Preeclampsia and Eclampsia: A Challenge in its Truest Sense: Bursting the Challenge

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Introduction: Preeclampsia is the major cause of morbidity and mortality worldwide. Approximately 72,000 pregnant women die every year because of eclampsia and severe pre-eclampsia. That is nearly 200 women every day. Pre-eclampsia-eclampsia rank second only to hemorrhage as a specific, direct cause of maternal death.The risk that a woman in a developing country will die of pre-eclampsia or eclampsia is about 300 times that of a woman in a developed country. (*Balancing the Scales: Expanding Treatment for Pregnant Women With Life-Threatening Hypertensive Conditions in Developing Countries, a Report on Barriers and Solutions to Treat Pre-eclampsia & Eclampsia' EngenderHealth 2007*)

Lifting the curtains: The revelations of the NER:The FOGSI-ICOG National EclampsiaRegistry (NER) has brought forth some revealing trends. Eclampsia prevalence among registry patients is 1.9%. National sample surveys in the past have shown prevalence to be 1 - 5%.This is out of the 1,11,725 deliveries analyzed reported by the 175 reporting centers. Most of these centers are either private(62%) or tertiary institutes (32%).Participation from Rural Medical Centers (RMC) is limited (6%).Number of cases of eclampsia are more than cases of imminent eclampsia. Thispoints to the lost opportunities of prevention. 17 % of preeclampsia patients are actually in the adolescent age group reflecting the very early age at marriage in spite of several awareness programs and legal guidelines. 76.34% of the patients were between 21-30 years of age thus rendering a very young population morbid and at risk of mortality. It also is a disease of the first time pregnant woman as 81% of the patients with preeclampsia were primigravid.

Antenatal care has been identified as the single intervention which could influence the maternal mortality of our country. Many women still seem to be unreached with this basic pregnancy evaluation. Most of the patients reported by the registry were registered for antenatal care either in the second(40.98%) or the third trimester (46.28%). Very few (12.54%) booked in the first trimester.

Eclampsia is a culmination of the pathogenesis started of by abnormal trophoblastic invasion initiating vasospasm, endothelial dysfunction and platelet aggregation. Many a times it is found to be not associated with any symptoms (57%:NER data),22% had headache and very few had vomiting, epigastric pain, giddiness etc.: Majority of the times, convulsions occur during ante-natal period(76.78%) ; however post-partum convulsions (13.72%) are also significant.40.5% mothers had 1-4 convulsions before admission while 23% had just one. Greater numbers of convulsions prior to care, may be due to lack of facilities nearby. Time spent in access to care is crucial and may alter maternal and fetal outcome.Convulsions post admission (76.6%), indicate lack of standardizedcare protocol, for eclampsia which is mandatory. Time spent between first episode of

convulsion and access to critical care is between 1 to 4 hours in majority (48.33%) of patients. This indicates the severe need to train paramedical personnel in remote interiors as well as better transport facilities to handle obstetric emergencies. Magnesium sulphate was used only in 44% cases of patients and that needs attention from all of us.

We need to tackle this: Preeclampsia is one condition which in spite of all progress in the medical field is on the rise.This trend is due to increasing risk factors like obesity, life style issues, delayed child bearing and increasing use of assisted reproductive procedures. We as an advocacy organization have to play a major role in reversing this trend and reducing this mortality andmorbidity.

How the plan of action:

1. By producing, distributing or promoting use of credible patient information in form of brochures, leaflets, pictorial cards or interactive website to enhance patient awareness.
2. by coming up with Good Clinical Practice Guidelines and simplified management algorithms for all the health workers in the field
3. by organizing research workshops and symposia to accelerate translation of research to influence clinical practice
4. To help overcome barriers of accessing care
5. To influence public policy

The clinical facts :Preeclampsia is defined by the new onset of hypertension (systolic BP > 140 mm of Hg or diastolic BP > 90 mm of Hg) accompanied by new onset proteinuria, defined as 300 mg or more per 24 hours. Severe preeclampsia is identified by the systolic blood pressure of 160 mm Hg or higher or diastolic blood pressure of 110 mm Hg or higher on two occasions at least six hours apart.Presence of proteinuria of more than 5 grams in a 24-hour collection or more than 3+ on two random urine samples collected at least four hours apart is also a feature of severe preeclampsia. Also presence of any symptoms or signs such as pulmonary edema,cyanosis,oliguria (< 400 mL in 24h),persistent headaches, epigastric pain and/or impaired liver function, thrombocytopenia, oligohydramnios, decreased fetal growth, or placental abruption feature severe preeclampsia.

