

Gyan Prakashan

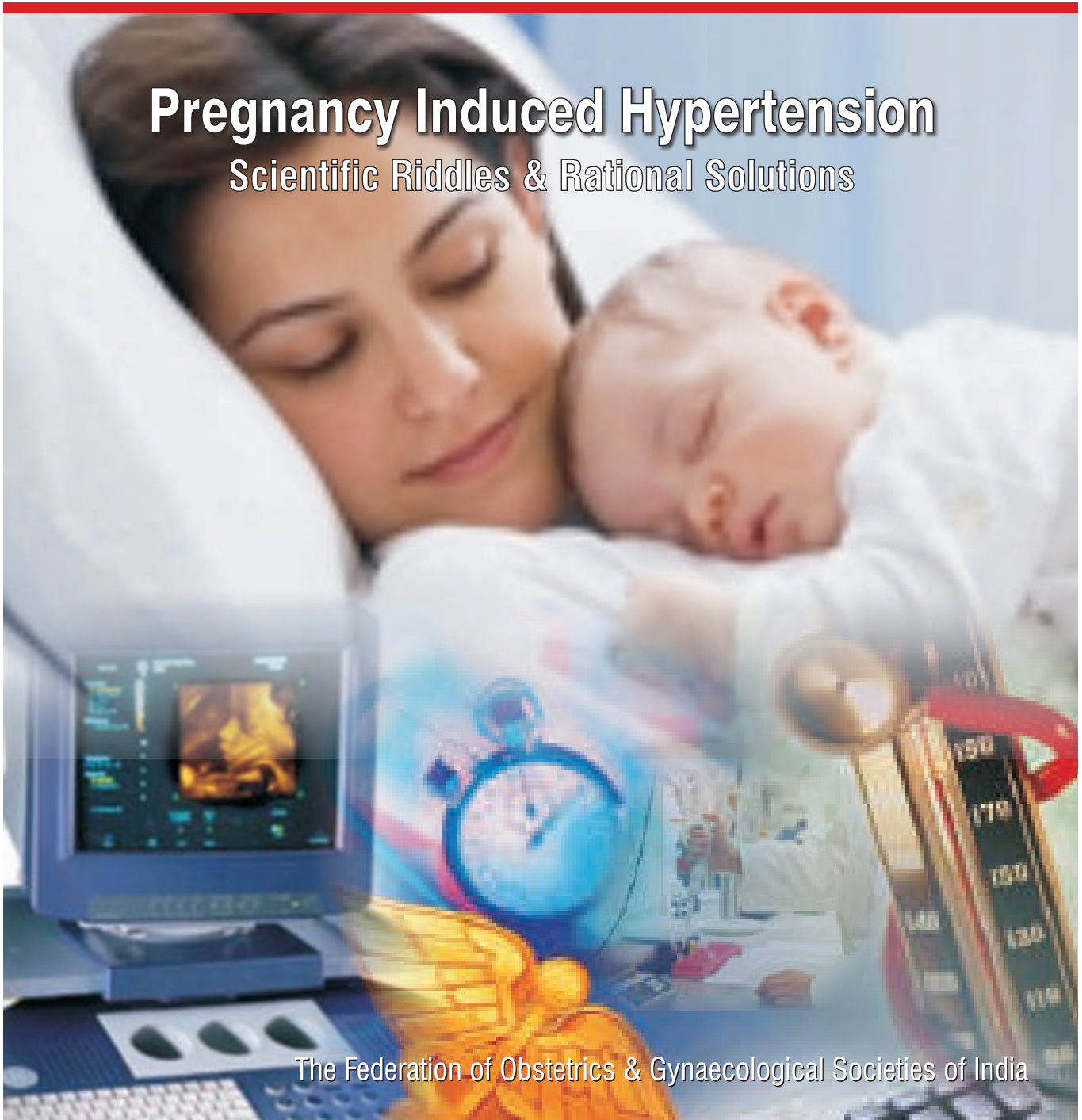
FOGSI Cares 2007

FOGSI**FOCUS**

May 2007



Pregnancy Induced Hypertension Scientific Riddles & Rational Solutions



The Federation of Obstetrics & Gynaecological Societies of India

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President's Message

Over a period of time PIH has revealed itself a little more and become a trifle more predictable. We still have profound mysteries of this condition to unravel for which we have to go right up to the electrons and the protons. While handling such profound mysteries, it is very important to manage such conditions most rationally. When less is known and more is hidden of any condition, our approach can become irrational. In the light of such a maze, the current issue of FOGSI FOCUS becomes very relevant. Under the philosophy of FOGSI- Cares-2007, we have identified one theme "Towards hemorrhage and eclampsia free India". Dr. Atul Munshi, the Senior Vice-President of FOGSI has aptly decided to cover this topic and disseminate the latest information on the subject. I am confident that FOGSI members will be able to handle PIH a little better after this FOGSI focus.

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Editor's Message



After an overwhelming response to FOGSI Focus - I on P.P.H., from all parts of the country, we are presenting next in the series on P.I.H.

It is impossible to cover the whole subject in this small booklet, that is why we have taken up a specific aspect-"P.I.H.-Scientific Riddles & Rational Solutions".

Our well chosen contributors from different fields of speciality have been asked to give you, definite carryhome messages.

This is a targeted approach to fulfill our promise of the year-"FOGSI Cares!".

If, at least few of the suggestion given in this FOGSI Focus by our experts, are implemented in practice, I think we will be a step closure towards Eclampsia Free India- Our theme of the year 2007.

We, TEAM 2007, headed by our President, are determined to serve FOGSI, in the best possible way.

Your views, suggestions & comments are welcome!

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Hypertensive Disorders with Pregnancy

- An Unsolved Problem

Hypertensive disorders continue to occur globally, complicating 5-20% of pregnancies. They are common cause of interventions / operative procedures, and cause around 15-20% maternal mortality and 20-25% perinatal mortality. The haemodynamic changes are complex and contradictory observations continue to be reported in various studies.

If we look at the past, present and think of future, it is evident that it's only that the names have been changing from toxemia to gestosis and so on, but the disease continues unabated with high maternofetal loss, though the research also continues. The risk factors are still not well understood so there is lack of sensitive predictive tests, though many have been introduced. From the understanding that there is a toxin involved, we now know that the causes are multifactorial, genetic, immune, placental and others. Insulin resistance may be an important contributor. Recent research also reveals that many changes precede any increase in blood pressure and though the symptoms and signs usually become apparent in the third trimester, the underlying pathophysiological mechanisms appear between 8-18 weeks of gestation. Since the exact aetiology is still unknown, not much can be done for prevention even though prophylactic calcium, aspirin, magnesium, zinc, antioxidants with life style change are being advocated.

Complications

Usually with increasing severity of the disease many complications occur in the mother and mean birth weight decreases, however in mild cases also fatal complications can occur. Abruptio placentae, convulsions, intracerebral



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haemorrhage, hepatorenal cardiac failure, blindness, intrauterine growth retardation, intrauterine death, preterm delivery, perinatal asphyxia, neonatal death are well known. HELLP or Partial HELLP syndrome, an atypical multi-organ disorder of vasoconstriction with endothelial cell dysfunction, widespread microangiopathic hemolytic anemia, thrombocytopenia, occurs in 1-12% of cases. Preclinical status and course is unpredictable, with high fatality for mother and baby. High dose dexamethasone therapy is believed to reduce mortality.

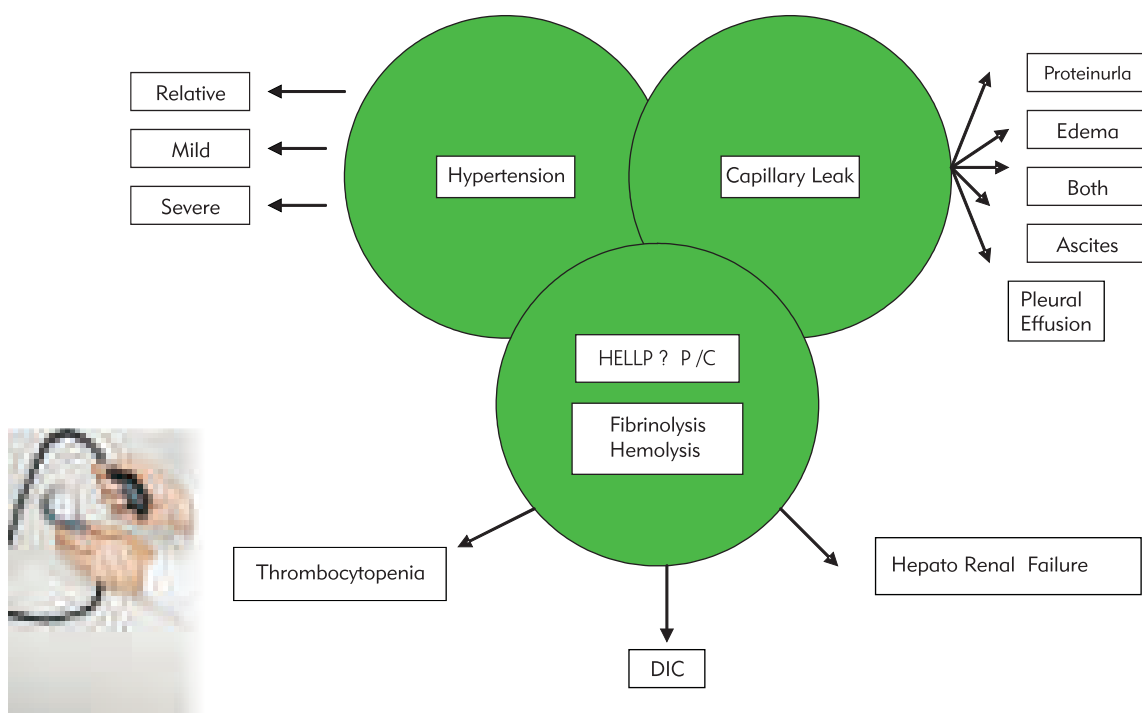
Elevated pregestational BMI, Lipid / Carbohydrate metabolism derangement, Insulin resistance have been linked to pathology. The development of early onset pre-eclampsia in pregnancies with very preterm birth is associated with an increased likelihood that the fetus is a female. A pregnancy complicated by preeclampsia later in gestation is more often associated with male fetal gender. This implicates that mechanisms for early-onset pre-eclampsia and later onset pre-eclampsia might be different. Altered intracellular sodium, body composition, distribution of the volume of water as a result of alterations in capillary permeability could be the hallmark of pathogenesis. Recent studies have revealed that transmembrane sodium transport disorder occurs which causes an increase in intracellular sodium concentration, sodium proton exchanger (NHE) with elevated Erythrocyte NHE activity. Role of the environmental seems

to be explained by the seasonality of the disease. The majority of women who succumb to hypertensive disorders are young. Now it is also known that the Cardiovascular risk of newborns of pre-eclampsic mothers may begin in utero.

Severe preeclampsia remote from term is an obstetrician's dilemma. Aggressive management

controlling hypertension and its sequelae, prevention of convulsions and organ failure, and delivery of a foetus who subsequently thrives. Quality critical care is essential to reduce mortality.

Search to identify those at risk, who should undergo extra evaluation and monitoring for



with immediate delivery might result in extremely high neonatal mortality and morbidity but attempts to prolong pregnancy may result in foetal demise and expose mother to severe morbidity mortality. Postpartum HELLP and late post partum eclampsia (beyond 48 hrs) are becoming real challenges.

Concluding Comments

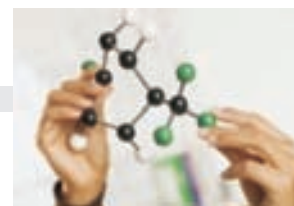
Quality antenatal care, early diagnosis of hypertensive disorders, remembering that a high index of suspicion is the key to early diagnosis of complications and timely intervention. It is very crucial to have a vigilant watch aiming at

prophylactic therapies by accurate, sensitive clinically acceptable screening tests, prior to or during pregnancy before the pathology sets in, must continue.

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The Electronics of P.I.H.



Electronics is defined as the science of the movement of electrons in a vacuum, gas, semiconductor, etc., esp. in devices in which the flow is controlled and utilized. There is increasing evidence that the movement of electrons from the molecules (oxidative stress) is an important contributing factor to the pathogenesis of PIH.

Stable molecules have paired electrons. A free radical is any molecule capable of independent (usually brief) existence that contains one or more unpaired electrons. Free radical species are unstable and highly reactive. They become stable by acquiring electrons from other molecules causing a cascade of chain reactions resulting in cellular damage and disease. There are two major types of free radical species: (a) reactive oxygen species (ROS) such as superoxide radicals (O_2^-), hydroxyl radicals (OH^-) hydrogen peroxide (H_2O_2) and (b) reactive nitrogen species (NOS).

