ADJUNCTIVE USE OF ESOMEPRAZOLE IN THE TREATMENT OF PRE-ECLAMPSIA: A CASE REPORT AND LITERATURE REVIEW

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ABSTRACT

Faced with the absence of suitable assays and/or kits for predictive biomarkers, medical practitioners in poor resource settings may be emasculated by the unrelenting upwards prevalence of and uncertain forecast associated with the pre-eclampsia/eclampsia and fetal growth restriction disease spectrum. Low-birth weight and pre-eclampsia due to placental malaria, multiple pregnancy and malnutrition may be reactive oxygen species - and anti-angiogenic factors – dependent. Adjunctive esomeprazole promises to be a treatment regimen that may lead to cure for it has been found to attenuate the known pathophysiologic mechanisms responsible for pre-eclampsia and IUGR which may be imbalance between pro-angiogenic and anti-angiogenic factors. The proton pump inhibitor, esomeprazole, decreases the excessive secretion of the anti-angiogenic factors soluble fms-like tyrosine kinase-I (sFlt-I) and soluble endoglin from the placenta responsible for the hypertension, endothelial dysfunction, multiorgan injury and foetal growth restriction in preeclampsia. sFlt-I binds the pro-angiogenic placenta growth factor (PIGF) and vascular endothelial growth factor (VEGF), the circulating free forms of which are low in preeclampsia. Case report is of a 32-year old Nigerian housewife who showed significant reduction in blood pressure, proteinuria and pedal oedema with esomeprazole add-on to a regimen of methyl- dopa for severe preeclampsia. The combination significantly (P < 0.05) decreased the selected indices of uteroplacental insufficiency of proteinuria, serum uric acid...
levels, blood pressure, umbilical resistance index, pulsatility index and systolic/diastolic ratio. This report corroborates the accumulating pre-clinical data on the safety and efficacy of esomeprazole in the treatment of preeclampsia, a precursor of eclampsia.

**KEYWORDS:** Preeclampsia, Eclampsia, sFlt-I, Esomeprazole.

**INTRODUCTION**

Hypertension is the most common medical problem encountered during pregnancy, complicating 2-3% of pregnancies.[1] Hypertensive disorders are classified into 4 categories as recommended by the National High Blood Pressure Education Programme Working Group in Pregnancy (NHBEP): 1) chronic hypertension, 2) pre-eclampsia – eclampsia, 3) pre-eclampsia superimposed on chronic hypertension, 4) gestational hypertension (transient or non-proteinuric hypertension of pregnancy or chronic hypertension identified in the later half of pregnancy).

Pre-eclampsia is a pregnancy-specific hypertensive syndrome that causes substantial maternal and fetal morbidity and mortality.[2][3] The incidence is 2-8% in the US and with higher incidence in African – Americans. It may also be a pregnancy-induced autoimmune disease in which key features of the disease emanate from autoantibody-induced angiotensin receptor activation.[4] Gene-environment interaction and level of obstetric care may explain region-specific causes and risk factors,[5][6][7] and the relatively higher incidence and prevalence in Africa compared to the downwards trend worldwide.[8][9][10]

Key features of pre-eclampsia include hypertension, proteinuria, glomerular endotheliosis (a classical lesion of preeclampsia), placental abnormalities and small fetal size.[11] The haemolysis, elevated liver enzymes, low-platelet count (HELLP) syndrome is a variant of severe pre-eclampsia or a complication.[12] Visual symptoms such as the posterior encephalopathy syndrome (PRES) may be found in 25% of pre-eclampsia patients and 50% of eclampsia patients.[13][14]

