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Foreword for Guideline

LDI:REACH PAKISTAN Right care, every birth

FIGO LDI REACH project Pakistan, was launched in April 2023. The project operates from its head office in Islamabad with a dedicated team of managers overseeing its execution, under the supervision of a six-member core committee.

Eclampsia remains a leading cause of maternal deaths in Pakistan. There was an urgent need to develop comprehensive guidelines to standardize the use of magnesium sulfate ($MgSO_4$) for the prevention and treatment of eclampsia.

I am particularly grateful to the FIGO UK team—Rachel Gooden, Mathew Pretty, Barina Gale, Esther Adoh, Jane Seok and Anyia Matzer—for their continuous guidance and support.

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I am deeply grateful to Rizwana Chaudhri, Chief Editor of SOGP journal, and Syed Aftab for issuing a special supplement to publish the guideline.

I am hopeful that this guideline will contribute to the standardization of $MgSO_4$ use for the prevention and treatment of eclampsia, ultimately helping to reduce maternal mortality caused by severe preeclampsia and eclampsia.

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بِسْمِ اللّٰهِ الرَّحْمٰنِ الرَّحِيْمِ

In the Name of Allāh, the Most Gracious, the Most Merciful

This Guideline Is Prepared by

Professor Azizunnisa Abbasi

President, SOGP & Project Lead, FIGO LDI REACH Pakistan

By Reviewing Literature, FIGO, WHO, and RCOG guidelines, along with local availability and feasibility for the use of $MgSO_4$ in Pakistan.

Introduction

Magnesium sulphate is the drug of choice for the prevention and treatment of convulsions in severe pre-eclampsia and eclampsia. This guideline provides comprehensive information on its indications, contraindications, dosage, monitoring, management of toxicity, and special considerations to ensure its safe and effective administration for the prevention and treatment of eclampsia.

Indications

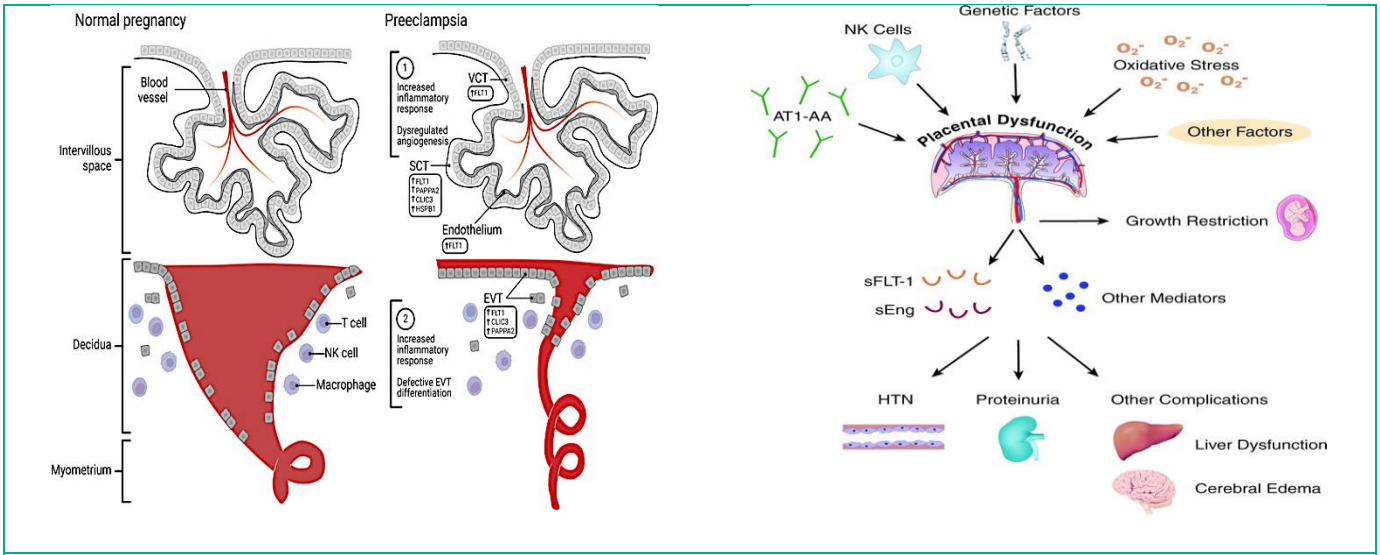
- Magnesium sulphate is indicated for the following conditions:
- **Severe pre-eclampsia** – To prevent the onset of convulsions.
- **Eclampsia** – To control and prevent further convulsions.