Under normal conditions, scavenging molecules known as antioxidants convert ROS to H_2O to prevent overproduction of ROS. There are two types of antioxidants in the human body: (a) Enzymatic (natural) antioxidants like superoxide dismutase, catalase, glutathione peroxidase and glutathione. (b) Non-enzymatic antioxidants (synthetic antioxidants or dietary supplements) such as vitamin C, vitamin E, selenium, zinc, glutathione etc. In a healthy body, ROS (reactive oxygen species) and antioxidants remain in balance. When the balance is disrupted towards an overabundance of ROS, oxidative stress (OS) occurs.

The genesis of PIH is related to deficient trophoblast invasion and failure of uterine artery



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remodeling. Maintenance of the muscular coat of the spiral artery may lead to intermittent placental perfusion, because the spiral arteries would retain susceptibility to maternal humoral and neuronal constrictor influences. Since the placenta as well as the fetus will continually extract oxygen, transient hypoxia will result. Together with frequent thrombotic occlusion followed by clot dissolution, this may lead to a repeated low-grade hypoxia/reoxygenation insult in the affected placenta throughout pregnancy. Hypoxia/reoxygenation is a potent stimulus to the activation of xanthine oxidase, an important source of superoxide generation, which is abundantly expressed in cytotrophoblast, syncytiotrophoblast, and villous stromal cells¹. Placental tissues from women with preeclampsia have demonstrated enhanced expression and activity of this enzyme¹. Recent reports^{2, 3} have also suggested an important role for placental trophoblast NAD(P)H oxidase in free radical generation in PIH. The placenta appears to be the principal source of free radical synthesis but maternal leukocytes and the maternal endothelium are also likely contributors.

The increased generation of pro-oxidants tilts the balance in favor of oxidative stress, which results in increased lipid peroxidation. Biomarkers of lipid peroxidation such as malondialdehyde (MDA) are elevated in pre-eclampsia^{4, 5}. The lipid peroxides alter cell membranes by increasing incorporation of cholesterol, oxidized free fatty acids and low-density lipoproteins with formation



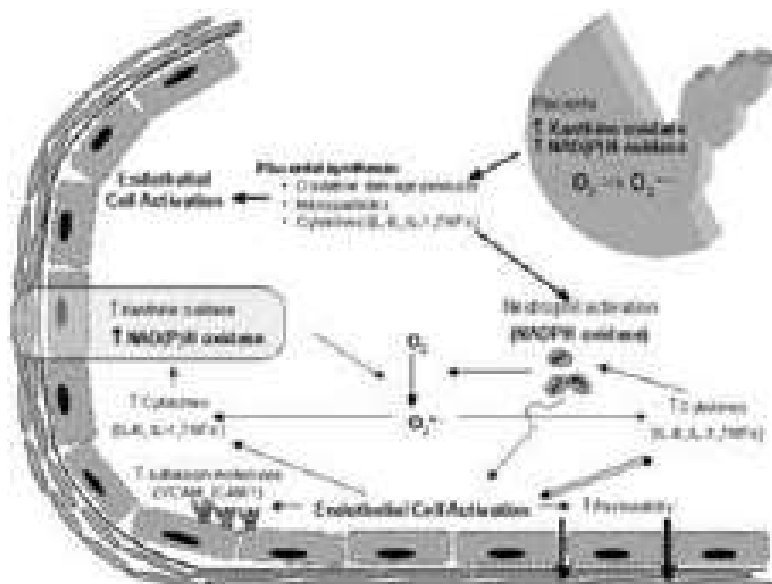
of foam cells⁶, which can exaggerate vasoconstriction. Lipid peroxides are directly involved in mediating maternal endothelial dysfunction by increasing the production of thromboxane A2 and the expression of cell adhesion molecules in the utero-placental vasculature and also in the maternal peripheral vasculature.

Dyslipidemia in women with PIH may also predispose to oxidative stress. Serum free fatty acids, triglycerides, and very-low-density lipoprotein concentrations are elevated, whereas concentrations of cholesterol, lipoprotein (a), and the other lipoproteins^{7, 8} are unchanged. The low-density lipoprotein particles are smaller than those of normotensive controls, which may facilitate their oxidation.^{9, 10}

Placental generation of ROS in preeclampsia might be facilitated by decreases in expression and activity of superoxide dismutase^{11, 12} and

glutathione peroxidase¹³. In pre-eclampsia, the anti-oxidant nutrients are presumed to be utilized to a greater extent to counteract the free radicals. This may provide the explanation for the reduced concentration of vitamin C in maternal circulation¹⁴. Although it is clear that maternal and placental antioxidant defences are reduced in pre-eclampsia, it is not known whether this is a primary or secondary event to excessive depletion through the increased generation of free radicals.

An oxidatively stressed placenta releases increased amount of apoptotic and necrotic trophoblastic debris. These debris¹⁵ may increase the inflammatory burden in the maternal blood, and initiate a cascade of increased activation of endothelial cells, granulocytes and monocytes, that increase the systemic inflammatory response resulting in maternal symptoms of pre-eclampsia.



Thus, oxidative stress appears to be playing a pivotal role in pathogenesis of pre-eclampsia. However, the role of anti-oxidants in prevention of the disease¹⁶ is unclear as of now.

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Predicting PIH: What is Rational?



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Being able to predict Pre-eclampsia or Pregnancy Induced Hypertension has been a dream of the obstetrician for quite some time. But it has remained as elusive as predicting monsoon in India. As the etiology of PIH is still unclear, the prediction remains equally difficult.

There have been myriad of tests in the past but none of them have stood the test of time. The risk factors in the patient's history still remain extremely important as far as the prediction is concerned. The knowledge of risk factor helps in pre pregnancy counseling and increased vigilance for early diagnosis.

List of risk factors to be considered are as follows

- I. Primigravida
Pre eclampsia is primarily a disease of 1st pregnancy (11.9%) compared to multigravidae (4.7%) ⁽¹⁾
- II. Previous History of preeclampsia :
Especially if severe or early and if the pregnancy interval is prolonged.
In severe preeclampsia & eclampsia :
Risk of eclampsia ---- 1.4%
Risk of preeclampsia-----45.5%
- III. Family history of preeclampsia in mother or sister
Associated with 3 fold increased risk of preeclampsia ⁽²⁾
- IV. Insulin resistant states :-
Hypertension & obesity ---overt type1 diabetes is associated with very high risk of preeclampsia. ⁽³⁾

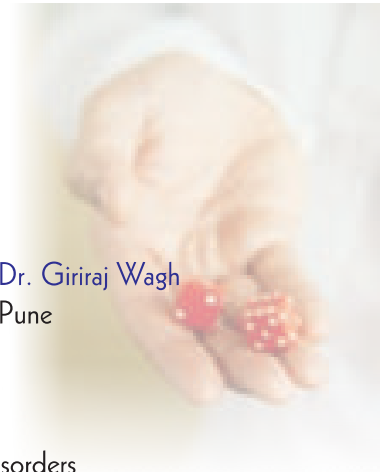


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- V. Thyroid disorders
- VI. Hyper prolactinemia
- VII. Chronic Hypertension:- Superimposed preeclampsia occurs in 30% of such women
- VIII. Presence of Antiphospholipid Antibodies
- IX. Factor V Leiden Mutation:
- X. Stress --- Working women have 2-3 times more risk of developing preeclampsia ⁽⁴⁾
- XI. Pregnancy associated risk factors:
 - a) Multiple pregnancy (Twins 4 fold risk & triplets even higher)
 - b) Some fetal abnormalities like hydrops fetalis, trisomy 13, triploidae & Hydatiform mole.
- XII. Nutritional Factor :-
Low calcium intake i.e below 600 mg / day have increased risk of developing preeclampsia. ⁽⁵⁾
On this background the 1st step in predicting or screening for PIH would be a detailed history to assess risk factors.

Predictive tests for PIH

1. Clinical tests
2. Biochemical tests
3. Renal tests
4. Hematological tests
5. Pressor response tests
6. Ultrasound tests
7. Hormonal tests
8. The newer cytokines



1. CLINICAL TESTS:

a) Mean arterial Pressure:

MAP of >87.5 mm of Hg in the 2nd trimester was thought to be predictive. It is calculated as : $MAP = DP + \frac{[SP-DP]}{3}$

3

Its sensitivity range from 0-9 % & specificity ranges from 53-97 % after evaluating 14 reports. Thus the sensitivity is very low. ^(6,7)

This means the mean predictive value is less than 10%.

b) Roll Over Test [Gant] : Done between 28 to 32 weeks. BP is measured in left lateral & then in supine position. If the difference in diastolic reading is more than 20 mm, it is taken as positive.

Sensitivity 0-93%

Specificity 54-91%



c) Isometric Exercise (Hand grip) test. : (Nisel 1985) This involves holding the BP cuff in hand to maintain the Hg at 200 mm of Hg for 3 mins & then reassessing the diastolic blood pressure. If the rise is more than 20mm it is taken as positive. It tests the role of cardiac output in changing BP & therefore is not specific.

2. BIOCHEMICAL TESTS :

a) Microalbuminuria: Urinary albumin excretion of more than 30mg/24hrs at 18 weeks can be thought to be good predictor. ⁽⁸⁾

b) Hypocalciuria : Reduced Calcium excretion in urine --- less than 195 mg in 24hrs urine collection has been shown to predict pre eclampsia in later Pregnancy. ⁽⁹⁾ [Maikranz et al 1989]

c) Calcium Creatinine ratio: False positive

rate of 33 % and false negative rate of 4%. (Taufield) ⁽¹⁰⁾

d) Plasma Fibronectin : It is found to be markedly elevated in patients with eclampsia & pre eclampsia even in 1st trimester ⁽¹¹⁾ [Ballegeer et al 1989].

3. RENAL TESTS

a) Uric Acid: Serum Uric Acid is raised in Pre eclampsia. In mild Pre eclampsia, the values range from 4-5.5 mg/dl while in severe Pre eclampsia, they are between 4.8- 7.8/dl. Rising level of serum uric acid in Pre eclampsia especially during the last trimester is an indicator of poor fetal prognosis [Voto et al 1988]. However it is a poor predictor of the disease as the values rise only with the clinical appearance of the disease. One study by Oney et al , 2004 from Germany found the predictivity value of a positive test [3.6 mg/dl at 28 weeks] quiet low [26%] & that of negative test relatively high [98%] ⁽¹²⁾

b) Urea & Creatinine: Raised plasma Urea & Creatinine values in presence of normal Uric Acid suggest renal impairment. These values help in deciding the severity but have very low predictive value.

c) Urinary Kallikrein : Creatinine Ratio: Estimation of inactive urinary kallikrein to creatinine ratio in a random urine sample collected between 16 & 20 weeks of pregnancy has shown to be of predictive value for the diagnosis of PIH. (Millar et al 1996). ⁽¹³⁾

Sensitivity 67 %

Specificity 75%



- d) **Metabolites of Nitric Oxide in Urine :**
The measurement of total urinary excretion of metabolites of nitric oxide (nitrite/ nitrate) which reflect the total production of systemic nitric oxide was thought to prove to be of value in evaluating the severity of PIH (Begum et al 1996) Further studies did not support the findings. ⁽¹⁴⁾

4. HEMATOLOGICAL TEST:

Platelet Count, Hematocrit, Red cell Morphology, Coagulation profile [D-dimer, Antithrombin 3 levels] all were researched for their predictivity in PIH. Only test that have shown some value is Serum Ferritin estimates. Hyperferritinemia in PIH could be a reflection of placental damage

5. PRESSOR RESPONSE TEST:

Angiotensin sensitivity test : Sensivity to infuse angiotensin II is regarded as one of the better predictor of PIH. Dose of A II to raise BP by 20 mm of Hg is calculated.

The Sensitivity of this test is 22% & Specificity is 85% ⁽¹³⁾

This test is difficult to perform in a clinical settings

6. ULTRASOUND TEST

So far Umbilical artery S:D ratio & Diastolic Notch have proved to be 2 useful tests for PIH . Diastolic notch on Uterine Artery doppler at 20-24 weeks

* Positive test	RR 7 Fold
* Negative test	RR 0.5 Fold
* Sensitivity for PE	40%
* For early onset PIH	80%

This is presently the most helpful test.