The pathogenesis: Etiologically preeclampsia develops in two stages viz; the asymptomatic stage involves abnormal placentation which is followed by placental elaboration of soluble factors that enter the maternal circulation and cause widespread endothelial dysfunction with signs and symptoms.

Clinical classification of preeclampsia: Clinically preclampsia also divided as early onset preclampsia (before 34 weeks of gestation)(EOPET) and late onset preclampsia (after 34 weeks of gestation)(LOPET). This distinction is now held important as there is a suspicion that these two are actually separate entities.

Early onset preeclampsia is afetal disorder that is typically associated with placental dysfunction,reduction in placental volume,intrauterine growth restriction,abnormal uterine and umbilical artery Doppler evaluation,low birth weight,adverse maternal and neonatal outcomes

Late onset preeclampsia is maternal disorder, due to underlying maternal constitutional factors, normal or larger placental volume, normal fetal growth, normal uterine and umbilical artery Doppler evaluation,normal birth weight, more favorable maternal and neonatal outcomes

Can we predict Preeclampsia? This remains the burning question today. Early prediction of preeclampsia and then prevention has been the dream of many obstetricians over the generations. Numerous tests have been described from physical to chemical in various eras.Altogether these are more than 60 tests but none of these is found to be reliable as a single test. Clinically the predictability was described as per the various high risk factors present in a particular patient which is more practical.

Screening tests for Preeclampsia include

1. Placental perfusion and vascular resistance dysfunction
2. Fetoplacental unit dysfunction.
3. Renal dysfunction
4. Endothelialand oxidant stress dysfunction

Clinical risk factors: But after exploring a lot of high end technological tests and predictors; we have again come back to recognize the importance of these clinical risk factors**.**Factors which includechronic hypertension/renal disease(15-40%),Pregestational diabetes (10-35%)**,**connective tissue disease (lupus, rheumatoid arthritis) (10-20%)**,**thrombophilia (acquired or congenital) (10-40%)**,**obesity/insulin resistance (10-15%)**,**age older than 40 years (10-20%)**,**limited sperm exposure(10-35%),family history of preeclampsia/ cardiovascular disease(10-15%)**,**woman born as SFGA(1.5 fold)**,**adverse outcome in a previous pregnancy: IUGR, abruptio placentae, IUFD(2-3 fold).

Color Doppler in 1st trimester: Apart from above studies since defective placentation was the key factor color doppler studies were sought after as predictor of preeclampsia. In the first trimester color doppler prediction rates were up to 53% and combined with maternal high risk factors 89%.(*Poon et al*).In second trimester diastolic notch on uterine artery doppler at 20-24 weeks has a positive test relative risk of 7 fold,negative test relative risk of 0.5 fold(*Albaiges et al- ObstetGynecol 2000*).Besides these it can also be used for fetal well being assessment can show decrease in fetal growth rate, fetal polycythemia, flow redistribution favoring vital organs, decreased amniotic fluid, absent end diastolic velocity in umbilical artery, loss of fetal movements, loss of fetal heart rate variability, reversed end-diastolic flow in umbilical artery, ductusvenosus (a-wave reversal),fetal circulatory collapse and death.

Prevention of preeclampsia: Prediction is only useful if prevention can follow. Unfortunately there are hardly any measures which can be taken to prevent preeclampsia.

1) Non pharmacological: daily bed rest, life-style changes, smoking, regular prenatal exercise

2)Nutritional:higher total dietary fiber intake, dietary protein and energy, garlic, dietary sodium restriction, weight reduction, fish oil supplementation

3)Pharmacological**:**vitamin D**,** magnesium, folic acid and other B-vitamins, zinc supplementation, nitric oxide**,** progesterone, low-dose aspirin, low-dose aspirin/heparin**,** calcium supplementation**,** antihypertensive drugs**,** diuretics**,** antioxidant supplementation**,** concomitant vitamin Cand E supplementation.