**Causes and risk factors**

Causes include a) genetics and epigenetic imprinting, b) abnormal placentation, c) previous or existing maternal pathology such as hypertension, obesity, antiphospholipid antibody syndrome, d) dietary factors such as malnutrition and low dietary calcium,[15][16] and e) environmental factors such as air pollution which increases risk for type 2 diabetes mellitus,
pre-eclampsia and foetal growth restriction.\textsuperscript{17}\textsuperscript{18} Risk factors include nulliparity, egg-donation (ED) pregnancies, diabetes mellitus, kidney disease, chronic hypertension, prior history of preeclampsia, family history of preeclampsia, advanced maternal age and obesity. Others are antiphospholipid antibody syndrome, multiple gestation, subclinical hypothyroidism or harbouring thyroid antibodies and placental abnormalities such as placental ischaemia. Placental infections with Plasmodium falciparum in pregnancy increases the anti-angiogenic soluble endoglin (sENG) levels and this impact is more severe in primigravidae.\textsuperscript{19} Also, sENG is increased in multiple pregnancies and may be a cause of the low-birth weight babies.\textsuperscript{20}

Pre-eclampsia is a pro-thrombotic state with enhanced microparticle associated p-selectin and thrombin levels and reduced generation of anti-thrombin III and protein C.\textsuperscript{21}\textsuperscript{22}\textsuperscript{23}\textsuperscript{24}

**Immunopathophysiology**

Adequate maternal immunological response during pregnancy is essential to maintain the semi-allogeneic foetus and prevent pre-eclampsia.\textsuperscript{25} Thus, egg-donation pregnancies have a much higher rate of pre-eclampsia and miscarriage. Th\textsubscript{2} T-cell responses are anti-inflammatory with increased IL-10, IL-4; IL-5 and TGF-\beta. Th\textsubscript{1} expression T-cell responses are pro-inflammatory with increased IL-1, IL-6, IL-12, TNF-alpha and IFN-gamma. Th\textsubscript{2}/Th\textsubscript{1} balance is mandatory for normal pregnancy and normal pregnancy is pro-Th\textsubscript{2}.\textsuperscript{26}

Recent advances in placental immunology sheds light on the 6 stages of pre-eclampsia:\textsuperscript{27} 1) Insufficiency of gestation immune tolerance between the foetus and the mother increases likelihood of poor placentation and pre-eclampsia. This may be due to a short interval between coitus and conception which leads to deficient preconception tolerance of the mother to the semen of the prospective father of the child.

2) During implantation, the above deficient tolerance affects growth and fate of the embryo. Inadequate expression of maternal HLA-G lead to deficient stimulation of uterine natural killer (uNK) cells, supervisors of vasculature construction in early decidua basalis,\textsuperscript{28}\textsuperscript{29}\textsuperscript{30} which then display a poor expression of vascular endothelial growth factor(VEGF) and placenta growth factor(PIGF) and an overactive expression of anti-angiogenic factors, soluble endoglin (sENG) and soluble fms-like tyrosine kinase-I (sFlt-I).\textsuperscript{25}\textsuperscript{31}\textsuperscript{32} VEGF-A binds and activates sVEGFR-I or sFlt-I (anti-angiogenic) and sVEGFR-2 (angiogenic).\textsuperscript{33} Abnormal suppression of VEGF-A by sFLT-I causes pre-eclampsia.\textsuperscript{34}\textsuperscript{35}\textsuperscript{36} Soluble VEGFR-I is a
soluble receptor for PIGF and suppresses the activation of PIGF.\textsuperscript{[37][38]} PIGF can regulate proliferation in first trimester trophoblast, apoptosis in term trophoblast and it can directly or indirectly regulate vascular growth, maturation and permeability. Soluble endoglin, a co-receptor for transforming growth factor (TGF)-β\textsubscript{1} and β\textsubscript{3}, is particularly important in contributing to foetal growth restriction (IUGR).\textsuperscript{[11][39]} The effects of sENG are amplified by co-administration of sFLT-I or sVEGFR-I leading to severe pre-eclampsia, IUGR and the HELLP syndrome.\textsuperscript{[40][41][42]} 

3) Defective placentation and poor supply of intervillous space by oxygenated blood is evident by week 8-13. This causes reduced utero-placental perfusion (RUPP). Increased circulating phosphodiesterase activity has been observed in women with pre-eclampsia which responds to the phosphodiesterase inhibitor, sildenafil. Esomeprazole, pravastatin, metformin, sildenafil which dilate blood vessels have promise in reducing umbilical artery pulsatility index (PI), systolic/diastolic ratio (S/D ratio) and resistance index (RI) while increasing middle cerebral artery pulsatility index, systolic/diastolic ratio and resistance index.\textsuperscript{[43][44][45][46][47]} These drugs attenuate the sequelae of decreased utero-placental perfusion which are foetal growth restriction and pre-eclampsia.

