Prophylactic treatment for preeclampsia in high-risk teenage primigravidae with nitric oxide donors: a pilot study

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Abstract

Objectives: Preeclampsia is associated with significant morbidity and mortality especially in high-risk groups. Impairment of endogenous nitric oxide has been shown to be associated with the disease and prophylactic therapy may ameliorate this condition and improve pregnancy outcome. This study evaluated nitric oxide donors prophylactic treatment for preeclampsia in high-risk teenage primigravidae.

Methods: The study included three hundred primigravidae aged $\leq 20$ years with singleton pregnancy. Abdominal pulsed color Doppler ultrasound was done at 24 weeks gestation and pregnancies with uterine artery diastolic notch were randomly allocated to a control group received placebo vaginal tablets and a study group received isosorbid mononitrate 20mg tablet once daily applied vaginally until delivery.

Outcomes: Incidence of preeclampsia and maternal, fetal, and neonatal outcome in both groups.

Results: The study group had significant lower incidence of preeclampsia, preterm birth, intrauterine growth restriction and of neonatal admission to the intensive care $(p < 0.05)$.

Conclusions: Nitric oxide donors prophylactic treatment for preeclampsia in high-risk teenage pregnancies decrease the incidence of preeclampsia and improve maternal, fetal, and neonatal outcomes. Further studies on larger sample size are required to confirm these results.

Keywords: Nitric oxide donors, preeclampsia, prophylaxis

Introduction

Preeclampsia (PE) affects approximately 5–7% of pregnancies and is associated with significant morbidity and mortality [1]. Antenatal care with the aim of identifying pregnancies at risk for development of PE and administration of prophylactic therapy could significantly ameliorate this condition and improve pregnancy outcome. A large number of clinical and biochemical tests have been employed to predict pregnancies at risk. In 1987, Campbell [2] used Doppler to assess utero-placental circulation and found that the impedance of flow in the uterine arteries decreases with gestation in normal pregnancies, while in PE there was a high resistance to blood flow. Studies have focused on uterine artery Doppler waveforms at 20–24 weeks gestation for screening and prediction of PE in high-risk pregnancies [3,4]. Pregnancies with abnormal uterine artery Doppler waveform have a six-folds likelihood of developing PE than in pregnancies with normal Doppler [5]. Attempts to prevent PE by the prophylactic use of calcium [6,7], vitamins and antioxidants [8], and other drugs were unsuccessful or had a small effect as in the case of anti-platelets largely low-dose aspirin [9,10]. Endothelial nitric oxide (eNO) synthesized from the essential amino acid L-arginine causes vasodilatation of the uterine arteries and increases the utero-placental circulation. Impairment of the L-arginine-NO pathway has been associated with PE, which may be prevented by nitric oxide donors [11–13] prophylaxis. Isosorbid mononitrate (IMN) is such a drug that release NO in vivo and is used in different obstetric indications but its role in the prophylaxis of PE is not yet settled.

Subjects and methods

This pilot clinical study was done at the antenatal care clinic of Banha University hospital after acceptance of the local ethical committee and consent from all participants. The study was registered at the Australian New Zealand Clinical Trials Registry (ACTRN 12613001354774). Primigravidae aged $\leq 20$ years with normal singleton pregnancy till 24 weeks gestation were examined by abdominal pulsed color Doppler ultrasound (Voluson, 730 Pro V, GE Medical System, Buckingham, UK). The uterine artery was identified where it crosses the external iliac artery and three successive uterine artery waveforms were displayed. Pregnancies with a diastolic notch in one or both uterine arteries were considered at higher risk for PE.