7. HORMONAL TEST:

Hyperprolactinemia : Diminished Dopaminergic activity in CNS influences both BP & prolactin secretion. Higher level of prolactin were found in positive AST cases. ⁽¹⁵⁾

8. THE NEWER CYTOKINES

Oxidative stress markers in normal pregnancy & pre-eclampsia Raised Oxidative stress markers glutathione peroxidase(GPX), superoxide Dismutase(SOD) & malondialdehyde(MDA) in maternal serum of patients with pre-eclampsia suggest that oxidative stress markers play a significant role in pathophysiology of pre-eclampsia. Their predictive value was found to be very low. ⁽¹⁶⁾

NEW MARKERS

1. Inhibin A, activin A, B-HCG & alpha protein may prove to be clinically useful biomarkers for PE, with activin A showing the highest sensitivity & efficiency. High maternal serum levels of these biomarkers may reflect trophoblast dysfunction & hyperplasia in preeclampsia. ⁽¹⁷⁾

2. SFLT1, PIGF & VEGF

5 weeks before the clinical onset of disease, women destined to develop preeclampsia had markedly elevated circulating, concentrations of soluble fms-like tyrosine kinase I (sFltI), and diminished concentrations of placental (PIGF) and (VEGF). ⁽¹⁸⁾

3. Endoglin concentrations increase well before the clinical manifestations of the disease. Furthermore, they increase most dramatically in women destined to develop preeclampsia.

Endoglins is a co-receptor for transforming growth factors beta1 .It prevents TGF-beta1 from binding to endothelial receptors, and

thereby impairs nitric-oxide synthetase-mediated vasodilatation.

4. Using multivariate analysis, Levine et al also demonstrated that the composite measure of (endoglin + sFlt1)/PIGF were the best predictor of both preterm and term PE.

Out of the known test so far this test promises to be the most useful & rationale as far as the prediction of Pre eclampsia is concerned.

5. Erythrocyte CR1: One of the recent theories of pre eclampsia suggest that excess immune complexes are primarily cleared by erythrocyte complement receptor type 1. Decreased expression of erythrocyte CR1 may help in predicting Pre eclampsia

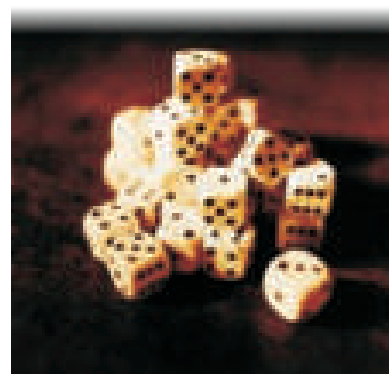
..There are more than 100 tests described for prediction of PIH . None of them have proved to be ideal as a screening test. But these test can act as stepping stones to evolve newer & better tests as our understanding the etiopathogenesis of PIH unfolds further.

Actual BP measurement on a longitudinal basis with particular attention to presence or absence of Mid trimester drop will remain the main clinical parameter to identify potential PIH.

The newer test could prove to be useful in near future as the etiopathogenesis of this disease unfolds making it easier to primarily prevent this disease.

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Preventing P.I.H. : Examining the Evidence



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As of now there are no clinically useful screening tests that are reliable, valid or economical (WHO)¹ So it is difficult to predict which patient will develop pre-eclampsia and hence primary prevention is out of question. The prevention of pre-eclampsia is possible only in cases where risk factors are known. At present there is no effective means of preventing pre-eclampsia, so early detection and prevention of severe disease and complications by regular antenatal back up and appropriate treatment of pre-eclampsia is important.

There are various methods to reduce the rate and severity of pre-eclampsia.

Methods proposed to prevent Pre-eclampsia:

1. Diet and exercise.
2. Salt restriction, Proteins, Magnesium and Zinc, Implementation.
3. Fish-oil supplementation.
4. Heparin (Low molecular weight heparin)
5. Low dose aspirin.
6. Calcium supplementation.
7. Antioxidants (vit-c & vit-E)
8. Antihypertensive Medications in chronic hypertension.

Recommendations after examining the evidence :
Role of Diet, exercise, Salt Restriction, Proteins, Magnesium & Zinc supplementation: Though there are few trials to assess benefits of exercise, well balanced diet etc to prevent pre-eclampsia, at present there is no sufficient evidence to recommend it^{2,3}.

Role of Fish-Oil Supplementation:

Initial reports showed benefits of fish-oil supplementation and other prostaglandin precursor supplementation, but either the sample size of the studies were small or minimum benefit was shown. Makrides et al (2001)⁴ have clearly shown insufficient evidence to recommend it for prevention of pre-eclampsia.

Role of Low Molecular weight Heparin:

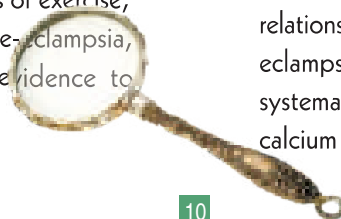
Looking at the evidence available to us, it is found to be useful only in cases of women with renal diseases & haemophilia⁵ As there is lack of double blind randomized trials, it is not recommended for use in general population to reduce pre-eclampsia.

Role of Low dose Aspirin:

It is postulated that by giving low dose aspirin 60mg-75mg per day, it may prevent pre-eclampsia given early in pregnancy by selective suppression thromboxane synthesis by platelets and sparing of endothelial prostacyclin production^{6, 7}. The complete meta-analysis of all trials to-date indicate that the use of low dose aspirin in pregnancy would prevent 1 in 100 women treated. The only women in whom the use of low dose aspirin may be justified are those at especially high risk of developing early onset pre-eclampsia. (an updated systemic cochrane review)^{8,9,10}

Role of Calcium supplementation:

Some studies have shown decreased incidence of pre-eclampsia with calcium supplementation of 1.5 - 2 gms / day.^{11,12} Historically also a relationship between calcium deficiency and pre-eclampsia was suggested¹³. Recently cochrane systematic review noted protective effects of calcium supplementation only in women with



low calcium intake¹⁴. WHO (2006)¹⁵ published results of a large multicentric randomized placebo controlled trial of calcium supplementation in pregnant subjects with low calcium intake (<600mg / day). Supplementation with 1.5 gm of calcium per day did not result in a statistically significant decrease in the overall incidence of pre-eclampsia.

Role of Antioxidants (Vit-C & Vit-E):

Antioxidants like Vit-C & Vit-E are believed to be useful in reducing oxidative stress and limit injury to endothelial cells and prevent or reduce the severity of pre-eclampsia. As per study by Chappell et al¹⁶, 60% reduction in incidence of pre-eclampsia was observed. If pre-eclampsia had set in, Vit-E was not found beneficial¹⁷. However two recent studies^{18,19} on role of Vit-C (1000mg) and Vit-E 400 IU per day have shown little benefit and potential for harm.

Role of Antihypertensive Agents in Women with Chronic Hypertension:

The risk of women developing severe hypertension was found to be reduced in such subjects by half, but there was no significant effect in reduction in evidence of pre-eclampsia.

Conclusion:

In absence of sufficient evidence to use methods to prevent pre-eclampsia routinely in pregnant women barring few exceptions as above, proper antenatal care, identification of risk factors early in pregnancy and treating them, timely referrals and timely delivery with all precautions to prevent complications, is all that can prevent pre-eclampsia and its complications.



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Hazards and Bearings of PIH Remote from Term



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Hypertensive disorders are the most common medical complications of pregnancy and are an important cause of maternal and perinatal morbidity and mortality worldwide. Women with preeclampsia require close observation because the disorder may worsen suddenly. The presence of symptoms (such as headache, epigastric pain, and visual abnormalities) and proteinuria increases the risks of both eclampsia and abruptio placentae; women with these findings require close observation in the hospital. The management should include close monitoring of the mother's blood pressure, weight, urinary protein excretion, urine output and a blood sample should be sent for platelet count, peripheral smear for hemolysis, hepatic enzymes, blood urea and serum creatinine. Fetal evaluation includes fetal heart rate monitoring, biophysical profile, ultrasound for growth parameters & liquor and if there is IUGR, umbilical artery Doppler study must be done. In addition, the woman must be informed about the symptoms of worsening preeclampsia. If there is evidence of disease progression, hospitalization is indicated. Early in gestation, however, prolongation of pregnancy with close monitoring may be indicated in order to improve neonatal survival and reduce short-term and long-term neonatal morbidity. Severe preeclampsia may be rapidly progressive, resulting in sudden deterioration in the status of both mother and fetus, so that prompt delivery is recommended regardless of the duration of gestation. Prompt delivery is clearly indicated when there is imminent

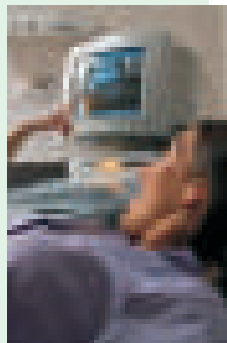
eclampsia, multiorgan dysfunction, or fetal distress or when severe preeclampsia develops after 34 weeks. Conservative management must be considered only at tertiary perinatal centers and must include very close monitoring of both mother and fetus. The aim of therapy is to keep the mean arterial pressure below 126 mm Hg (but not less than 105 mm Hg) and the diastolic pressure below 105 mm Hg (but not less than 90 mm Hg).

Our objective of treatment is to avoid vascular damage due to blood pressure elevation without causing excessive reduction in blood pressure that would critically affect uteroplacental perfusion and to prevent cerebral complications such as encephalopathy and hemorrhage. As pre-eclampsia is associated with vasospasm, endothelial cell dysfunction and activation of coagulation-hemostasis systems and as the biochemical studies suggest that these abnormalities are probably caused by an imbalance in the production of prostaglandins, prostacyclin and thromboxane-A₂ with balance tilted in favour of thromboxane-A₂. Low dose aspirin (50-150mg/day) therapy during pregnancy selectively inhibits platelet thromboxane-A₂ biosynthesis with minimal effects on prostacyclin production, thus altering the balance in favour of prostacyclin. The largest trial to date was the CLASP study, a multicenteric trial where the use of low dose aspirin in pregnant women was associated with a 12% reduction in the incidence of pre-term

delivery in the high-risk group (19.7% in aspirin group versus 22.3% in placebo group).

Table 1. Features of severe preeclampsia remote from term

Blood Pressure
>160-180 mm Hg systolic
or >110mm Hg diastolic
Proteinuria
>5 g per 24h
or >3 on dipstick
Oliguria <500ml per 24h
Pulmonary edema
Eclamptic seizures
Hepatic rupture
Elevated serum creatinine
Microangiopathic Hemolysis
Thrombocytopenia
Impaired Liver Function
Disseminated intravascular coagulation
Symptoms of end-organ involvement
Headache or visual disturbances
Clonus of deep tendon hyperreflexia
Epigastric or right upper quadrant pain
Fetal involvement
Intrauterine growth retardation
Oligohydramnios
Absent fetal movements
Absent or reversed umbilical end-diastol
Doppler flow velocity waveforms



In severe early-onset preeclampsia with possible manifestations of renal, hepatic and cerebral involvement delivery can be postponed for fetal indication of corticosteroid administration. In selected cases of severe preeclampsia expectant management beyond the time required for administration of corticosteroids can be recommended but only in a tertiary care center with adequate maternal intensive care facilities. As such, early onset preeclampsia is a strict reason for transferring a patient to a perinatal

center . Women with severe preeclampsia especially when associated with marked intrauterine growth restriction, absent or reversed umbilical Doppler flow velocities, and a gestational age <23 weeks need detailed counseling with respect to the maternal risks versus the expected poor perinatal outcome. Even extensive aggressive therapy will rarely result in a prolongation of gestation of more than 10-14 days. In case of extremely compromised and early gestations such prolongation often does not impact favorably on neonatal survival.

Beyond 34 weeks gestation perinatal outcome is generally good, at least in developed countries. Mode of delivery is determined according to the usual obstetric indications.

To conclude severe PIH remote from term is probably a unique disease separate from term PIH & has worse prognosis & may necessitate expectant management under supervision for better fetal survival.

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Managing Hypertensive crisis and preventing Eclampsia



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Advances in the management of chronic hypertension have made the occurrence of hypertensive crises relatively rare. However, it is likely that most primary care physicians will at some point encounter a patient with critically elevated blood pressure.

Definitions

Hypertensive crisis is defined as a critical elevation in blood pressure in which diastolic pressure exceeds 120 mm Hg. The presence of acute or ongoing end-organ damage constitutes a hypertensive emergency, whereas the absence of such complications is known as a hypertensive urgency.

The terms "accelerated hypertension" and "malignant hypertension" were formerly used to describe severe hypertension accompanied by certain retinal findings. Accelerated hypertension was associated with retinal hemorrhages and exudates (group 3 Keith-Wagener-Barker retinopathy), whereas malignant hypertension was associated with papilledema (group 4 Keith-Wagener-Barker retinopathy). It is now known that clinical outcomes do not differ simply on the basis of these funduscopic findings¹. Thus, the current preferred term is "accelerated-malignant hypertension."