4) Stage 4 occurs in second trimester of pregnancy. There is increased maternal endothelial cell activation by leukocyte membrane particles and syncytiotrophoblast membrane particles,\textsuperscript{[48]} and excess placenta-derived factors such as cell-free fetal DNA in mother’s blood secondary to placental damage. These lead to vasoconstriction due to upregulation of lipid peroxides, endothelin-I, COX-2, thromboxane A2 and decrease in prostacyclin.

5) Clinical diagnosis of pre-eclampsia is usually made around 20 weeks of gestation.

6) Superimposition of atherosis of decidual spiral arteries which further reduces uteroplacental perfusion.

The immune-inflammatory cascade

Pre-eclampsia with increased expression of Th\textsubscript{1} T-cells may be an alteration or exacerbation of the systemic inflammatory response associated with normal pregnancy.\textsuperscript{[26][49][50][51]} HLA-G\textsubscript{14} bp polymorphism and subsequent deficient activation of uterine natural killer cells activity may be a risk factor for pre-eclampsia.\textsuperscript{[26][29]} Alteration in immune system regulation, inadequate fetal allo-recognition, infection and inflammatory triggers cause activation of immune system cells in pre-eclampsia, for example leading to increased TLR-4 response. Th\textsubscript{1}
helper T-cell predominance, oxidative stress and insulin resistance also occur. There is then altered secretion of cytokine profile with increased IL-16, Th1 and Th17 T-cell with low Tregs. Also, the anti-inflammatory cytokines IL-10, IL-4 are decreased with upregulation of interferon-gamma, TNF-alpha, and TGF-β1,3 which inhibit MMP-9 and spiral artery remodelling. A role for visceral fat in simultaneously mounting an anti-inflammatory response with increased Th2 helper T-cells, increased TLR 3, CSF2 and insulin sensitivity has been hypothesized.

The above prevents the trophoblast from acquiring invasive properties leading to inadequate placentation and hypoxia. The hypoxia provokes the release of ROS, angiogenic and inflammatory cytokines, for example hypoxia-inducible factor-I while decreasing heme oxygenase-I (HO-I) and its metabolite carbon monoxide. Changes in sFLT-I and PIGF precede clinical development of pre-eclampsia only. While changes in sEGN and PIGF precede delivery of small-for-gestational age neonate. Finally, the cascade culminates in maternal endothelial damage. For example, CD 19 (+) CD 5 (+) B-cell population, a potential source of the angiotensin agonistic autoantibody (ATI AA), which is significantly elevated in maternal circulation of pre-eclamptic women. The titre of ATI AA significantly correlates with levels of sFLT-1.

Pre-eclampsia and small-for-gestational age (SGA) pregnancies have differential expression of complement split products with increase in C5a in pre-eclampsia; placental growth hormone (increased in pre-eclampsia and lower in pre-eclampsia and SGA); alpha-klotho (lower in mothers with SGA); and tyrosine kinase endothelial cell receptor, sTie-2 (decreased in pre-eclampsia and SGA than those of normal pregnancy).

