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Identification of Potential Prophylactics against Pre-Eclampsia through Magnesium and Zinc Supplementation

Charles Malcolm Rees

Senior House Officer, St James University Hospital

Literature Review

Pre-eclampsia is a life-threatening multisystem disorder, affecting approximately 2-3% of all pregnancies and remains a leading cause of perinatal and maternal death.[1] Pre-eclampsia is characterised by gestational or pregnancy-induced hypertension in previously normotensive individuals and accompanied with new-onset proteinuria, typically from 20 weeks gestation.[2,3]It is described as the 'disease of theories' which reflects the considerable amount of uncertainty surrounding its aetiology and pathophysiology. However an abnormal maternal inflammatory response is considered to ensue following placentation.[4]

The placenta becomes hypoxic when the maternal spiral arteries that supply blood to the foetus become maladapted.[5]This is due to the abnormal invasion of the placentas trophoblastic cells, which would normally aid in embryo implantation.[6] This causes villous growth restriction, breakdown of syncytial integrity via necrosis,[7,8] and endothelial dysfunction via the release of inflammatory cytokines.[9] Raised systemic vascular resistances occur as does an increased aggregation of platelets via activation of the coagulation cascade.[4] This leads to reduced organ perfusion. The CNS, heart, lungs, kidneys and liver are most susceptible to under-perfusion if systemic inflammation becomes excessive.[10]

If perfusion to multiple organs becomes compromised, serious maternal complications can arise, including HELLP (haemolysis, elevated liver enzymes and low platelets) syndrome and eclampsia.[11] Each is associated with higher rates of maternal mortality and may be difficult to detect due to the prodromal signs of pre-eclampsia.[12] There is currently no effective treatment to prevent or prolong the disease, with the exception of premature elective delivery.[13]As a result, pre-eclampsia is concomitant with roughly 15% of premature births with a consequential rise in infant morbidity and mortality.[14]

Magnesium is a versatile cofactor that plays a pivotal role in blood pressure regulation through its involvement with monitoring vagal tone, reactivity and contractility by activating multiple enzyme pathways.[15,16] Zinc is crucial for normal genetic expression through its involvement with normal protein synthesis and nucleic acid metabolism.[17] Deficiencies in either have been implicated with an increased risk of pre-eclampsia.[18] Studies have shown promising results when supplementing Magnesium and Zinc during pregnancy. Magnesium supplementation has reduced the rates of intrauterine growth retardation and preterm birth.[19] Likewise Zinc supplementation may improve the foetal immune system and reduce the frequency of pregnancy-induced hypertension.[20]

A recent study has shown a possible link between pre-eclampsia and serum levels of Magnesium and Zinc. Higher levels of these micronutrients were observed in normal pregnancies whereas much lower levels were apparent in patients with pre-eclampsia. A gradual decrease in both elements was also observed throughout gestation in both normal and pre-eclamptic pregnancies.[21]This may be a result of increased foetal uptake and/or hemodilution. As such, Magnesium and Zinc levels need to be continuously monitored and replenished as pregnancy progresses. This reinforces the ideology that pre-eclampsia is implicated from micronutrient deficiency[22] as shown by its increasing prevalence in developing countries.[23]Therefore it would be rationalistic to consider that supplementation with these elements may be a possible solution in reducing risk of pre-eclampsia.

Magnesium and Zinc supplementation has been tested in former studies; however they were predominantly administered to patients where pre-eclampsia was already established rather than before its onset as a prophylaxis. These studies also tested both micronutrients separately rather than a combination of the two. An initial small study has since shown promising results between reduced risk of pre-eclampsia and combined supplementation with Magnesium and Zinc.[25] However larger clinical trials are necessary to corroborate these findings. If this study proves successful, Magnesium and Zinc supplements can be prescribed during pregnancy to reduce the occurrence of pre-eclampsia and its complications.

Research Question

Is there a difference between the rate of women developing pre-eclampsia amongst those treated with Magnesium and Zinc supplements and those that are not?

Proposed Investigation

The purpose of this study is to investigate the effects combined Magnesium and Zinc supplementation has with risk of developing pre-eclampsia. It will involve a double blind randomised placebo-controlled trial, with 1204[A]women assigned in equal ratios to either an intervention (n=602) or placebo group (n=602).

The intervention group will be given 350mg of Magnesium and 20mg of Zinc, whereas the other group will be given a placebo matched in appearance and taste. Doses are calculated from the dietary reference rates recommended by the office of dietary supplements, national institutes of health, and the institute of medicine of the national academy of sciences.