Evaluation

Apart from the usual workup of the armamentarium in Preeclampsia laboratory tests should be performed immediately after

presentation that can provide crucial clues to underlying conditions. A complete blood cell count may confirm the presence of microangiopathic hemolytic anemia. Urinalysis may reveal hematuria or casts in the presence of azotemia or renal failure. Elevated serum urea nitrogen and creatinine levels, metabolic acidosis, and hypocalcemia detected on blood chemistry tests often indicate renal insufficiency. Hypokalemia, which reflects secondary aldosteronism, occurs in about 50% of patients with hypertensive crisis. In patients with pressure-induced natriuresis, however, serum sodium levels are usually lower than in those with primary aldosteronism.

Finally, it is important to consider secondary causes of hypertension (eg, renovascular hypertension) that may have precipitated the crisis. A single-dose captopril (Capoten) challenge test may be performed (table 1), particularly in patients who have not received previous medical therapy for hypertension. Baseline plasma renin activity is measured and the patient is given 25 to 50 mg of captopril; measurement is repeated 60 minutes later². Test sensitivity is excellent but specificity is poor. Thus, further testing (eg, renal arterial Doppler ultrasonography, renal magnetic resonance angiography, contrast angiography) may be necessary to confirm diagnosis. Before initiating drug therapy, metanephrine levels can be measured by performing a spot urine test to rule out the presence of pheochromocytoma³. Plasma aldosterone and renin levels should be tested to rule out primary hyperaldosteronism in patients with significant hypokalemia who are not taking diuretics at the time of presentation.



Table 1. Captopril screening test for secondary causes of hypertensive crisis

Method

Patient maintains normal salt intake and receives no diuretics

Withdraw all antihypertensive medications 3 weeks before test, if possible

Patient should be seated for at least 30 minutes; draw venous blood sample and measure baseline plasma renin activity

Dilute 50 mg captopril (Capoten) in 10 mL of water; patient immediately drinks solution

After 60 minutes, draw venous blood sample and measure stimulated plasma renin activity

Interpretation

Test is positive in presence of:

- * Stimulated plasma renin activity of 12 ng/mL/hr or more
- and
- * Absolute increase in plasma renin activity of 10 ng/mL/hr or more
- and
- * >150% increase in stimulated plasma renin activity or >400% increase if baseline plasma renin activity is <3 ng/mL/hr

Adapted from Muller et al (2), p 633, and from Kaplan NM. Renal vascular hypertension. In: Kaplan NM, ed. Clinical hypertension. 6th ed. Baltimore: Williams and Wilkins, 1994:330.

Therapy for hypertensive emergency

The goal of treatment in a hypertensive emergency is a prompt but gradual reduction of

blood pressure. Depending on the clinical situation, a reasonable goal is a 25% reduction of the mean arterial pressure or a reduction of diastolic pressure to 100 to 110 mm Hg over the course of several minutes to several hours³. Careful observation is critical because end-organ ischemia or infarction can occur when pressure is reduced too rapidly. This is particularly true in the presence of an ongoing cerebrovascular accident. If symptoms worsen (eg, an increase in chest pressure, a decline in mental status) during the reduction of systemic blood pressure, the rate of reduction should be slowed or treatment should be temporarily halted.

Many drugs are available for the treatment of hypertensive emergencies. Nitroprusside sodium (Nitropress) is used most often because its onset of action is nearly instantaneous and its dose can be carefully adjusted for a smooth reduction in blood pressure⁴. However, nitroprusside tends to cause cyanide or thiocyanate toxicity when it is given for more than a few days, particularly in patients with renal or hepatic insufficiency. Nitroprusside also has the potential to increase intracranial pressure, which may limit its usefulness in patients with possible or known central nervous system complications. Fenoldopam mesylate (Corlopam) is approved by the US Food and Drug Administration for treatment of hypertensive crisis. This selective dopamine receptor agonist causes peripheral vasodilatation by stimulating dopamine-1 receptors⁵. It increases renal blood flow and glomerular filtration rate, which often improves renal function in patients who present with renal insufficiency⁶. Fenoldopam has a few minor side effects, such as headache, dizziness, and flushing, but it tends to increase intraocular pressure and thus should be used with caution in patients with glaucoma. Patients should be closely monitored for dose-related tachycardia, which tends to diminish over time. Fenoldopam

may also cause significant hypokalemia⁷. The efficacy of fenoldopam appears to be similar to that of nitroprusside in treatment of severe hypertension⁶.

Hypertensive emergencies can be treated with intravenous vasodilators, such as diazoxide (Hyperstat IV), which is rarely used, hydralazine hydrochloride (Apresoline), enalapril maleate (Vasotec I.V.), and nicardipine hydrochloride (Cardene). Intravenous adrenergic inhibitors, such as phentolamine (Regitine), esmolol hydrochloride (Brevibloc), and labetalol hydrochloride (Normodyne, Trandate), can also be effective. Drug selection data are limited, and solid guidelines are not yet available because outcomes with specific agents have not been compared. Currently, drug selection is primarily determined by rapidity of action, ease of administration, and the potential for side effects

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Management of Eclampsia



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Background

Pre-eclampsia / eclampsia is an unpredictable, multiorgan disorder unique to human pregnancy. It is associated with significant maternal and fetal morbidity and mortality. Treatment of this disorder remains a challenge to even the most experienced obstetrician, mainly because the exact etiology is unknown.¹

Eclampsia is defined as the occurrence of generalized convulsion(s) associated with signs of pre-eclampsia during pregnancy, labor or within 7 days of delivery and not caused by epilepsy or other convulsive disorders. In the absence of a high blood pressure or if the convulsion occurs after day 7 postpartum, the condition is referred to as atypical eclampsia.²

The occurrence of convulsions associated with signs of pre-eclampsia (hypertension and proteinuria) vary widely from 1 in 100 to 1 in 2000 pregnancies. The symptoms and signs of impending eclampsia are:-

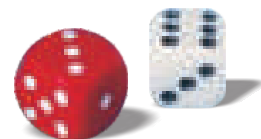
1. Severe frontal headache
2. Epigastric pain / tenderness
3. Nausea / vomiting
4. Visual blurring
5. Hyper - reflexia / sustained clonus

The following factors have been identified as risk factors for maternal morbidity and mortality - late referral to a tertiary hospital, delay in hospitalization, lack of transport, unbooked status of patients, high parity ; a state of unconsciousness and multiple seizures prior to admission.⁴

What should be used to treat the convulsions?

The Collaborative Eclampsia Trial was set up in 23 centres in eight countries to determine which, if any, is superior- magnesium sulphate, diazepam or phenytoin. There were nearly 1,700 women randomised to treatments in two separate trials - magnesium sulphate against diazepam (910 subjects) and magnesium sulphate against phenytoin (777 subjects). The primary outcomes were recurrence of convulsions and maternal death. Women allocated magnesium sulphate had significantly lower risk of recurrent convulsions than those allocated diazepam or phenytoin. Maternal mortality was nonsignificantly lower among women allocated magnesium sulphate. Women allocated magnesium sulphate were also less likely to be ventilated, to develop pneumonia, and to be admitted to intensive care facilities. The babies of women who had been allocated magnesium sulphate before delivery were significantly less likely to be intubated at the place of delivery, and to be admitted to a special care nursery.³

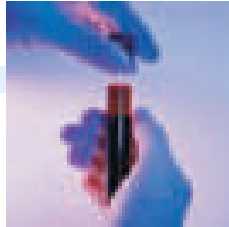
There is now compelling evidence in favour of magnesium sulphate, rather than diazepam or phenytoin, for the treatment of eclampsia.



MANAGEMENT OF ECLAMPSIA

The principles of management of eclampsia include⁴ -

1. Immediate care
 - maintain airway
 - left lateral position
 - oxygen administration
2. Abort convulsions
Diazepam 10 mg i.v. or
Clonazepam 1 mg i.v.
3. Seizure prophylaxis
Magnesium sulphate (MgSo₄)
4. Maintain diastolic blood pressure of 95-105 mmHg
5. Coagulation screen / renal function / platelet count
6. Hemodynamic stabilization followed by delivery with 6-8 h
7. Postpartum
24-48 h of intensive care



8. Ventilatory support for at least 24 h, if :
 - poor arterial blood gases
 - unconsciousness / Glasgow coma scale < 8
 - laryngeal oedema

For the purpose of practical management guidelines, treatment can be divided into that for the eclamptic who has no impairment of consciousness following a seizure, and those who have marked impairment.⁴

Minimal or no impairment of consciousness

If the patient is convulsing, this should be shortened or aborted with the administration of diazepam 10mg i.v. or clonazepam 1 mg i.v. MgSo₄ is then used to prevent further convulsions.

MgSo₄ may be administered by various regimens (Table 1).⁵⁻⁷

Table-1. MgSo₄ regimens used in eclampsia

REGIMEN	LOADING DOSE	MAINTENANCE DOSE
Pritchard et al ⁵	4 g over 3 - 5 min i.v. 10 g i.m.	5 g, 4 hourly i.m.
Zuspan ⁶	4 g over 5 - 10 min	1-2 g/h i.v.
Sibai ⁷	6 g over 20 min i.v.	2 g / h i.v.
i.m. intramuscularly ; i.v., intravenously		

If the intramuscular regime is used, ensure that before administration of each subsequent maintenance dose:

- (i) urine output is above 30 ml / h
- (ii) patellar reflexes are intact ; and
- (iii) respiratory rate is adequate

The intravenous regime is advantageous to utilize as the patient does not need to receive repeated intramuscular injections which can be painful and may be associated a risk of abscess development. The intravenous regimen, however, necessitates

close maternal surveillance with availability of appropriate resuscitative facilities. Serum magnesium levels should be preformed in select cases, viz. oliguric patient, development of symptoms and signs of magnesium toxicity, renal failure and recurrent convulsions.⁸

The blood pressure should not be lowered too rapidly as cerebral perfusion may be lowered with exacerbation of cerebral ischemia. Furthermore, uteroplacental blood flow may also be adversely influenced with resultant fetal

jeopardy. The diastolic blood pressure should be gradually lowered to 90-100 mmHg and systolic blood pressure to 140-150mmHg. Dihydralazine (6.25mg, i.v.) administered as a bolus over 4-5

minutes is the drug of choice. A labetalol infusion 120?g/min is an alternative in the presence of maternal tachycardia. Other rapid acting agents, viz. diazoxide, sodium nitropruside and nitroglycerine, are usually preserved for use in the intensive care unit setting.

Nifedipine is a cheap and easily available alternative to the above drugs. Oral form of Nifedipine (capsule form) lowers blood pressure in 5 - 10 mins by sublingual route and in 10 - 30 mins by oral route. Only oral capsule is recommended which can be repeated every 15 - 30 mins to a maximum of 30 mg / dose. Use of sublingual capsule is not recommended worldwide.

The eclamptic patient warrants meticulous surveillance, especially the cardiovascular system. The heart rate should be monitored continuously with an ECG monitor as these patients are prone to ventricular arrhythmias. Non invasive blood pressure monitoring and pulse oximetry should be documented every 15 min.⁹ Invasive hemodynamic monitoring may prove beneficial in a select group of patients, viz intractable cardiac failure, severe renal disease, refractory hypertension, oliguria or pulmonary edema.¹⁰

Marked impairment of consciousness

This group of patients has raised intracranial pressure (ICP) and thus it is important to lower blood pressure gradually or the ICP may rise even further. Airway management may necessitate intubations if the patient is extremely restless (due to cerebral oedema), deeply unconscious, has poor arterial blood gases or

has extensive laryngeal oedema. In such situations, a caesarean section should be performed following hemodynamic stabilization with postoperative ventilation for at least 24 h. The use of steroids and / or diuretics should be considered to reduce cerebral oedema. CT scanning and MRI may be performed in select cases, viz . the presence of focal neurological signs or atypical eclampsia.²

FURTHER MANAGEMENT

Investigations performed should include a hemoglobin level, platelet count, urea, electrolyte status and a coagulation screen. A peripheral smear and liver function test is indicated in presence of thrombocytopenia. A platelet transfusion is indicated for operative procedures or during second stage of labor if thrombocytopenia exists. Urine output should be monitored hourly. Fetal surveillance is necessary in the viable fetus.¹¹

MODE OF DELIVERY

A cesarean section is recommended in the following situations:

- i) all deeply unconscious patients (unless delivery is imminent)
- ii) all un co-operative patients due to restlessness
- iii) if vaginal delivery is unlikely to occur with 6-8 h of the onset of First eclamptic seizure.
- iv) there is an obstetric indication for a cesarean section
- v) fetal distress

Regional anesthesia has become the preferred technique for women with severe pre-eclampsia and eclampsia. However, it is contraindicated in the presence of a coagulopathy because of the potential for hemorrhagic complications.¹²

If the patient is delivering vaginally, cut short the second stage of labor in order to avoid the

rise in maternal blood pressure with each uterine contraction. Furthermore, ergotrine is contraindicated in the third stage. In the postpartum period, the first 24-48 h are especially important as blood pressure may fluctuate and patient is still at risk for developing complications. Oliguric patients who have not responded to fluid challenge may benefit from low doses of dopamine (1-5 µg/kg/min) to improve urine output.¹³ Antihypertensives are usually required for 24-48 h and need to be gradually decreased. MgSO₄ is administered for 24 h post delivery.