Pathophysiology of Pre-Eclampsia and Eclampsia

The exact cause of pre-eclampsia remains unknown. It is a complex multisystem disorder that develops during pregnancy, particularly after 20 weeks of gestation.

A key mechanism involves abnormal placental development, specifically impaired spiral artery remodeling. During a healthy pregnancy, fetal trophoblast cells invade the maternal spiral arteries, causing them to dilate and lose their muscular layer. In pre-eclampsia, this invasion is incomplete, leaving the arteries narrow and with high resistance. This results in poor placental perfusion and hypoxia, which triggers oxidative stress and inflammation.

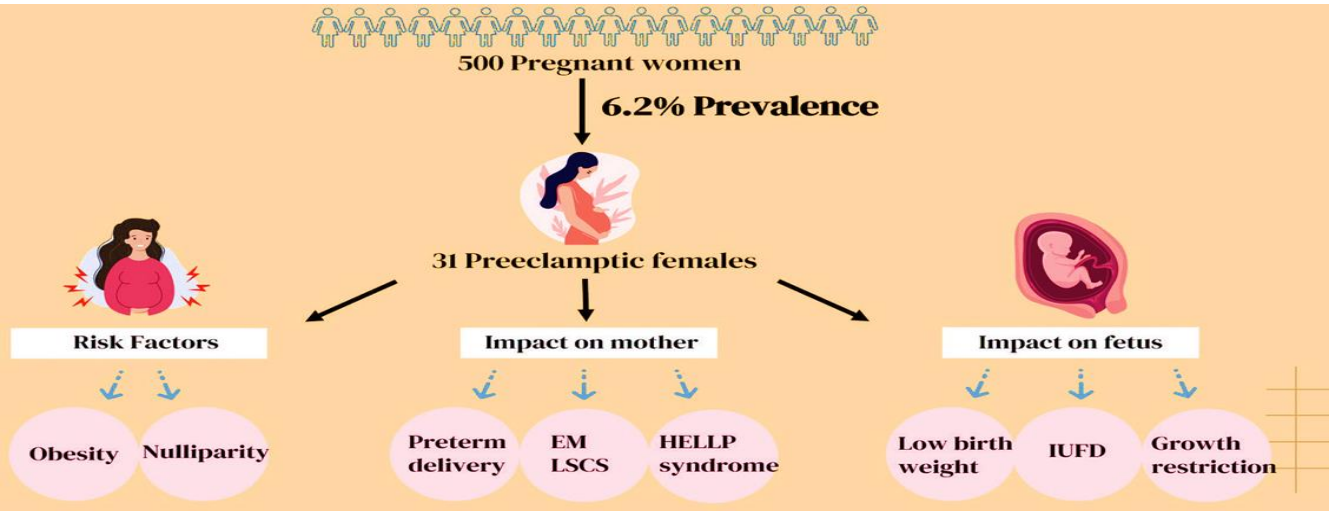
Endothelial dysfunction and widespread inflammation due to release of antiangiogenic factors like tyrosine - kinase, vascular endothelial growth factors and placental growth factors are also the possible causes of severe preeclampsia and eclampsia



An imbalance in vasoactive molecules (increased endothelin-1, decreased nitric oxide, and prostacyclin) leads to systemic vasoconstriction, which increases blood pressure and reduces organ perfusion.