Biochemical markers for prediction of pre-eclampsia

Increasingly, novel biochemical markers are coming to the fore in the early prediction and diagnosis of pre-eclampsia and intra-uterine growth restriction. Cell-free foetal DNA, p-selectin (before 20 weeks), pentraxin 3 (all trimesters), free foetal Hb F, the anti-plasmin alpha 2-microglobulin, cystatin –C and beta-2 microglobulin, maternal serum netrin-I are increased while pregnancy-associated plasma protein A (PAPP-A), placental protein-13 and disintegrin (all trimesters) and metalloproteinase-12 (ADAM-12) are low in pregnancies complicated by pre-eclampsia and intra-uterine growth restriction. Low PAPP-A (for still-birth), high uterine pulsatility index (for IUGR) and nuchal translucency (for major anomaly) have high negative predictive value.
Proteomics: value in predicting pre-eclampsia

Integrated and urinary proteomics yields novel biomarkers for predicting pre-eclampsia.[54][63] Increased urinary fibrinogen alpha chain, collagen alpha chain and uromodulin fragments predict pre-eclampsia after gestational week 28 with good confidence. Insulin-like growth factor acid labile subunit, soluble endoglin, placental growth factor, melanoma cell adhesion molecule, selenoprotein P, mid-region-pro atrial natriuretic peptide (proANP) and blood pressure are also novel biomarkers.

Diagnosis of pre-eclampsia

A) Blood pressure: Values greater than 140/90 mmHg at two successive occasions 6 hours apart is diagnostic. Values greater than 160/110 mmHg are diagnostic of severe pre-eclampsia. Mild hypertensives have diastolic blood pressure less than 100 mm/Hg. Treatment is recommended when diastolic blood pressure is above 105 to 110 mmHg. Korotkoff phase V is recommended for determination of diastolic blood pressure with manual sphygmomanometers (NHBEP). Patient should be in sitting position, legs uncrossed and back supported. In recumbent hospitalised patients, blood pressure should be determined in left lateral decubitus position to minimise pressure on vena cava by the gravid uterus.

B) In women with essential hypertension, blood pressure rise of more than 30 mmHg systolic and more than 15 mmHg diastolic is diagnostic.

C) There is also significant proteinuria in pre-eclampsia with values > 1 g/24 hours or ≥ 30 mg/dl or urine dipstick reading of I+ or greater.[3][29] Proteinuria is a poor predictor of major maternal and fetal complication in women with pre-eclampsia.[64] Protein values greater than 0.3 grams in 24 hours may be diagnostic. Threshold for spot urine protein: clearance ratio is 500 mg/mmol and 900 mg/mmol. Values less than 0.21 are safe.

D) Uterine/umbilical artery systolic diastolic ratio, pulsatility index: Ultrasound velocimetry detects impedance and reduced or absent end-diastolic flow. It has a predictive value for fetal distress and of time-to-delivery intervals in combination with the Manning’s score for biophysical profile.[65][66] It is combined with measurements of the middle cerebral artery systolic/diastolic ratio, resistance index and pulsatility index. High uterine artery pulsatility index > 0.58 may be considered abnormal. Low middle cerebral artery Doppler resistance indices can predict future development of pre-eclampsia.[47] Also, ultrasound can be used to determine the amniotic fluid index and Manning’s score.[67]
E) Increased xanthine oxidase activity in pre-eclampsia causes increased uric acid production.

F) sFlt-1/PIGF ratio and other appropriate biomarkers.

**Predictors of outcome in pre-eclampsia**

sFlt-1/PIGF ratio of $> 655$ demands delivery within 48 hours in order to prevent adverse outcomes.$^{[65]}$ While blood pressure and proteinuria has a predictive value of only 30% for pre-eclampsia-related adverse outcomes, estimation of the Flt-1/PIGF ratio is a predictor for pregnancy outcome and the risk of developing pre-eclampsia,$^{[68]}$ especially when combined with other biomarkers (see above). Correlation of biochemical factors (biomarkers) with Doppler ultrasound parameters has predictive value for pre-eclampsia, maternal complications in pre-eclampsia and prognostic value for perinatal complication.$^{[24][69]}$