The neonatal assessment is important, especially in the scenario of preterm deliveries, abruptio placenta or a maternal ocagulopathy.

CONTRACEPTION

Steroidal contraception may be prescribed. Puerperal tubal ligations should be avoided because of the attendant risks of thrombo-embolic disease and pulmonary embolism.

POSTNATAL ASSESSMENT

At the 6th week postnatal assessment, the presence of hypertension or proteinuria necessitates referral to a physician for further investigations. Counsel the patient on booking early in future pregnancies. The advantages include possible administration of low dose aspirin and detection of pre-eclampsia as early as possible.

RECURRENCE

The risk of recurrence varies from 1.9% to 24.9%.¹⁴ Daughters of eclamptic patients have a 3% risk of developing eclampsia and 25% risk of developing pre-eclampsia.



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Low Dose Magnesium Therapy in Eclampsia



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Eclampsia is second most common cause of maternal mortality and morbidity in underprivileged population. Dr. J.A. Pritchard gets the credit of popularizing Magnesium Sulphate for the management of eclampsia.

Pritchard¹ suggested that the dose of Magnesium should be limited in women who are known to be or appear to be small. With this in mind the dose of regime of magnesium sulphate was modified and a standardized protocol has been formulated to suit our Indian women who on an average weigh much less than their counterparts in the Western World.

Low dose Magnesium therapy protocol

Loading dose	4gm MgSO ₄ IM/IV diluted & injected slowly
Maintenance dose	2gm MgSO ₄ IM/IV diluted every 3hrly for 24hrs. after delivery or last convulsion which ever is later.

Recurrence of convulsion:- In case of recurrence of convulsion an additional dose of 2gm IM/IV is given and previous dose schedule is continued.

In 600 cases of eclampsia² treated by this regime the convulsions were controlled in 552 i.e. 92%. While in 48 women i.e. 8% there was recurrence of convulsion, which was controlled, with an additional dose of 2gm. Maternal and perinatal mortality and morbidity was very similar to Pritchard regime.

A study was under taken to compare the low dose regime with Pritchard regime. The comparison was done clinically and Biochemically by comparing the serum Mg levels³ in 60 cases in each group. Range of serum Magnesium level was 5.47 ± 1.98 mg/dl in Pritchard regime and low dose regime group it was 4.23 ± 1.52 mg/dl. The effective serum Magnesium levels could be achieved with low dose regime also.

The low dose Magnesium regime is also recommended as prophylaxis in all patients of imminent eclampsia. This low dose prophylaxis is effective in 98.75% women in preventing eclamptic convulsion.

The key issue in our country is maternal transport especially in rural areas after woman starts getting convulsions and the need to be transported to tertiary referral centre. Low dose regime is small safe and very easy to administer and safe in the hands of Auxiliary nurse midwife. This regime is being practiced in many centres in Maharashtra with excellent results.

In years to come it will be an established treatment protocol in India.

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Approach to Management of Complications Of PIH: An Overview



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Preeclampsia is a multisystem organ disorder that may lead to life threatening complications in mother and fetus in severe cases. Early recognition and proper management of PIH may serve to avoid serious maternal and fetal complications. Various complications include

1. HELLP syndrome
2. Acute renal failure
3. Eclamptic seizure
4. Liver rupture
5. Pulmonary edema
6. Cerebral edema and cerebro-vascular accident
7. Abruption placentae,
8. IUGR and
9. Intrauterine death.

HELLP SYNDROME: It complicates almost 20% of women with severe pre-eclampsia and eclampsia¹. The hematocrit may be low or normal and is the last to appear. Decreased serum haptoglobin confirm on going hemolysis when the hematocrit is normal. Milder elevations of serum transaminase levels are typical, however may be elevated to as high as 4000 U/L. Platelet count may fall to as low as 5000-10 000, but count below 150,000 warrant attention. Patients with full blown HELLP syndrome (all three abnormalities) are at higher risk of complication, including DIC, than patients with partial HELLP syndrome (one or two abnormalities).

Once diagnosis of HELLP syndrome has been established the best markers to follow are maternal platelet count and lactate dehydrogenase level². Prompt recognition and timely initiation of therapy are vital to ensure best outcome for the mother and fetus. Traditional management by prompt delivery has been challenged by considering the period of gestation and the severity of HELLP syndrome. Women with partial HELLP syndrome, less than 34 weeks period of gestation, are managed conservatively for the sake of fetal pulmonary maturity³. Besides corticosteroids for fetal pulmonary maturity, high dose dexamethasone (10mg intravenous 12 hourly) has been shown to improve the laboratory abnormalities⁴.

RENAL COMPLICATIONS: In contrast to normal pregnant patients, in patients with preeclampsia have decreased renal perfusion and glomerular filtration. Levels of serum uric acid are typically elevated. In severe cases however, severe intrarenal vasospasm and glomerular endothelial swelling is profound and the serum creatinine level increases⁵. Acute renal failure from acute tubular necrosis may develop and is characterized by oliguria or anuria and rapidly developing azotemia. Drakeley and co-worker described 72 women with preeclampsia and renal failure, half of whom had HELLP syndrome and a third of women had placental abruption⁶. Aggressive management may help to prevent permanent renal damage. Management include daily urine output charting and termination of pregnancy when renal function compromises.

Consultation of a good nephrologist is an essential part of management. When azotemia is evident and severe oliguria persists, hemodialysis should be initiated. Adjustment of the dose of medication is important in patients with renal failure.

CENTRAL NERVOUS SYSTEM COMPLICATIONS:

The two distinct but related cerebral pathologies include gross intracranial hemorrhage due to rupture of arteries caused by severe hypertension and diffuse cerebral edema. With improved CT scan and MRI, all women with eclampsia found to have abnormal brain finding⁷. Imaging studies should be advocated when ever there is a doubt and in cases of eclampsia. Expert opinion of neurologist and neurosurgeons should be taken depending on the imaging findings. Control of blood pressure is of utmost importance in cases of severe preeclampsia to prevent the CNS complications. Blindness following eclamptic convulsion is seen in 10% of patients and resolves completely. Patients should be reassured as blindness lasts for 4 hours to 8 days. With sudden blood pressure elevation, vasogenic edema worsens and consideration is given for treatment with mannitol and dexamethasone.

ABRUPTIO PLACENTAE: Complicates 1 in 200 pregnancies. Once abruption is diagnosed, pregnancy has to be terminated. Our policy is to deliver by cesarean section when the fetus is viable and bishops score is unfavorable (<6). In case of dead fetus however vaginal delivery should be considered first and Oxytocin augmentation with early amniotomy should be advocated. Amniotomy both decrease bleeding from implantation site and reduce the entry of thromboplastin into maternal circulation. Monitoring coagulation profile and volume replacement in the form of blood and blood products are important. With

small abruption expectant management may prove beneficial when the fetus is immature⁸. However periodic monitoring of maternal coagulation status is very important.

ECLAMPSIA: Development of eclamptic convulsions and /or unexplained coma during pregnancy or postpartum in patients with signs and symptoms of preeclampsia.

- The first priority in a patient with eclampsia is to prevent maternal injury and to support respiratory and cardiovascular function. Maternal oxygenation 8-10 liters/ min is essential.
- Prevention of recurrent seizure by magnesium sulphate.
- Control blood pressure
- Termination of pregnancy
- Judicious use of antihypertensive and fluid management is important.
- Postpartum magnesium sulphate to prevent postpartum eclampsia.

(Detail management of eclampsia is dealt in details in other chapter)

Intrauterine Growth Restriction:

When preeclampsia affects the uteroplacental circulation, growth restriction of variability severity occurs. Monitoring patients with growth restriction with strict daily fetal movement count, biweekly non-stress test and biophysical profile is very important. Doppler velocimetry of fetal umbilical and middle cerebral arteries is a valuable tool for monitoring growth restricted fetuses.

INDICATION OF TERMINATION OF PREGNANCY IN CASES OF PREECLAMPSIA

1. Severe hypertension not controlled by two antihypertensive medications in their maximum dose.

2. No growth of the fetus for three weeks on ultrasound
3. Reversal of diastolic flow on doppler of
4. Abruptio placentae
5. Poor biophysical profile
6. HELLP syndrome
7. Intrauterine fetal demise
8. Severe IUGR at 34 weeks
9. Eclampsia

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Coagulation Failure in Pregnancy-Induced Hypertension (PIH)

Hypertension is a common complication of pregnancy, occurring with a frequency of 10 to 15 percent. Preeclampsia complicates about 5 to 10 percent of hypertensive pregnancies and remains a major cause of maternal and neonatal morbidity and mortality¹.

Normal pregnancy is associated with a transient hypercoagulable state, which most likely evolved in response to the dangers of post-partum hemorrhage. This prothrombotic state is balanced by adaptations in the fibrinolytic pathway. In eclampsia and preeclampsia, this delicate balance is disturbed. There appears to be excess platelet activation, as well as endothelial damage and dysfunction, with the consequences of thrombosis, low birth weight, fetal loss, and maternal morbidity and mortality.

CHANGES IN HEMOSTASIS DURING NORMAL PREGNANCY

In pregnancy, there is a marked increase in some of the coagulation factors, as well as changes in endothelial function, platelet activity, and fibrinolysis. The fibrinogen level in pregnant woman at delivery is often double the amount present in the non-pregnant state. There is also a significant increase in von Willebrand factor, clotting factors VII, VIII, X, XII, and prothrombin, which can be detected from the third month of gestation. In contrast to the increases in coagulation factors, the levels of physiological anticoagulants remain normal. There is also an increase in fibrinolytic pathway activity during normal pregnancies, resulting in an increased generation of plasmin, which cleaves the polymerized fibrin and releases fibrin degradation products².



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The mean platelet count decreases during pregnancy. There is an increase in platelet activation and platelet survival time is decreased during normal pregnancy^{3,4}. Prostacyclin, a potent vasodilator and inhibitor of platelet aggregation, produced by endothelium is increased during pregnancy.

HEMOSTATIC CHANGES AFTER HYPERTENSION IN PREGNANCY

Alterations in coagulation, fibrinolysis, and platelet and vascular endothelial function are believed to play an important role in the pathogenesis of preeclampsia and are shown in table 1. The fall in the platelet count is most frequent abnormality and is probably due to consumption during low-grade intravascular coagulation⁵. In addition to changes in absolute platelet numbers, the platelets also appear to circulate in a more activated state. There is also a reduction in physiologic anticoagulants in preeclampsia.

CLINICAL IMPLICATIONS OF PIH

The abnormalities of clotting and platelet function lead to widespread damage to the endothelium resulting in vasoconstriction. It also promotes platelet adhesion and aggregation as well as the activation of coagulation factors, resulting in further hypoxic damage to the endothelium. These changes lead to placental hypoperfusion and infarction, fibrin deposition, consumptive thrombocytopenia, and coagulopathy.

MANAGEMENT OF COAGULATION FAILURE IN PIH

Upto 50% of patients with preeclampsia develop thrombocytopenia and severity is generally proportional to the underlying disease.

Platelet count continues to fall for an additional 1-2 days after delivery, with recovery of the platelet count taking additional 2-3 days. Hence, for most patients, the syndrome resolves and the platelet count raises to greater than 100,00-150,000/uL by day 5-6 following delivery.

Avoid all platelet transfusions in these patients unless there are signs of active bleeding, There is a possibility that platelet transfusions could contribute to the thrombotic events which can occur in this syndrome. Prophylactic platelet transfusions should not be given. Platelet transfusions may be given prior to cesarean section to raise the platelet count above 50,000/umm with appreciation that survival of transfused platelets may be short.

The subset of preeclampsia is identified according to laboratory abnormalities which include hemolysis (H), elevated liver enzymes (EL), and low platelets (LP) which together comprise the HELLP syndrome. Management of HELLP is generally supportive. The primary treatment of the HELLP syndrome like preeclampsia, is as rapid delivery as possible. Treatments include blood pressure control with appropriate oral or parenteral antihypertensive agents. Seizures are controlled by using standard treatment.