Of these the important ones are :

Strict bed rest: Rest for 4-6 hours/daymay reduce risk of preclampsia for women with normal BP *(level 2 evidence) (Cochrane Library 2006 Issue 2:CD005939*). Strict bed rest is not recommended for improving pregnancy outcomes in women with hypertension (with or without proteinuria) in pregnancy.(*WHO Guidelines 2011).*

High job stress: poses greater risk of preeclampsia (*Sharmaand Mittal, 2006*). Reducing job stress may be beneficial in the prevention of Preeclampsia

Light exercise: Stretching exercises are more effective at reducing the risk of preclampsia than walking (*University of North Carolina,2008)*

Smoking: Stoppage of smoking causes reduced risk for preclampsia (*Sibai et al, 2005).*Nicotine causes inhibition of interleukin-2 and tumor necrosis factorandaffectsangiogenic proteins). Smoking also causes abnormal fetal growth**,** preterm birth**,** abruption**,** adverse effects on maternal health.

Low dose Aspirin: Aspirin is associated with a 10-19% reduction in preclampsia risk and a 10-16% decrease in perinatal morbidity and mortality.This risk reduction was seen in women who were in the 'moderate to high risk category'.(*Duley I et al*) - *antiplatelet agents for preventing PE and its complications (Cochrane Review) the library 2006. (Askie l et al)- antiplatelet agents for prevention of PE; a meta-analysis of individual patient data- Lancet 2007*.

Calcium supplementation:Reduces the risk of preclampsia, particularly in populations that have diets deficient in calcium.*level 1 evidence (Cochrane Sytematic review, 2006).*High quality studies have shown that calcium supplementation of at least 1g.daily started around mid-pregnancy is associated with a modest reduction in PE and a more notable reduction in its severe manifestations among women with low dietary calcium intake.(*HofmeyrGj et al)- WHO trial of calcium supplementation to prevent PE Am J ObstetGynecol 2010.*

The only preventive measures which seem feasible are low dose Aspirin, Calcium, MgSO4 (for Eclampsia).(*Prof. Arulkumaran- Clinical Obstetrics and Gynecology 2011*).If prevention is not possible then at least early detection and better management should be the aim. Presently

unfortunately when we so called “TREAT” preclampsia; we are only treating the symptoms and not the cause and that must be clearly borne in mind.

MANAGEMENT OF PREECLAMPSIA AND ECLAMPSIA:

Assessment of risk factors early in pregnancy: Presence of any one of these factors should be identified early in pregnancy.They includemultiple pregnancy, preclampsia in any previous pregnancy, preexisting hypertension,10 years or more since last baby, preexisting renal disease, age 40 years or more, preexisting diabetes, BMI of 35kg/m2 or more, antiphospholipid antibodies, family history of preclamspia, booking diastolic pressure of 80mm of Hg or more.

While managing a case of preclampsia taking references of standard protocols and guidelines like the FOGSI guidelines and the WHO guidelines should be undertaken**.** Interventions that are recommended for prevention or treatment of pre-eclampsiaandeclampsia are:

- Women with severe hypertension during pregnancy should receive treatment with antihypertensive drugs.The choice and route of administration should be based primarily on the clinician's experience with that particular drug, its cost and local availability.
- Magnesium sulfate is recommended for the prevention of eclampsia in women with severe pre-eclampsia.Magnesium sulfate is recommended for the treatment of women with eclampsia the full intravenous or intramuscular magnesium sulfate regimens are recommended for the prevention and treatment of eclampsia.
- For settings where it is not possible to administer the full magnesium sulfate regimen, the use of magnesium sulfate loading dose followed by immediate transfer to a higher level health-care facility is recommended for women with severe pre-eclampsia and eclampsia.Induction of labour is recommended for women with severe preeclampsia at a gestational age when the fetus is not viable (usually before 25 weeks).
- In women with severe pre-eclampsia, with viable fetus (25 to 34 weeks), a policy of expectant management is recommended, provided that uncontrolled maternal hypertension, increasing maternal organ dysfunction or fetal distress are absent and can be monitored.In women with severe pre-eclampsia, a viable fetus and between 34 and 36 weeks of gestation, a policy of expectant management may be recommended, provided that uncontrolled maternal hypertension, increasing maternal organ dysfunction or fetal distress are absent and can be monitored.
- In women with severe pre-eclampsia at term, early delivery is recommended.In women with mild pre-eclampsia or mild gestational hypertension at term, induction of labour is recommended.In women treated with antihypertensive drugs antenatally, continued treatment postpartum is recommended.Treatment with antihypertensive drugs is recommended for severe postpartum hypertension