**Differential diagnosis of pre-eclampsia**

**These include**

Chronic hypertension, chronic renal disease, primary seizure disorders, gall-bladder and pancreatic disease, immune thrombocytopenic purpura, antiphospholipid antibody syndrome, haemolytic-uraemic syndrome, hypothyroidism, renal artery stenosis with fibromuscular dysplasia, phaeochromocytoma and substance abuse. There is high serum uric acid and sFlt-1 in pre-eclampsia which is unknown in lupus erythematosus. The breath of symptoms that can be attributed to severe pre-eclampsia makes it clear that distinguishing it from active lupus, which affects 35-70% of women in their reproductive years, is difficult and sometimes impossible.$^{[70]}$

**Role of esomeprazole in management of pre-eclampsia**

A study protocol has shown that the proton pump inhibitor, esomeprazole, is safe in pregnancy and superior to pravastatin in treatment of early onset pre-eclampsia.$^{[71]}$ Other workers recently reported in pre-clinical studies using placental explants that proton pump inhibitors decrease sFLT-I and sENG secretion, decrease hypertension and rescue endothelial dysfunction.$^{[43][72]}$ Proton pump inhibitors were found safe in pregnancy and decrease sFLT-I and sENG release from trophoblast and placental explants from pre-eclampsia and endothelial cells. They decrease VCAM-I, endothelin-I and TNF-alpha-induced endothelial dysfunction. They upregulated anti-oxidant activity. Esomeprazole has been found to be the most potent proton pump inhibitor in decreasing sFlt-1 and sENG.$^{[71]}$ Use of esomeprazole
dilates blood vessels and upregulates HO-I which attenuates VEGF-I induced sFlt-I release.\[43\]

**CASE REPORT**

In December, 2016, a 27-year-old pregnant house-wife with diagnosis of pre-eclampsia on management with methyl-dopa bought esomeprazole in place of omeprazole for her dyspeptic symptoms in a pharmaceutical store. We found that the esomeprazole decreased her blood pressure significantly. The oedema also regressed but the 2+ level of proteinuria did not change. She agreed she had a greater sense of well-being since she took the medication and slept better.

In February, 2017, a 32-year-old multiparous (gravidae 4) house-wife presented in our clinic, Oseghale Oriaifo Medical Centre, Idumebo-Ekpoma, with diagnosis of moderate pre-eclampsia. She lost her term pregnancy 3 years previously due to severe pre-eclampsia. At presentation (30-week gestational age), she had proteinuria 2+, pedal oedema and blood pressure of 160/110. There were no visual symptoms or dyspepsia. Clinical diagnosis of severe pre-eclampsia was made. Doppler velocimetry in the Teaching Hospital revealed umbilical artery impedance with reduced end-diastolic flow (Ut-PI). There were no facilities for estimation of sFlt-I/PIGF ratio. Administration of esomeprazole (Nexium) 20 mg daily for 14 days as adjunct to her anti-hypertensives (Methyl-dopa 500 mg 6-hourly) increased the end-diastolic flow (Figure I) as revealed by ultrasonography at 32, 34 weeks with decrease in PI, systolic/diastolic ratio and resistance index. Also, the blood pressure was reduced to 130/90 mmHg after 10 days. The Manning’s score also improved with esomeprazole compared to the control without. The proteinuria turned to 1+ at 34 weeks and the oedema regressed. Serum uric acid decreased from 5.85 mg/dl to 3.96 mg/dl after 12 days while the blood creatinine was reduced from 1.84 mg/dl to 0.71 mg/dL. The mildly elevated liver enzymes were also down-regulated. A live baby with normal Apgar score was delivered after 35 + weeks by caesarean section because of the breech presentation.
Effect of esomeprazole (ESMP) and its combination with methyl-dopa (MD) on selected ultrasonographic and biochemical indices in pre-eclampsia.