Moderate Risk	High Risk
First pregnancy	Hypertension (HT) in previous pregnancies
Maternal age >40 years old	Chronic kidney disease
Pregnancy interval of >10 years	Systemic lupus erythematosus
Pre-conception BMI >35 kg/m^2	Antiphospholipid syndrome
History of preeclampsia (PE) in a patient's mother	Diabetes mellitus type 1 or type 2
Multiple pregnancy	Chronic hypertension (HT)

BMI – Body Mass Index, HT – Hypertension, PE – Preeclampsia



Mechanism of Action of MgSo4

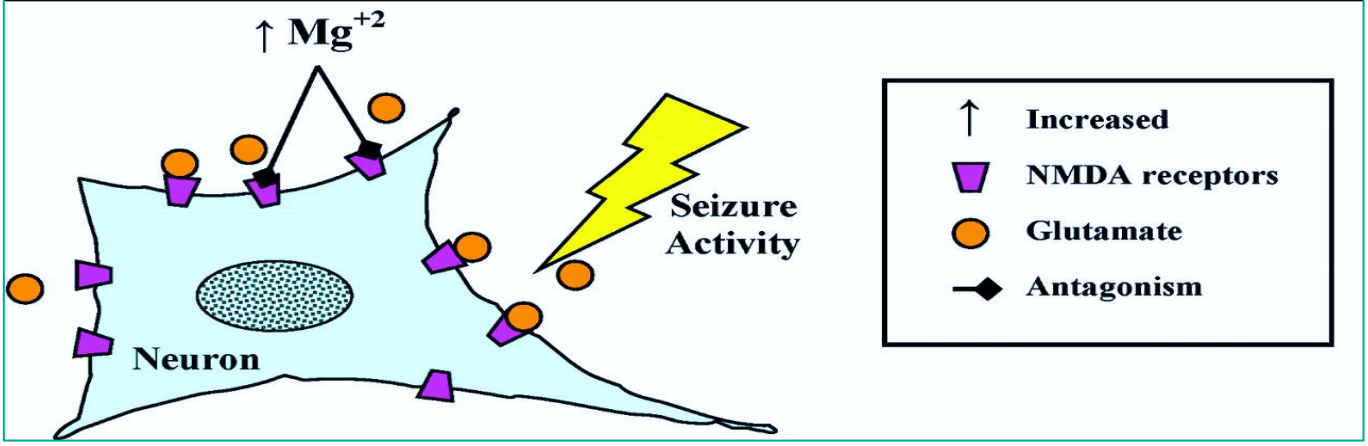
Its mechanism of action is mostly multi – factorial, comprising of both vascular and neurological mechanism. Being calcium channel antagonist, it effects on vascular smooth muscles to promote relaxation and vasodilation. MgSo4 acts as competitive antagonist at N-methyl-D-aspartate receptors in the brain, this reduces neuronal excitability and prevents seizures. It also causes nerve cells membranes stabilization by reducing calcium influx in to the neurons.

Magnesium relaxes the cerebral blood vessels, improving blood flow and reducing cerebral edema and vasospasm.

Magnesium also blocks calcium entry in to the vascular smooth muscles leading to systemic vasodilation

Anticonvulsant Activity of Magnesium Sulfate.

Cellular Target	Mode of Action	Possible Mechanism
Neurons	Increased Seizure Threshold	N-Methyl-D-Aspartate (NMDA) Receptor Antagonism ↓ Decreased Effect of Glutamate, Limiting Massive Neuronal Depolarization



Contraindications

- Magnesium sulphate should not be administered in the following conditions.
- Myasthenia gravis, due to the risk of severe muscle weakness.
- Severe renal impairment, as magnesium is excreted by the kidneys and can accumulate to toxic levels.
- Heart block, which can be exacerbated by the drug's effects on the heart's conduction system.