Red cell transfusions are given to maintain the hemoglobin level. Coagulopathy resulting from DIC should be managed with Fresh Frozen Plasma and cryoprecipitate to replace fibrinogen.

Subset of patients display prolonged

thrombocytopenia and multi organ dysfunction with increased LDH following delivery. Some of these patients do respond to plasma exchange. Maternal mortality in severe cases can range from 1-3%.

The offspring of mothers with HELLP and preeclampsia may also become thrombocytopenic and may not develop until after delivery. Cordblood platelet count and platelet counts at 48 hours after birth needs to be monitored.

Table - 1

Abnormalities of Hemostasis in PIH compared to normal pregnancy

Protein C	Normal to decreased
Protein S	Decreased
Anthrombin III	Decreased
Tissue Plasminogen activator	Increased
Soluble fibrin (uterine vein)	Decreased
Fibrin D-dimer	Increased
Thrombin generation	Increased
Platelet count	Reduced
Platelet activation	Increased
Von Willebrand factor	Increased
Fibronectin	Increased

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Management of Neonate with Maternal PIH



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Maternal PIH is one of the common causes of fetal compromise. Fetal risk is related to severity of Pre-eclampsia, duration of disease and degree of proteinuria. The following problems in fetus can be seen -

1. **Intrauterine growth restrictions (IUGR)** - Due to chronic placental insufficiency
2. **Prematurity** - Due to spontaneous preterm labor or due to preterm induction
3. **Asphyxia**
4. **Death** - Due to spasm of uteroplacental vessels leading to accidental hemorrhage.

Accurate monitoring of fetal growth is one of the most critically important components of prenatal care. The ramifications of abnormal fetal growth have both short-term and long-term sequelae for early neonatal life and beyond. Although not perfectly accurate, ultrasound and other monitoring technologies have markedly improved the ability to follow abnormalities of fetal growth and to decide if early intervention or early delivery is necessary. Clearly, perinatal morbidity and mortality are decreased with close surveillance of these at-risk fetuses.

The first step in the management of the IUGR fetus is diagnosis. Fundal height is the best screening tool, and ultrasound biometry is the best method for detecting the small fetus. Doppler velocimetry is the most important means of diagnosing the IUGR fetus that is at risk for adverse perinatal morbidity and mortality. Most of the interventions to limit the intrauterine growth

restriction and diagnose its cause start as soon as serial USG detects it.

Best time to deliver

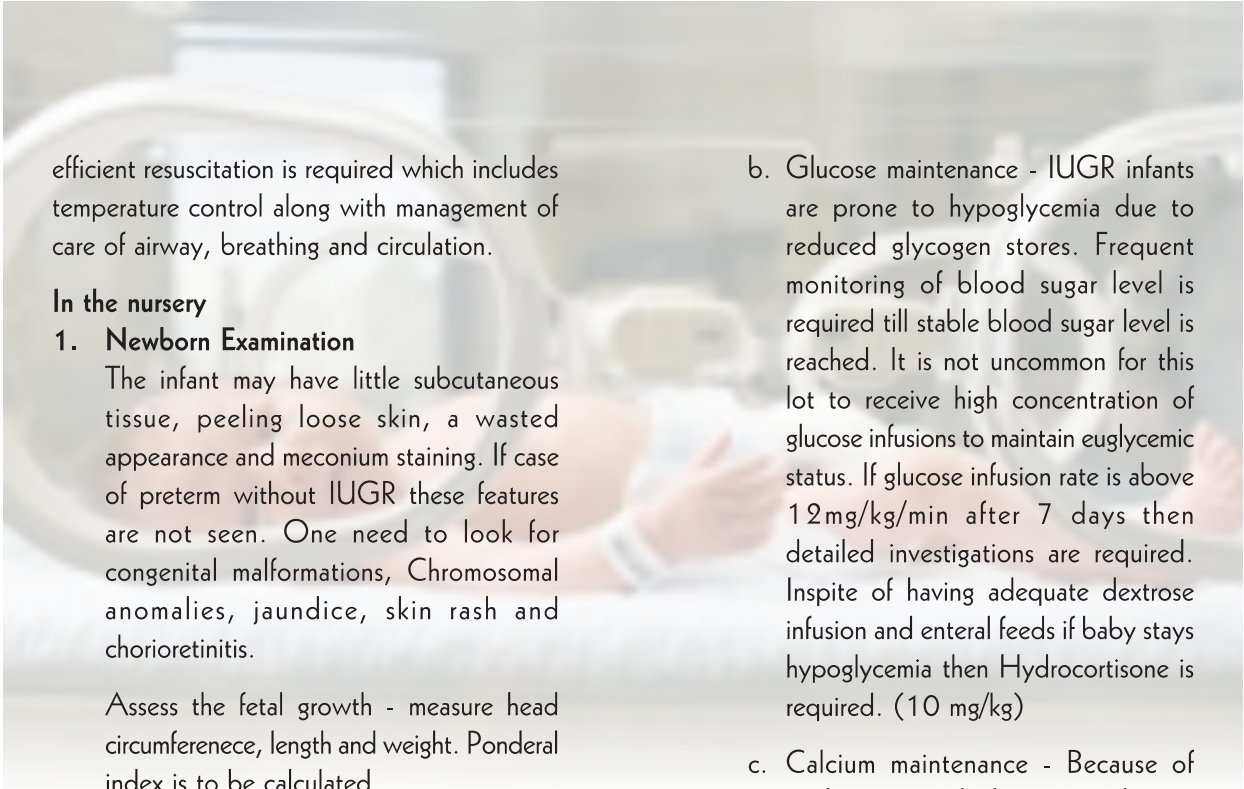
It is difficult to determine the best time to deliver the IUGR fetus. One must balance the risks of prematurity with the risks of further intrauterine decompensation. Timing of delivery must be aimed at maximize gestation and minimize the risk of continuing intrauterine life. For the very preterm fetus, there may be some benefit to delaying delivery until after venous evidence of circulatory decompensation is present, but before the biophysical profile becomes very abnormal. Two complicating factors in the management of IUGR are its varied causes and the fact that not all IUGR fetuses demonstrate the same patterns of decompensation.

Early delivery is necessary if the risk to the fetus staying in utero is considered greater than the risk of early delivery. Generally, indications for delivery are arrest of fetal growth, fetal distress and pulmonary maturity near term, especially in a mother with hypertension. Acceleration in pulmonary maturity with steroids is **MUST**. If there is poor placental blood flow, the fetus may not tolerate labor and may require cesarean delivery.

During Delivery

Very SGA infants are at risk of perinatal problems and often require specialized care in the first few days of life; if possible delivery should occur at a centre with a high risk nursery. The delivery team should be prepared to manage fetal distress, perinatal depression, meconium aspiration, hypoxia and heat loss.

In cases where mother is given magnesium sulfate, baby is likely to be depressed at birth. An



efficient resuscitation is required which includes temperature control along with management of care of airway, breathing and circulation.

In the nursery

1. Newborn Examination

The infant may have little subcutaneous tissue, peeling loose skin, a wasted appearance and meconium staining. If case of preterm without IUGR these features are not seen. One need to look for congenital malformations, Chromosomal anomalies, jaundice, skin rash and chorioretinitis.

Assess the fetal growth - measure head circumference, length and weight. Ponderal index is to be calculated.

Ponderal Index = weight in Gms/ length in cm³ x 100

Babies who have index < 2 means baby having sparing of head growth suggesting Asymmetrical IUGR. Whereas babies with affection of both length and weight are Symmetric IUGR and index will be > 2. The advantage of PI is that race , gender and gestational age do not affect the ratio for the full term infants. When it is been used for preterms it is affected by gestational age.

2. Pathological examination of Placenta

This is not been practiced in our country. Ideally placenta needs to be looked for infarction any other causes related to IUGR.

3. Routine care includes

- a. Temperature control - Prevention of heat loss is important because thermoregulation is compromised in these babies. Nurse the baby under radiant warmer or incubator if required.

- b. Glucose maintenance - IUGR infants are prone to hypoglycemia due to reduced glycogen stores. Frequent monitoring of blood sugar level is required till stable blood sugar level is reached. It is not uncommon for this lot to receive high concentration of glucose infusions to maintain euglycemic status. If glucose infusion rate is above 12mg/kg/min after 7 days then detailed investigations are required. In spite of having adequate dextrose infusion and enteral feeds if baby stays hypoglycemia then Hydrocortisone is required. (10 mg/kg)

- c. Calcium maintenance - Because of inadequate transfer from maternal stores and partially active compensatory feedback mechanism IUGR babies may end up with hypocalcemia. This will require calcium supplementation.

- d. Watch for jaundice as they are polycythemic

- e. If severely compromised gut flows then high possibilities of developing NEC - Like any other LBW babies they need to be on oral feeds as early as possible. One needs to be very watchful about acceptance of enteral feeds by baby. High gastric residues, abdominal distension, not passing meconium at regular interval are very early indications of poor intestinal motility. They require parenteral nutrition and total rest to intestine depending on severity of the problem.

- f. Renal parameters and sodium levels as renal insufficiencies are known

- g. Thrombocytopenia, leucopenia and

neutropenia particularly in hypertensive mothers. This neutropenia is not associated with a shift to immature forms as seen in bacterial infections.

- 4) **Long Term Outcome - IUGR** infants are prone to poor postnatal growth and adverse developmental outcome. Ultimate developmental prognosis depends on the cause for IUGR. These handicaps occur even in the absence of specific fetal disease. This is especially true in infants who have proportional IUGR, suggesting early onset and in those who suffered perinatal asphyxia or hypoglycemia (or both) at birth.

Further Reading.

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PIH: Scenario 2027



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Pre-eclampsia has been a recognized pathological entity since the time of Hippocrates and ancient Greeks.¹ It is one of the commonest medical disorder diagnosed by obstetricians in clinical practice.² Approximately 1,00,000 women die worldwide per annum because of eclampsia.³ It is said that pre-eclampsia and eclampsia contribute to death of a woman every 3 minutes worldwide.⁴ Majority of these conditions are preventable. So it will be definitely innovative to think of 2027 as far as scenario of PIH is concerned.

We know understanding of PIH has been changed over years and is going to change in coming years with more and more studies and research.

Advanced Technology has helped us in taking better care of our patients. It has really changed



the prognosis of various diseases. Let us see in next 20 yrs. to come, what are the changes in mortality and morbidity associated with PIH?

Diagnosis:

It is important to diagnose hypertension or PIH accurately. Korotkoff V is accurate for measurement of diastolic blood pressure as this corresponds more closely to the intra-arterial pressure. But we often find in practice that there are many lacunas in it. Either BP is improperly recorded or even if there is increased BP, patients are not counseled properly for several reasons.

It is not uncommon that patients are casually called after a week or so. Many of these women don't turn up or come with severe complications. I am sure after 20 years with increased awareness, better means of communication and better technological advances for BP recording, this scene will be rare.

Prediction of PIH:

Predicting PIH and treating the condition early will no doubt reduce the maternal as well as perinatal mortality and morbidity. For this various tests have been proposed. But except Roll over test, other tests are not very practical. Even Roll over test is not very reliable because of its high false positive rate. The test which will be mostly commonly used after 20 yrs. will be

- Fibronectin level
- Beta human chorionic gonadotrophin and human placental lactogen.⁶
- Maternal serum inhibin A⁷
- Homocysteine level
- Fetal DNA

Over 160 substances have been found increased in women with pre-eclampsia but all these studies are still conflicting. In 2027, few of these tests or some new tests may develop and will be used effectively for prediction of PIH.

Genetics & PIH: It was assumed since many years that there could be some association of genetic factors in PIH. By 2027, knowledge necessary to direct therapeutic strategies may develop. Many studies are expected by then for fine mapping of potential candidate genes as it was possible in 11-Beta-hydroxysteroid dehydrogenase (11-beta-HSD) deficiency.⁸ Genetic engineering, gene therapy or advances in cloning may change the picture in these cases in future.

Treatment: Ideal antihypertensive drug is one,

which lowers blood pressure, reduces vasospasm, conserves blood supply to placenta and vital organs and without any maternal and fetal side effects. At present there is no such drug available. But looking at various drugs added in PIH over years, we can hope to find a drug that may be close to these ideal characteristics by 2027.

Similarly we have seen the journey of anticonvulsants from Lytic Cocktail to magnesium sulphate. Today magsulph remains a drug of choice. After 20 years we may be able to find more effective drugs.

Prevention: There are many substances used for prevention of PIH empirically and with limited success. Few more will be invented in 2027.

Future: Spurrette & Cork found marked difference in incidence of PIH and eclampsia in developed and developing countries.⁹ This needs to be corrected with improvement in antenatal care, transport, regular supply of drugs and use of proper protocols.