<table>
<thead>
<tr>
<th>GESTATION AGE</th>
<th>30 WEEKS</th>
<th>32 WEEKS</th>
<th>34 WEEKS</th>
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<tbody>
<tr>
<td>Drug</td>
<td>MD</td>
<td>MD + ESMP</td>
<td>MD</td>
</tr>
<tr>
<td>Umbilical Artery PI</td>
<td>1.119 ± 0.11</td>
<td>1.118 ± 0.10</td>
<td>1.112 ± 0.16</td>
</tr>
<tr>
<td>Umbilical Artery S/D ratio</td>
<td>3.212 ± 0.47</td>
<td>3.210 ± 0.49</td>
<td>3.214 ± 0.44</td>
</tr>
<tr>
<td>Umbilical Artery resistance index</td>
<td>0.766 ± 0.127</td>
<td>0.760 ± 0.125</td>
<td>0.768 ± 0.12</td>
</tr>
<tr>
<td>Amniotic Fluid Index</td>
<td>16</td>
<td>16</td>
<td>12</td>
</tr>
<tr>
<td>Uric Acid mg/dl</td>
<td>5.89 ± 0.15</td>
<td>5.85 ± 0.14</td>
<td>6.12 ± 0.17</td>
</tr>
<tr>
<td>Creatinine mg/dl</td>
<td>1.86 ± 0.10</td>
<td>1.84 ± 0.09</td>
<td>1.86 ± 0.14</td>
</tr>
<tr>
<td>Mean arterial pressure</td>
<td>163.32 ± 4.20</td>
<td>163.35 ± 4.76</td>
<td>140.22 ± 5.44</td>
</tr>
<tr>
<td>Biophysical Profile (manning’s score)</td>
<td>6</td>
<td>6</td>
<td>6</td>
</tr>
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</table>
**Figure 1:** Methyl-dopa use was significantly associated with increased resistance index (RI), pulsatility index (P1) and systolic / diastolic ratio of umbilical artery while its combination with esomeprazole significantly decreased these parameters ($P < 0.05$). Methyl-dopa significantly increased maternal serum uric acid levels ($P < 0.05$) at 34 weeks gestation. Both agents were significantly associated with decreased mean arterial blood pressure (MAP).

**DISCUSSION**

Report indicates that the proton pump inhibitor had a favourable effect in decreasing some of the major indices of pre-eclampsia such as the high umbilical resistance index, blood uric acid and creatinine levels. Esomeprazole is an S-isomer of omeprazole which is reported safe in pregnancy with no teratogenic effect and exhibiting better safety profile than lansoprazole and pantoprazole.\(^{[73]}\)\(^{[74]}\) It inhibits competitively liver microsomal isoenzymes,\(^{[75]}\) and may increase the effects of diazepam and other drugs metabolised by the P 450 (CYP) system. Present consensus is that it has no effect on the action of clopidogrel.\(^{[76]}\) Its half-life is approximately 1 - 1.5 hours. Less than 1% parent drug is excreted in urine. Approximately 80% of an oral dose is excreted in urine as inactive metabolites. It is metabolised in the liver by P450 (CYP) system, predominantly by the CYP2C19 isoenzyme. It may cause enterochromaffin-like cell hyperplasia in humans but not carcinoid tumours as in rodents. (https://dailymed.nlm.nih.gov) Dose of esomeprazole used in this study is less than the 40 mg daily used in reported studies.\(^{[71]}\)

Although intravenous labetalol (a selective $\alpha$-blocker and non-selective $\beta$-blocker) may have a quicker onset of action than methyl-dopa ($\alpha_2$- adrenoceptor agonist),\(^{[77]}\) it may more be associated with spontaneous onset of labour and doubts exist about its effect on fetal tolerance to hypoxic stress. Selective $\beta$-blockers such as atenolol may be associated with increased risk of IUGR in first trimester (www.ncbi.nlm.nih.gov/pmc 1768605). Methyl-dopa has a limited effect on utero-placental blood flow,\(^{[1]}\) and may be the preferred drug (AAFP, 2001). Methyl-dopa did not decrease the umbilical artery resistance index, rising uric acid levels and proteinuria in this study, confirming previous reports that anti-hypertensives including labetalol do not affect the course of events in pre-eclampsia though they may normalise maternal blood pressure and pulse.\(^{[78]}\)\(^{[79]}\)\(^{[80]}\) The anti-excitotoxic, magnesium sulphate decrease umbilical artery resistance in pre-eclampsia and may attenuate its progression to eclampsia.\(^{[81]}\) The WHO recommendation does not support the use of
diuretics, especially the thiazides, in pre-eclampsia as they can cause further vascular volume contraction.[3][15]