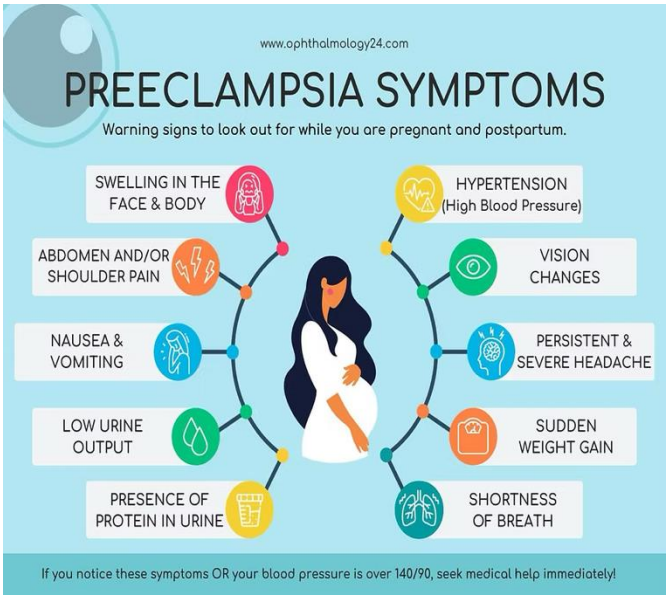
HELLP Syndrome

HELLP syndrome is usually considered as severe form of preeclampsia.

H: hemolysis. E: elevated Liver enzymes & L; low platelets

Severe Pre-eclampsia/impending eclampsia

- BP 160/110 or more.
- Headache, visual disturbances. Epigastric pain, vomiting.
- 3+/>3gm/24 hours proteinuria
- HELLP Syndrome



Complications of severe preeclampsia and eclampsia

Severe preeclampsia and eclampsia can lead to life threatening complications for both mother and baby.

Complications of Pre-Eclampsia	
Maternal	Foetal
Eclampsia (tonic-clonic/grand mal seizure)	Intrauterine growth restriction
Cerebral haemorrhage	Intrauterine death
Placental abruption	Iatrogenic preterm delivery
Renal failure, oliguria	
Pulmonary oedema, acute respiratory distress syndrome	
Disseminated intravascular coagulopathy	
HELLP (haemolysis, elevated liver enzymes, low platelets) syndrome, liver haemorrhage and rupture	
Thromboembolism	
Cortical blindness	
Laryngeal oedema	

Dosage and Administration

Loading and maintenance dose regimen is same for both severe preeclampsia and eclampsia.

- Loading dose; 1 ampule 10 ml contain 5gm of 50 % MgSo4 (only 50% ampule is available in Pakistan)
- Add 4gm (8ml) of MgSo4 in 10 ml (2 ampules) of distilled water in 20ml syringe and administer slow I/V over 20 minutes.
- Maintenance dose; 20gm (4 ampules) MgSo4 /500ml Normal Saline infuse at the rate of 1gm/hour through dial a flow, up to 24 hours of delivery or last fit.
- Recurrence of convulsions; 2gm (4ml) of MgSo4 dilute in 1ampule (5ml) of distilled water and infuse in 10 minutes.

Regimen for referral from the primary care/community/private health facility

Loading dose, I/V as mentioned above

OR

1ampule 5gm MgSo4 at each buttock I,e total of 10gm.

Referral should be directly to a tertiary care hospital and on referral notes clearly mention the dose and route of MgSo4 administered

Monitoring Parameters for MgSo4 therapy

To ensure patient safety and prevent toxicity, the following parameters should be closely monitored:

- Respiratory rate: Should remain ≥ 16 breaths per minute.
- Urine output: At least 30 ml/hour to confirm adequate renal function.
- Deep tendon reflexes: Presence of the patellar reflex indicates non-toxic magnesium levels.
- Serum magnesium levels (not mandatory): Maintain a therapeutic range of 4-7 mEq/L.

Signs and Symptoms of Magnesium Toxicity

- Loss of tendon reflexes
- Respiratory depression (< 16 breaths per minute)
- Oliguria (< 30 ml/hour)
- Hypotension
- Cardiac arrest

Management of Magnesium Toxicity

- Immediate cessation of magnesium sulphate infusion.
- Administer calcium gluconate 1 gram IV slowly over 10 minutes as an antidote.
- Provide supportive care, including respiratory support if needed.
- Continuous monitoring of vital signs and renal function.

Duration of Therapy

- The standard duration is 24 hours after the last seizure or delivery, whichever occurs later.
- In cases with persistent symptoms or a high risk of seizure recurrence, consider extending therapy while monitoring magnesium levels closely.

Special Considerations

- Renal impairment: Reduce the dose and monitor serum magnesium levels closely to prevent accumulation and toxicity.
- Availability of resuscitation equipment: Ensure that facilities for respiratory support and calcium gluconate administration are accessible during treatment.
- Postpartum monitoring: Continued monitoring is essential as the risk of seizures may persist after delivery.
- Patient education: Inform the patient about potential side effects, such as flushing, nausea, and muscle weakness.