Literature supports preventive, curative and rehabilitative role of Yoga and relaxation in pregnancy. However there are limited studies in PIH. In next 20 years this role will be confirmed by more studies.

Conclusion: Scenerio- 2027

- A Clear understanding of pathophysiology
- Early diagnostic measures- Role of oxidative stress detection,
 - PGD
 - Advanced colour Doppler.
- Awareness, Education and Easy Accessibility to Medical Aids.
- Early transfer to tertiary care centre.
- Timely detection & Prevention of complication to Mother & Baby.

Health care for all will lead to possible Eclampsia free Obstetrics.

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Pregnancy Induced Hypertension at a Glance



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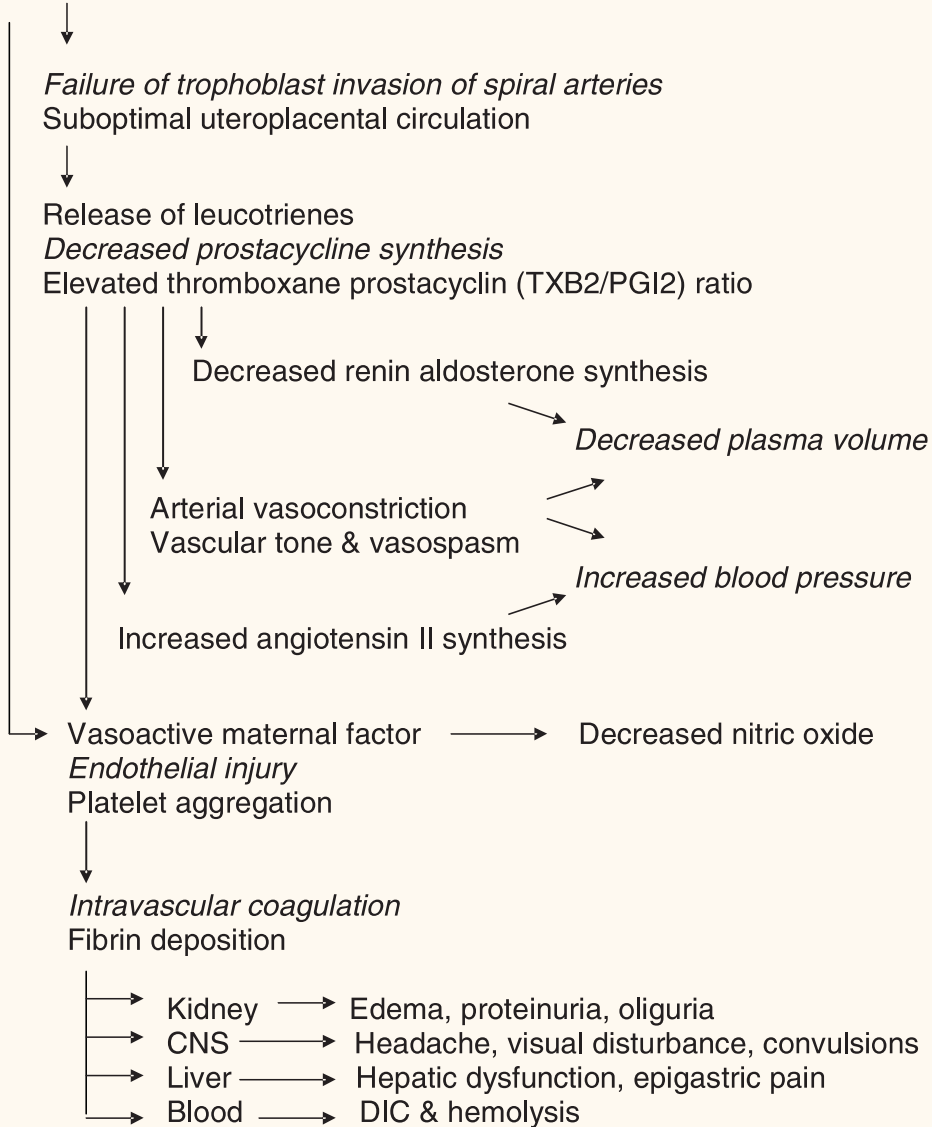
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Etiopathology of Pregnancy Induced Hypertension

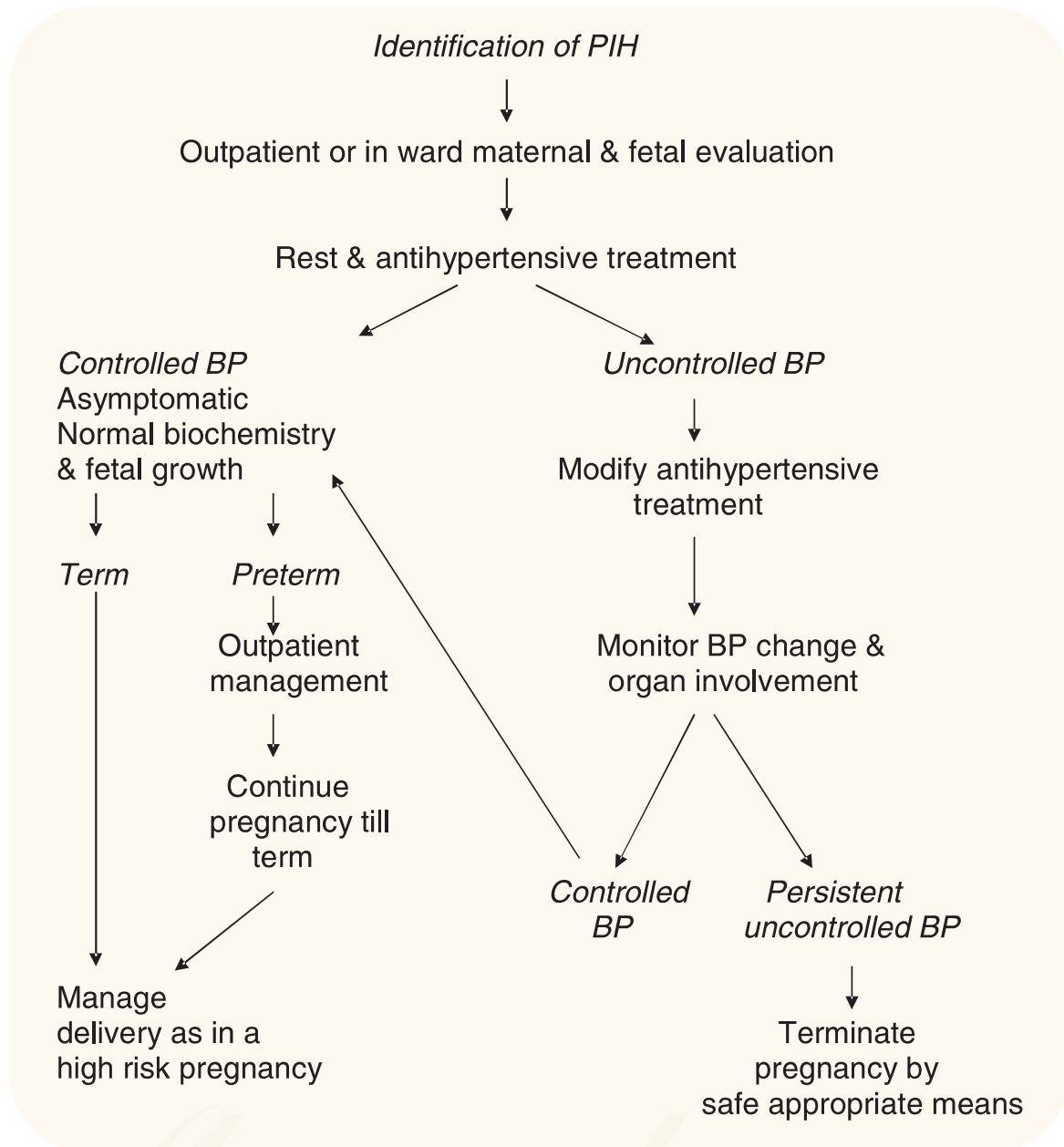
Ultimate cause of PIH

Genetic

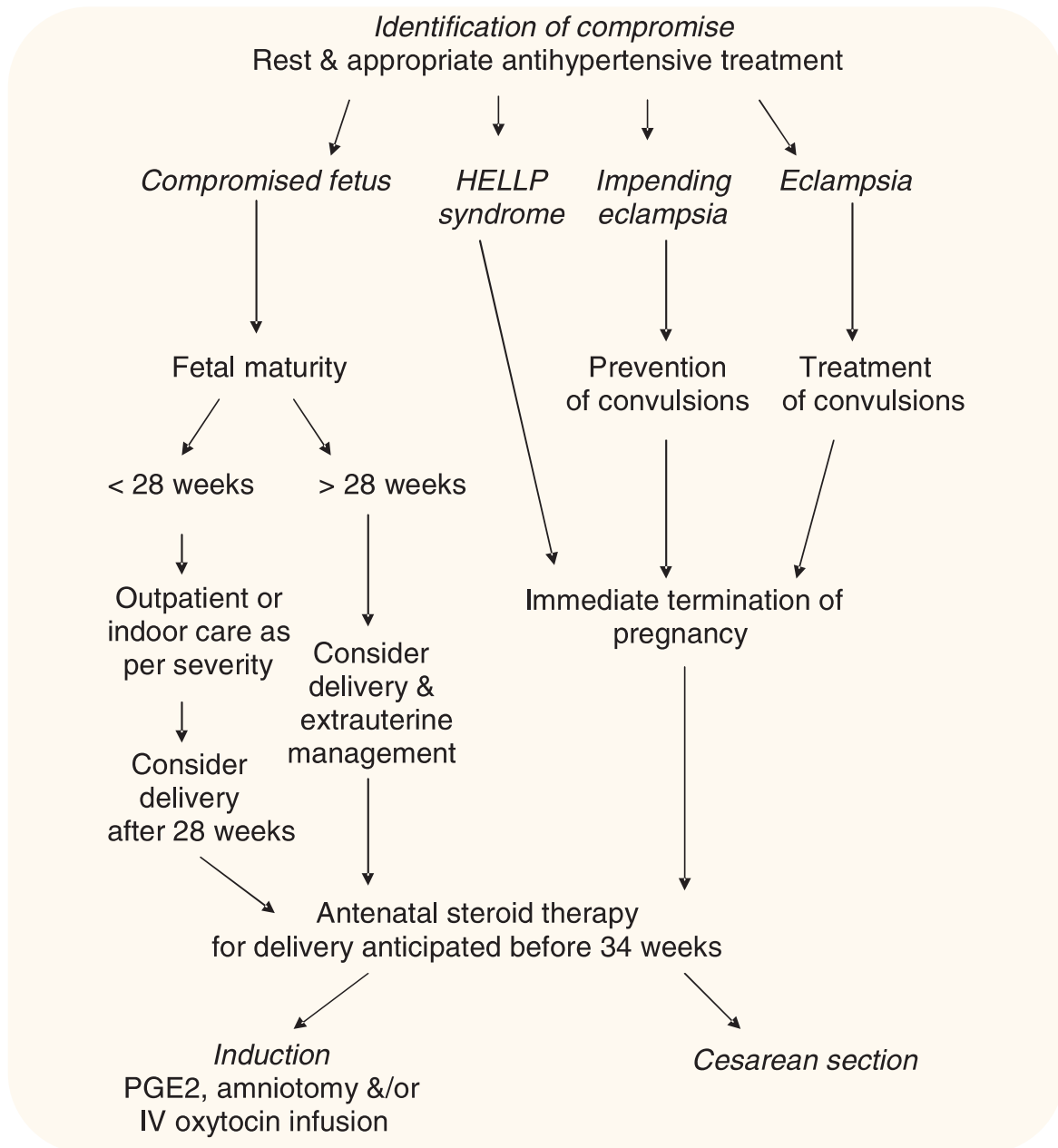
Immunological



Management Response to Antihypertensive Treatment



Management of Maternal & Fetal Compromise



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Antihypertensives usually recommended for use in pregnancy

<i>Drugs</i>	<i>Types</i>	<i>Comments</i>
Methyldopa	Centrally acting	Has been used extensively in pregnancy without reports of serious adverse effects on the fetus. Does not alter uteroplacental or renal blood flow, fetal haemodynamics, or maternal cardiac output, and there is no evidence of long-term adverse effects in infants exposed <i>in utero</i> .
Labetalol	Beta-blocker	A combined alpha- and beta-blocker, which has been used extensively in pregnancy without reports of adverse effects on the fetus. Other beta-blockers are seldom used, due to limited safety data. Atenolol should be avoided, as use in early pregnancy has been associated with fetal growth retardation.
Hydralazine	Vasodilator	Hydralazine appears to be safe in pregnancy although a few cases of fetal thrombocytopenia have been reported. Normally restricted to intravenous treatment of hypertensive emergencies. Taken orally as monotherapy, it is poorly tolerated because of adverse effects such as palpitations, headache, and dizziness. It is therefore usually combined with methyldopa or labetalol.
Nifedipine	Calcium-channel blocker	No evidence of harm to the fetus. The modified release preparation is recommended in preference to the standard-release product, which may cause a precipitous fall in blood pressure. There is less experience with the use of other calcium-channel blockers.