Participants will take their tablets once a day orally, from 8-14 weeks gestation until delivery. The participant's blood pressure and proteinuria levels will be taken initially one week after their trial start date, and every two weeks after that until delivery. To increase adherence, participants will be given a weeks' worth of supplements after their first follow up visit, and two weeks' worth of supplements in 7-day pill dispensers after each subsequent follow up visit. Participants will be advised to leave any unused pills in their dispensers so they can be accounted for. If adherence falls below 80%, these participants will be excluded from the trial to prevent inaccuracies in the results. Supplementation will also be terminated if pre-eclampsia, severe hypertension or perinatal mortality occurs.

Prior to supplementation, participants must undergo an anthropometric nutritional assessment to eliminate nutritional confounding factors by showing participants are of normal health and are not currently nutrient deficient. Assessment will include measurement of mid arm circumference, triceps skinfold, weight and haemoglobin.

Eligibility Criteria

- Eligible participants will be women aged 18-34 years and gestational age between 8-14 weeks.
- Women will also have one or more of the known clinical risk factors:
  -Any previous pregnancy, requiring delivery before 37 weeks gestation.
  -Diagnosis of HELLP syndrome or eclampsia in any previous pregnancy at any gestational stage.

Exclusion Criteria

- Already taking Magnesium and Zinc supplementation.
- Suffers from malabsorption syndrome, malabsorptive disorders, or chronic illness which would intensify loss of endogenous Zinc/Magnesium and decrease their absorption.
- Have a pre-existing hypertensive disorder and is receiving antihypertensive therapy.
- Participants unwilling to provide written consent.

Outcomes

The studies primary outcomes are pre-eclampsia, severe hypertension and perinatal mortality.

- Pre-eclampsia is defined as gestational or pregnancy-induced hypertension (Systolic≥140mmHg or diastolic≥90mmHg) in previously normotensive individuals and accompanied with new-onset proteinuria (≥300mg within 24 hours), typically from 20 weeks gestation.
- Severe hypertension is defined as a single diastolic blood pressure measurement of ≥120mmHg or two successive measurements of ≥110mmHg with a minimum of 4 hours in between readings. These definitions are taken from the International Society for the Study of Hypertension in Pregnancy (ISSHP).[2]
- Proteinuria could also be recorded by two measurements of ≥2+ specific gravity via dipstick analysis for Midstream samples of urine (MSSU) or catheter specimens of urine (CSU).

Recruitment

Study-specific research midwives will be recruited to high risk antenatal clinics to discover potentially eligible participants. They will also distribute trial information to primary care trusts, GP surgeries and ultrasound departments, requesting their cooperation in referring eligible women. Researchers will then disclose all the trial information to the interested participants and request their involvement. To avoid allocation bias the participants will not be made aware of which group they will be assigned to.

Ethical Issues

Giving Information

Competent participants will be provided with all the necessary information in order for them to make an autonomous decision as to whether they consent to partake in the trial. They will also be informed that they can leave the trial at any point, and their normal medical care will not be compromised.

Beneficence and Non-maleficence

Although evidence suggests that Magnesium and Zinc supplementation may be beneficial in preventing pre-eclampsia, participants need to know the possible side-effects hypermagnesemia and hyperzincaemia may provoke. These include lethargy, headaches, nausea and reduced deep

tendon reflexes. If any such complications arise the participants can be withdrawn from the trial.

Ethical Approval

Ethical approval from the North West Centre of Research ethics Committee must be granted before the trial commences.

Appendix 1- Sample Size Calculation

The primary outcome of this study will be the development of pre-eclampsia. Pre-eclampsia is defined as gestational or pregnancy-induced hypertension (Systolic≥140mmHg or diastolic≥90mmHg) in previously normotensive individuals and accompanied with new-onset proteinuria (≥300mg within 24 hours), typically from 20 weeks gestation.[1] The participant's blood pressures will be taken one week after the trial start date and every subsequent fortnight after that until delivery date. Blood pressure will be measured as a dichotomous variable in units of mmHg using a standard sphygmomanometer.

Pre-eclampsia is the most important outcome in this study as it affects numerous pregnancies and is the leading cause of preterm births, perinatal morbidity and maternal death.[2,3] In 5% of cases this condition can progress to conditions of higher severity including eclampsia and HELLP syndrome.[11] If this study shows promising results, it will prompt need for further research and clinical trials regarding multiple mineral supplementations. This is important to patients as it could lead to significant reductions in pre-eclampsia and its complications.

From previous research I am expecting a modest decrease in incidence of pre-eclampsia. If pre-eclampsia affects 2-3 women in every hundred pregnancies I am expecting only one women to develop pre-eclampsia out of 100 women.[24,25]

Probability of event in control group = 0.08
Probability of event in experimental group = 0.04
Controls per case subject = 1
Alpha = 0.05
Power = 0.8

This gave a sample size of 1106 participants (553 in both placebo and intervention group). Taking non-adherence and withdrawals from the study into consideration, the number of participants will be increased by 10% and rounded to the nearest even number. This gives a total sample size of 1204 participants with 602 cases in each group.

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