Additional Precautions

- Assess for concurrent use of other central nervous system depressants, as they may potentiate the effects of magnesium sulphate.
- Avoid using magnesium sulphate in combination with calcium channel blockers due to the risk of severe hypotension.

Delivery

Patients with severe pre-eclampsia /HELLP syndrome/eclampsia should be monitored in HDU (High Dependency Unit).

- All these patients should be delivered once the condition is stable.
- The mode of delivery depends on the Bishop's score. If the Bishop's score is favorable, induce or augment labor.
- If Bishops is unfavorable expedite delivery by caesarian section (early delivery should be the aim).

Patients with severe pre-eclampsia/eclampsia should not go home undelivered especially in Pakistan due to unpredictable follow-up.

After delivery if condition is stable keep in HDU with close monitoring.

If unstable and need multidisciplinary involvement, shift to intensive care (ICU).

Prevention of severe preeclampsia /eclampsia

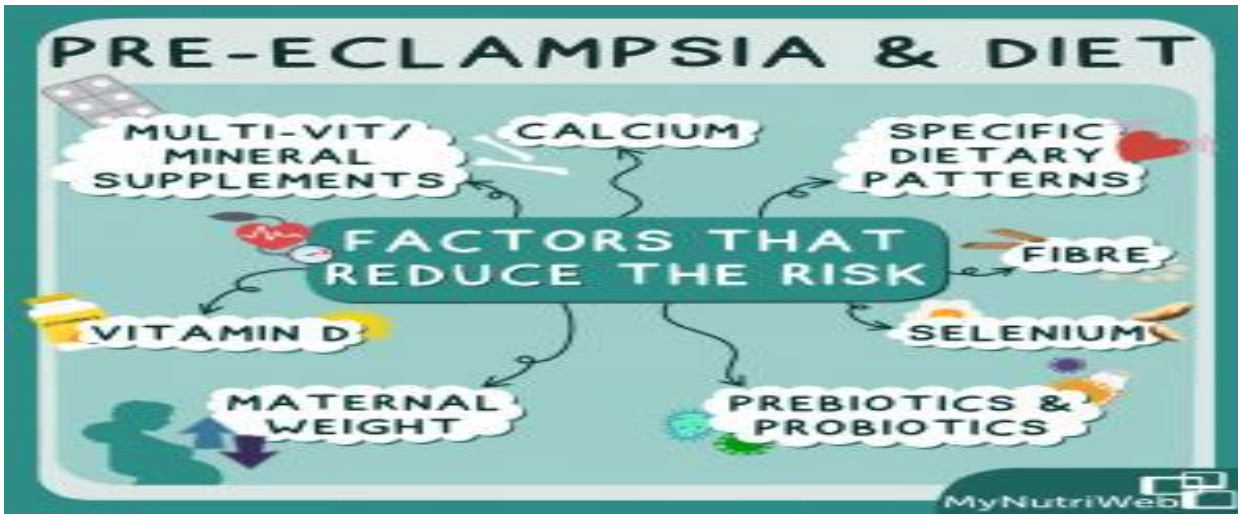
Prevention involve managing risks factors and monitoring for early signs. While there is no guaranteed way to prevent it, risk can be reduced by

- Regular antenatal care. Early and consistent prenatal visits allow monitoring of blood pressure, proteins in urine and other warning signs.
- Healthy life style choices (weight management, balanced diet, regular exercises, adequate hydration helps maintain cardiovascular health.
- Blood pressure control in patients with chronic hypertension to avoid superimposed preeclampsia.

Medications

Aspirin 75 mg/150 mg starting from 12 weeks to 36 weeks of pregnancy in patients with previous severe preeclampsia /eclampsia. (CLASP Study)

- Calcium/Multivitamins/Magnesium/Co-enzymeQ10 helps in prevention of preeclampsia.