Investigators have reported that targeting sFlt-I-induced pathways may be an avenue for the treatment of pre-eclampsia.[82] and recent reports indicate the safety and efficacy of esomeprazole in decreasing sFLT-I/PIGF ratio. The mitochondrial complex I inhibitor, metformina and the cholesterol-lowering agent, pravastatin, down-regulate sFLT-I/PIGF ratio,[83][84] but may not be recommended until more trials due to the uncertain effects of mTOR inhibitors on pregnancy outcomes, especially in first trimester.[85][86][87] This may be more important in Africa where lack of nutrients stir up pathogenesis of placental malaria which negatively impacts fetal growth by further downregulating mTOR signalling pathways which link growth factors, insulin, IGF-I and VEGF in nutrient supply to fetus.[88] Similar to metformin, esomeprazole activates AMPK and inhibits mTOR necessary for optimal autophagy induction via hypoxia-inducible factor-1α, a survival mechanism necessary to maintain pregnancy.[89] Additionally, esomeprazole most significantly suppresses sFlt-I and sENG release more than other PPIs, metformin or pravastatin. Decrease in autophagy induction and increased sENG by extra-villous trophoblasts in a hypoxic placental microenvironment contribute to low-birth weight babies in pre-eclampsia, placental malaria and multiple pregnancies.[19][90][91][92] Esomeprazole thus stand to most efficaciously upregulate VEGF-induced vasorelaxation and nutrient supply to foetus.[71][93][94] Sildenafil has beneficial effects in prolongation of pregnancy in pre-eclampsia both in animal and clinical studies but its cardiodepressant and arrhythmogenic effects may be made worse by nitrates and drugs that release endothelial nitric oxide such as calcium channel blockers, β-blockers and diuretics.[95][96] We report here that esomeprazole decreases fetal and maternal risk due to pre-eclampsia and thereby prevents progression to eclampsia. Anti-hypertensives alone prevent maternal morbidity but have no effect on disease progression or preventing eclampsia.[11]

Pre-eclampsia may induce IUGR (birth weight below the 10th percentile), which may give rise to reduction in nephron number. This oligonephropathy increases risk for systemic and glomerular hypertension in adult life.[97][98] Additionally, the hypoxic and pro-inflammatory environment of the maternofetal unit results in epigenetic programming which impinges on the child’s cardiometabolic and neuropsychiatric health.[99][100] Fetal and developmental origins of adult disease may explain the concept by Dr. D. J. Barker that “the womb may be
more important than the home”. Prenatal programming most commonly occurs through epigenetic mechanisms and is implicated in understanding the relationship between cardiometabolic and neuropsychiatric illnesses.\textsuperscript{[101][102][103]} The anti-platelet drug aspirin is recommended for pre-eclampsia prevention.\textsuperscript{[15][97]} It reduces endothelial senescence.\textsuperscript{[104]} Esomeprazole, although sold over-the –counter, is not now recommended for prolonged periods as it may increase endothelial senescence.\textsuperscript{[105]} It may be combined with aspirin for improved efficacy.\textsuperscript{[106]} Esomeprazole has been observed to be anti-inflammatory, anti-oxidant and anti-apoptotic via directly down-regulating ROS, upregulating the anti-oxidants nuclear factor 2-related factor-2 (Nrf\textsubscript{2}) and heme oxygenase-I (HO-I).\textsuperscript{[107]}

In conclusion, case report points esomeprazole out as a drug that may contribute to a favourable forecast in the pre-eclampsia syndrome and safely attenuate the major ultrasonic and biochemical indices of pre-eclampsia. Appropriate national and international trials would delineate its place not only in the treatment but also in the prevention of pre-eclampsia and intra-uterine growth restriction (IUGR).

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