy with an increase or doubling of the dose.		
11	Observation of patient. Measure blood pressure during 1 hour of observation.		
12	Consultation of a neurologist. "Glasgow Scale"" evaluate by signs: speech, response, eyes, movements, pain. If assessing the total score - 12 points or less - a violation of consciousness.		
13	Scheme of anticonvulsant therapy: 1 ml of 25% Magnesia sulfate solution contains 250 mg of dry matter, and 10 ml (1 ampoule) contains 2.5 grams of dry matter. During the infusion, the main rule is to inject at a rate of 1 gram of dry matter for 1 hour, or 2.5 grams (1 ampoule) of dry matter for 2 hours and 30 minutes. That is, it will be very easy to calculate - 5 grams in 5 hours, etc.		

14	**Loading dose:** magnesia sulfate 25% - 20 ml dilute in 20 ml of isotonic solution (loading dose) in two syringes: 10 ml of magnesia and 10 ml of isotonic solution in each syringe I/V slowly for 5-10 minutes. If the seizures recurred, the administration of magnesia should be repeated 2.0 g intravenously for 5-10 minutes. **Maintenance dose:** Preparation of a solution of 20 ml of 25% magnesia sulfate: dilute 5 g of dry matter in 200 ml of 0.9% isotonic sodium chloride solution. Administer at a rate of 1-2 g / h (40-80 ml / h or 15-20 drops / min when using a standard system for intravenous infusions of 20 drops / ml).		
15	If developed seizures, if a patient with preeclampsia has already received loading and subsequent continuous doses of magnesia sulfate, then an additional 2 g of IV should be administered. If a woman has not received loading and subsequent magnesia therapy, then a loading dose of 4-6 g of MgSO4 I/V for 15-20 minutes is necessary, then a maintenance dose of 2 g / h with constant monitoring (knee reflex, diuresis, RR) is prescribed.		
	FOLLOW-UP ASSISTANCE		
16	Induction of labor (amniotomy) is performed (record the time)		
17	Transferred to the operating room for Caesarean section (record time)		
18	Was an additional dose of magnesia or another drug administered:		
	MONITORING (DYNAMIC MONITORING)		
19	**Have the following standards been met:**	**Yes**	**No**

20	During magnesia therapy, knee reflexes, diuresis, and respiratory rate are monitored at least once an hour.		
21	10% calcium gluconate should be available in cases of magnesia overdose.		
22	In the postoperative / postpartum period, the rate of intravenous infusion should not exceed 80 ml per hour (except for the need to replenish the BCV during bleeding).		
23	In the period below 28 and above 35 weeks of pregnancy, it should be delivered within 24 hours after the diagnosis of severe preeclampsia. At the gestation period of 29-34 weeks, if the woman's condition allows, pregnancy can be prolonged for 48 hours in order to prevent fetal distress.		
24	During vaginal delivery anesthesia (epidural) must be prescribed.		
25	Endotracheal anesthesia is prohibited when blood pressure is above 170/110 mmHg. Spinal anesthesia is the method of choice of anesthesia during cesarean section. PLEASE comment on the quality of the assistance provided:		
26	Did the woman stay alone for any time in the presence of a danger of developing seizures?		
27	Was help provided politely?		
28	Was she informed about the procedures?		
29	Was the situation nervous, chaotic, or calm?		
30	Have there been any delays in the necessary treatment?		
31	If yes, in connection with what medications/procedures and why?		
32	Were there many medical staff involved? Why?		

33	The results of the survey of the student and the knowledge assessment test.		
	Number of correct answers:		
	Number of incorrect answers:		
	Result:		

Checklist №2

Set of medicines for emergency care for preeclampsia

	Criteria	Yes	No
1	List of medicines and consumables		
2	Algorithm of assistance		
3	Magnesium sulfate 25% 10 ml at least 10 ampoules		
4	NaCl 0.9% solution in 10 ml ampoules of at least 10 ampoules		
5	Diazepam – at least 2 ampoules		
6	NaCl 0.9% solution of 200 ml of at least 2 pieces		
7	Clonidine 0.01% per 1 ml at least 2 ampoules		
8	Nifedipine 10 mg in tablets		
9	Dopegit (methyldopa) 250 mg in tablets		
10	Calcium gluconate 10%- 10 ml, at least 3 ampoules		
11	System for intravenous infusions of at least 2 pieces		
12	Syringes 20 ml at least 5 pieces		
13	Venous canula (vasocan) with a diameter of 0.8 (20 at least 2 pieces)		
14	Sterile gloves at least 3 pairs		
15	Adhesive plaster		
16	Air duct		
17	Spirits, cotton, tourniquet		
18	Oxygen cushion		
19	Oxygen mask		
20	Tonometer		
21	Urinary catheter		

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FOR NOTES