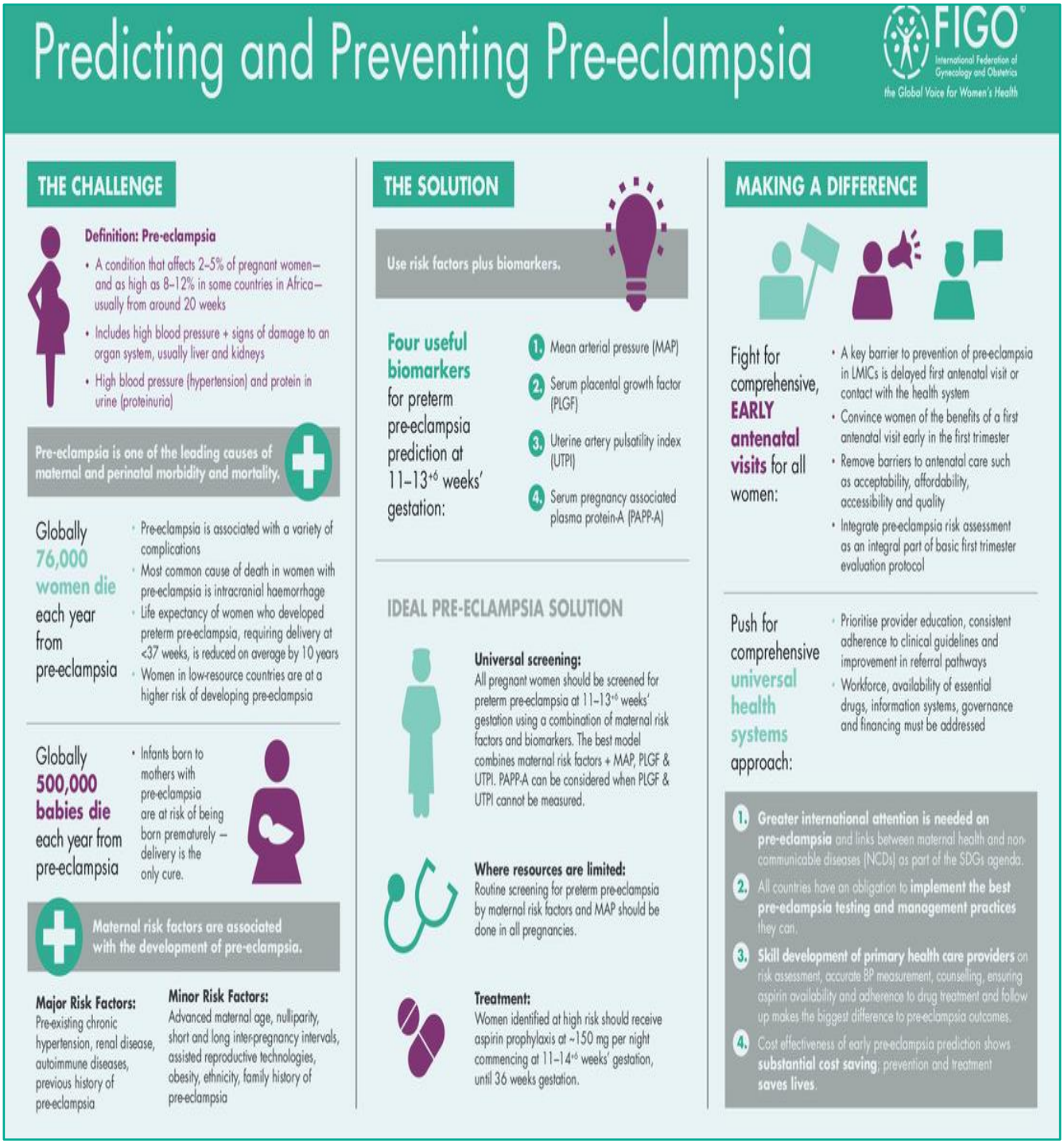
Public Awareness & Celebration of Eclampsia Day

Public awareness can help with early detection, prevention and timely medical intervention can save mothers from this life-threatening condition.