The theory of pathogenesis of preclampsia: Today, we have a novel andunifyingtheory about the pathophysiology of preeclampsia. This was originally proposed by *Feinberg et al from USA in 2005*. It is the GESTOSIS theory which states that there is excess of immune complexes produced because of placental antigenicitywhich are not cleared by maternal immune system.Hence they are deposited in the various endothelial layers causingpro- inflammatorycytokinesand oxidative

stress.This results in clinical preeclampsia which is inflammatory response of pregnancy.Support for this theory comes from the facts that this Disorder is more frequent in primigravidas,adaptive protection is afforded in subsequent pregnancies of the same paternity, baseline risk returns with first pregnancies of a new partner. Higher incidence is seen in oocyte donation pregnancy, is common in pregnancy with hyperplacentation and is cured after placenta is removed.This is a clinical turning point in the disease process. This maternal oxidative stress in turn stimulates further placental apoptosis and necrosis generating, an auto amplification process.This leads to varying severity of clinical preeclampsia.Neutrophils accumulated in the inflammatory site are activated by the immune complexes. They release proteases and toxic oxygen radicals which cause further damage the so called'oxidative stress' seen in preeclampsia. The main immune complex clearance mechanism in the humans is via the erythrocyte complement receptor type1(CR1). Erythrocytes express approximately 500 CR1 receptors per cell. A decreased expression of erythrocyte CRI in pre eclamptic patients correlates with severity of disease – as happens in anemia. If low CR1 is matched with low immune complex production, no adverse sequelae would be anticipated. Hence all anemic patients don't get preeclampsia. This is where other factors come into play. (eg: genetic, lifestyle, nutrition etc.).The degree of complement activation reflects the severity of the disease.Pregnancies complicated by HELLP syndrome have increased plasma levels of C3a and C5aas compared to women with preeclampsia without HELLP syndrome.

Things that can be done at a grass roots level include **earlyreferral** from medical officer to specialist **especially** in the circumstances like multiple pregnancy, preclampsia in any previous pregnancy, underlying medical conditions, preexisting hypertension or booking diastolic BP>/= 90 mm of Hg, Preexisting renal disease or booking proteinuria (>/= 1+ on more than one occasion or quantified at >/= 0.3g/24h), preexisting diabetes, presence of antiphospholipid antibodies, first pregnancy, age 40 years or more, BMI of 35kg/m2 or more, family history of preclampsia, booking diastolic BP >/=80mm of Hg < 90 mm oh Hg.

Immediate admission should be arranged for a woman whose diastolic BP>/= 110 mm of Hg and new proteinuria >/= 1+ on dipstick, systolic BP>/= 170 mm of Hg and new proteinuria >/= 1+ on dipstick, diastolic BP>/= 90 mm of Hg and new proteinuria >/= 1+ on dipstick and significant symptoms.

National Eclampsia Registry:

The National Eclampsia Registry (NER) is the first web enabled registry in our country. Centralized forum for collecting latest data on incidence, prevalence and burden of eclampsia with ultimate goal is to achieve uniform treatment practices nationwide which will help in reducing incidence.

So far more than 100 centers & FOGSI members are reporting their cases. The data is kept anonymous so that one need not worry about privacy issues. If all of us FOGSI members keep on collecting such data it will be of great help in controlling & finally reducing the mortality & morbidity due to eclampsia in our country. So please enroll your name as a "NER reporter" & communicate on ner.fogsi.icog@gmail.com

Summary:

Preeclampsia has always played a major role in maternal mortality and morbidity. The least we can do is to create awareness amongst the patients, expect alertness from our fellow obstetricians, continue research to find the causes and new treatment modalities.It seems that we have come a full circle calling it toxemia of pregnancy 100 years back because it was thought that there were toxins in the blood and now again finding that there are subcellular soluble factors in the blood which may be the reason for this scourge. We may not have solved the enigma as yet but if we remember simple messages like

- Think of the clinical preconceptional risk factors
- Advise good nutrition
- Insist on correct BP measurement and look for proteinuria
- think of aspirin and iron and calcium supplements
- use anti-hypertensive and magnesium sulfatecorrectly
- take help of color Doppler when feasible
- Deliverpatient at a proper time and a proper facility.

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