Drug Therapy



Interesting Cases

A case of Spontaneous hepatic rupture

Spontaneous hepatic rupture with hemoperitoneum is a rare but devastating complication of pregnancy induced hypertension. The mortality is very high and survival usually depends on prompt diagnosis and management. I am presenting a case report of spontaneous hepatic rupture in case of eclampsia which, I suspected in early days of my lecturer ship, and was managed with the help of surgeons of our institute NSCB Medical College, Jabalpur.

A 25 year old, second gravida, para one was admitted in our obstetric unit as 31 weeks of gestation with severe preeclampsia and with fetal growth retardation. On admission she was conscious here blood pressure was 180/120mm, with evidence of proteinuria. She was put on Pritchard's regime and labor was induced with dinoprostone gel, within two hours of start of the treatment, she had generalized tonic clonic convulsion and delivered a male preterm baby weighing 700gms which did not survive beyond one hour. Six hours following delivery, she complained of severe epigastric pain radiating to right shoulder, with features of peripheral circulatory collapse. I suspected hepatic rupture and asked residents to stabilize her general condition and take opinion of surgeons, radiologist and physician. Women was stabilized with two units of fresh blood transfusions.

Ultrasonography revealed ascites, surgeon's and physician's opinion was in conclusion at this stage.

She was kept under observation, magnesium sulphate was withheld after profound peripheral circulatory collapse. After 24 hours the patient had a second episode of convulsion with uncontrollable fall in haematocrit. A second ultrasonography by senior sonologist revealed a



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tear in the right lobe of the liver with free fluid in the peritoneal cavity. Repeat surgical consultation resulted in peritoneal paracentesis revealing frank blood.

Interestingly all her laboratory values were within normal limits except raised serum bilirubin (3.9mg/dl). Because of urgency of the situation incomplete coagulation profile was done which was also within normal limits.

She underwent laparotomy, 2500ml blood was evacuated from the peritoneal cavity, gel foam packing was done over 2 cm tear in the liver, peritoneal lavage and drainage was done. Four more blood transfusion were given. Her postoperative course was uneventful and was discharged on 10th day from the hospital.

Spontaneous rupture of the liver was first described by Abercrombie in 1844. In pregnancy complicated by preeclampsia, the incidence is approximately 1 in 45,000 deliveries.¹ Although preeclampsia is more common in primi gravidas but hepatic rupture is reported more in multi gravidas.² In case of PIH, women with HELLP syndrome or presenting with severe right upper quadrant or epigastric pain, radiating to shoulder and hemodynamic instability should be promptly diagnosed and treated.³ Ultrasonography, doppler flow study, emergency angiography, computed tomography scan, and magnetic resonance imaging are done for preoperative diagnosis.

Treatment depending on the severity of rupture ranges from conservative management to liver transplantation.

The surgical approach uses packing and drainage or hepatic artery ligation either alone or in various combinations. In stable patient non operative management may be possible with intensive medical support and infusion of fluids and blood products, with or without radio graphically guided arterial embolization.¹ In these patients relapsing hypotension signal life threatening rupture of liver and should be taken for surgery. Hemostasis is attempted by packing, gelfoam, Nu.- Knit (oxidized regenerated cellulose, hemostat, absorbable that can hold suture, Johnson & Johnson Inc.). The modified rapid deployment hemostat (MRDH) is a novel topical hemostatic agent, reported to have excellent hemostasis in case of liver hemorrhage refractory to conventional interventions.⁴

This case is presented in order to alert obstetricians, radiologists and surgeons to the risk and appearance of this rare grave complication. As increased awareness of this complication can lead to early diagnosis and better prognosis.

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Operative Management in case of PIH

I was called in to see Mrs K as a locum. She was 24 yrs old, one FTND, **O Rh Negative**. She received Anti-D after birth of previous daughter. She developed a blood pressure of 140/100, about a week ago, with urine albumin +. She was receiving Depin, 10 mg daily. Her ante-natal was otherwise uneventful. She was admitted at 6 am at 39 wks of gestation, with APH. Her previous sonography indicated normal placentation.

Examination revealed a Full Term pregnancy, good general health, B.P. 160/90, contracting uterus with absent foetal heart. With a provisional diagnosis of accidental haemorrhage, she was taken up for a Caesarean operation. One blood could be cross-matched with a lot of running around. At surgery, the foetus was dead with a 250 gms retroplacental blood clot. The uterus did not contract well, but with the battery of oxytocin, ergometrin, prostaglandins, we completed the suturing. Still, the uterus was not contracting completely, black patches on uterine surface indicating Couvelier uterus, suture line was oozing and now patient had tachycardia. By that time we realized that collected peripheral blood refused to clot, even after ten minutes.



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The available blood bottle was ordered, we ordered more blood and components from other blood banks, called in a physician who was in charge of an ICU, and with provisional diagnosis of disseminated intravascular coagulation, obtained a reluctant consent for hysterectomy. A subtotal hysterectomy was completed, with abdominal closure in next 9 minutes.

The physician clinically confirmed the diagnosis and shifted the patient to ICU. With second transfusion running, her blood pressure was still maintained at 120/70, pulse 94/min. In ICU, she received 32 units of fresh frozen plasma and other components. She recovered completely in three days.

This was a hazardous complication of pregnancy hypertension. Vigilance for abruption placentae and later for DIC, and wonderful management of clotting disorder could save the life of mother.

This is of special importance for **Rh Negative** Patient as availability of blood is a problem.

Reference:

1. Hypertension in pregnancy, ACOG Technical Bulletin no. 219, 1996; 1-8
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A Case of Recurrent PIH

26yr old Primi with POG (D) 25 wks (U) 20 wks. referred from private in view of high Blood pressure and oligohydroamnios. She was very sure about her dates & this was a planned conception .There was no history of headache or blurring of vision .

Pt was admitted and monitored for vitals & investigated (complete hemogram including platelets, BUN, Se creatinine, uric acid , SGOT, SGPT,

Her USG at 11 weeks and 18 weeks were normal .Triple marker test was screen negative

On admission - Her GC was Fair .

She was Afebrile , no pallor or icterus was present.

Pulse-90/ min ,BP-150/98mmHg (both arms)

P/A - ut 16 weeks.

P/v - ut bulky, 20 weeks , os closed , cx tubular

Urine albu mine/ trace.

Fundoscopy -NAD

She was given high protein diet. Tab.Aldomet 250 mg TDS and Tab Aspirin 75 mg were started. Haematinics & Calcium were also added. Doppler was done for fetal surveillance which showed high resistance pattern in left uterine artery.

Her investigations were repeated weekly.

However, her BP stabilized for few days and then kept on rising.

Pt was monitored regularly by repeated blood investigations & USG .Her BP kept on rising gradually.



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By 28 wks of gestation her BP rose to 180/110mmhg. Pt developed

oliguria .Coagulation profile was sent .Urine albumin was 1 + .Reflexes were not brisk.

USG Doppler s/o bilateral uterine notch with severe IUGR, clinically

Since the Blood pressure was not responding Pt and her relatives were counseled and a decision to terminate the pregnancy was taken.

She was started on a Sodium nitroprusside drip . She was induced with prostaglandin gel and later pitocin .

She delivered a preterm fetus of 550 gms which survived for a few hours hrs. There was no obvious congenital anomaly

Post termination Blood pressure settled gradually and was maintained T. Methyl dopa 500 QID for 2 weeks . Maternal course was uneventful.

At 4 weeks Physician advised tab Amlodipine 5mgs OD.

Pt was investigated with battery of tests to determine the cause of early onset PIH with severe IUGR

- Captopril Test - Negative, Renal artery doppler - NAD
- Urinary VMA levels - normal
- APLA - Lupus anticoagulant was raised but ACL was negative,
- DRVVT was negative ANA & anti DNA were negative

She had a regular follow up and was advised to use condoms for contraception atleast for 1 year. Gradually the Amlodipine dose was reduced to 2.5 mgs OD.

She conceived 16 months later. In her second pregnancy, she was started on T. Aspirin 75 mg OD from 12 wks onwards & Inj. Low molecular weight Heparin from 16 wks onwards

USG done at 16 wks showed no abnormalities and Doppler flow of uterine & umbilical arteries were normal..

All PIH investigations including coagulation profile were within normal limits

Patient monitored on an OPD basis for BP , other blood investigations and fetal growth with serial Doppler ultrasounds

Inj Betamethasone was given 12 mg two doses, at 24 hrs interval at 26 weeks

Patients BP and fetal growth were within normal limits till 32 wks

As her pregnancy progressed ,BP again started rising from 32 wks onwards.

T. Aldomet 250 mg 1-1-1 was added.

Doppler done showed a single live foetus corresponding to the gestational age with high resistance pattern in left uterine artery

T. Aspirin was stopped at around 34 wks of gestation

Daily NST were done & strict daily fetal kick count was maintained.

Serial dopplers were done to detect any abnormality

Repeat Doppler at 34 wks which showed bilateral uterine notching with mild IUGR

Decision to terminate the pregnancy was taken i/v/o maternal & fetal risk

Cervix was not inducible and pt was very apprehensive in view of her past pregnancy mishap so a decision for cesarean section was taken

Inj. Heparin was stopped 48 hrs before elective LSCS

Patient delivered a healthy male baby of 2.2 Kg & discharged on day 5 of surgery. BP was normal.

Case is presented to show the risk of recurrent PIH is quite significant in a case of previous severe pre eclampsia.

Reference

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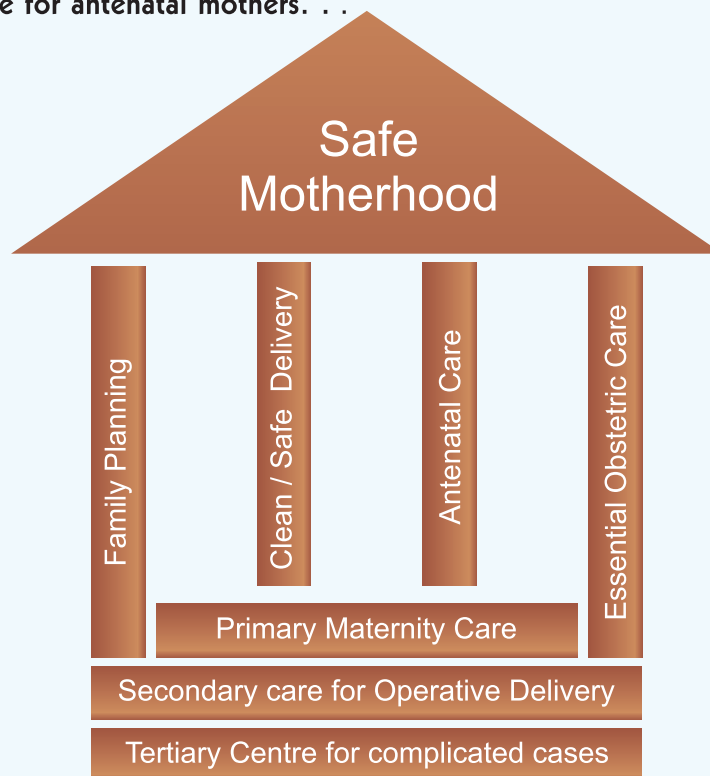


PIH

Realities; Perspectives & Challenges. . . .

- Contributes a lot to maternal mortality rate in India.
- A preventable tragedy!
- One of the causes of Direct obstetric Death.

FOGSI care for antenatal mothers. . .



Providing Basic maternity care is essential.

Let's care for all mothers in India

Regular Antenatal Care & BP monitoring.

OUR Role

- Inform, educate, and mobilize the community regarding danger signs of preeclampsia/eclampsia and work with communities to improve access to care
- Strengthen the referral system
- Improve human resources
- Develop and use case Mx protocols, monitor standards

Avoid

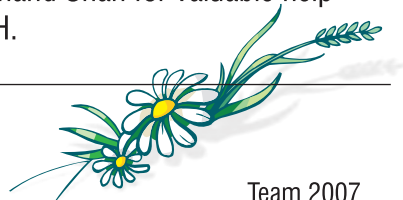
- Delay in decision
- Delay in transport
- Delay in providing service

Timely action saves life!
Let us try for ECLAMPSIA FREE Obstetrics.

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