Conclusion

Magnesium sulphate is a critical and life-saving medication in the management of severe pre-eclampsia and eclampsia, it has been proven to be more effective than other anticonvulsants in reducing maternal and neonatal morbidity and mortality. MgSo4 works by stabilizing the central nervous system, reducing neuronal excitability and improving cerebral blood flow. Proper dose , proper administration, vigilant monitoring and timely intervention in the event of toxicity are essential to ensure maternal and fetal safety. Regular training of health care personnel and adherence to these guidelines can significantly reduce the risk of complications and improve patient's outcome.

Overall, MgSo4 therapy remains a life saving intervention in the management of eclampsia, significantly improving maternal and fetal outcome.


Predicting and Preventing Pre-eclampsia
FIGO
International Federation of Gynecology and Obstetrics
the Global Voice for Women's Health
THE CHALLENGE
Definition: Pre-eclampsia
• A condition that affects 2–5% of pregnant women—and as high as 8–12% in some countries in Africa—usually from around 20 weeks
• Includes high blood pressure + signs of damage to an organ system, usually liver and kidneys
• High blood pressure (hypertension) and protein in urine (proteinuria)
Pre-eclampsia is one of the leading causes of maternal and perinatal morbidity and mortality.
Globally 76,000 women die each year from pre-eclampsia
• Pre-eclampsia is associated with a variety of complications
• Most common cause of death in women with pre-eclampsia is intracranial haemorrhage
• Life expectancy of women who developed preterm pre-eclampsia, requiring delivery at <37 weeks, is reduced on average by 10 years
• Women in low-resource countries are at a higher risk of developing pre-eclampsia
Globally 500,000 babies die each year from pre-eclampsia
• Infants born to mothers with pre-eclampsia are at risk of being born prematurely – delivery is the only cure.
Maternal risk factors are associated with the development of pre-eclampsia.
Major Risk Factors:
Pre-existing chronic hypertension, renal disease, autoimmune diseases, previous history of pre-eclampsia
Minor Risk Factors:
Advanced maternal age, nulliparity, short and long inter-pregnancy intervals, assisted reproductive technologies, obesity, ethnicity, family history of pre-eclampsia
THE SOLUTION
Use risk factors plus biomarkers.
Four useful biomarkers for preterm pre-eclampsia prediction at 11–13+6 weeks' gestation:
1. Mean arterial pressure (MAP)
2. Serum placental growth factor (PLGF)
3. Uterine artery pulsatility index (UTPI)
4. Serum pregnancy associated plasma protein-A (PAPP-A)
IDEAL PRE-ECLAMPSIA SOLUTION
Universal screening:
All pregnant women should be screened for preterm pre-eclampsia at 11–13+6 weeks' gestation using a combination of maternal risk factors and biomarkers. The best model combines maternal risk factors + MAP, PLGF & UTPI. PAPP-A can be considered when PLGF & UTPI cannot be measured.
Where resources are limited:
Routine screening for preterm pre-eclampsia by maternal risk factors and MAP should be done in all pregnancies.
Treatment:
Women identified at high risk should receive aspirin prophylaxis at ~150 mg per night commencing at 11–14+6 weeks' gestation, until 36 weeks gestation.
MAKING A DIFFERENCE
Fight for comprehensive, EARLY antenatal visits for all women:
• A key barrier to prevention of pre-eclampsia in LMICs is delayed first antenatal visit or contact with the health system
• Convince women of the benefits of a first antenatal visit early in the first trimester
• Remove barriers to antenatal care such as acceptability, affordability, accessibility and quality
• Integrate pre-eclampsia risk assessment as an integral part of basic first trimester evaluation protocol
Push for comprehensive universal health systems approach:
• Prioritise provider education, consistent adherence to clinical guidelines and improvement in referral pathways
• Workforce, availability of essential drugs, information systems, governance and financing must be addressed
1. Greater international attention is needed on pre-eclampsia and links between maternal health and non-communicable diseases (NCDs) as part of the SDGs agenda.
2. All countries have an obligation to implement the best pre-eclampsia testing and management practices they can.
3. Skill development of primary health care providers on risk assessment, accurate BP measurement, counselling, ensuring aspirin availability and adherence to drug treatment and follow up makes the biggest difference to pre-eclampsia outcomes.
4. Cost effectiveness of early pre-eclampsia prediction shows substantial cost saving; prevention and treatment saves lives.