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treated with vasodilators or sensitive to NO donors were excluded. Three hundred primigravidae were eligible for the study, of whom 40 cases had diastolic notch and were randomly allocated into a control group received placebo vaginal tablets and a study group received 20 mg isosorbid mononitrate (IMN) vaginally once daily until delivery (Effox, Mina Pharma Co, Egypt; under license of Schwartz Pharma, Monheim am Rhein, Germany). Clinical and ultrasound examinations were done every 2 weeks and weekly during the ninth month. Preeclampsia was defined according to the International Society for the Study of Hypertension in Pregnancy [14] which requires two recordings of diastolic blood pressure of 90 mmHg or higher at least 4 h apart or one recording of diastolic blood pressure of at least 120 mm Hg in a previously normotensive woman, and urine protein excretion of at least 300 mg in 24 h or two readings of 2+ or higher on dipstick analysis of midstream or catheter urine specimens. Preterm birth (PTB) was defined as birth before 37 weeks and intrauterine growth restriction (IUGR) was defined as birth weight <10th percentile of normal weight for gestational age. If PE developed, IMN was discontinued.

**Statistical design**

Data were analyzed using the SPSS version 16 (SPSS Inc., Chicago, IL). The mean ± SD and the Fisher Exact test were used for analysis. Result was considered significant at p values <0.05.

**Results**

Figure 1 shows the flow chart of the study. Table 1 shows no significant differences between the demographic characteristics of the study and control groups at 24 weeks gestation. Table 2 shows that the IMN study group had significant higher incidence of full term birth and significant lower incidence of preterm birth, preeclampsia, intrauterine growth restriction, and of neonatal admission to the intensive care unit.

**Discussion**

Persistence of diastolic notch in the uterine artery till 24 weeks gestation is a predictor of preeclampsia and other complications of utero-placental insufficiency [14,15]. Teenage primigravidae are at high risk for preeclampsia and Doppler examination of 300 cases revealed 40 cases (13.3%) with diastolic notch that were at a higher risk for preeclampsia. In a previous study [16], high uterine artery pulsation index (>1.6) was used for screening in low risk population and reported a high index in 4.2%. In the present study, 20 mg IMN applied vaginally decreased significantly the incidence of PE compared with the control group (10% versus 45%, p <0.05). Endothelial nitric oxide (eNO) causes vasodilatation of the uterine and peripheral arteries leading to increase of the utero-placental circulation [17] and lowering of the systemic blood pressure [18]. In addition, it has anti-thrombotic and anti-inflammatory effects by inhibiting platelets aggregation and adhesions of neutrophils to the vessel.
wall [19] and causes relaxation of the myometrium [20]. Previous data showed that alteration in the L-arginine-NO pathway has been associated with PE and that diminished NO synthesis contributes to its pathophysiologic changes [21]. In a Cochrane review [22], there was insufficient evidence to draw reliable conclusions about whether NO donors and precursors prevent PE or its complications, but more recent studies [23–25] found a beneficial role. In the present study, IMN decreased not only the incidence of PE but also of PTB, IUGR, and neonatal admission to ICU. In a previous study [26], administration of the NO donor glyceryl trinitrate was followed by reduction of the resistance to blood flow in the feto-placental circulation of pregnant with mild PE. Other investigators [27] reported that trans-dermal administration of isosorbide dinitrate improved feto-placenta circulation and avoided maternal hypertension and oligohydramnios. In another study [28], L-arginine was found to improve the utro-placental circulation in women with bilateral notching and high uterine artery resistance index and nitroglycerin was used for treatment of preterm labor [29] and for treatment of acute intra-partum fetal distress [30].

**Conclusion**

Teenage pregnancy is common in Egypt especially in ruler areas and is associated with a higher incidence of pre-eclampsia. In the present pilot study, screening of this high-risk group and prophylactic treatment for pregnancies with uterine artery diastolic at 24 weeks gestation with vaginal NO donors decreased the incidence of the disease and improved maternal, fetal, and neonatal outcomes. Other definitive studies on larger sample size are required. For designing such a study, the calculated sample that confirm clinically relevant outcome with a power of 90% and a significance level of 5% would expect 13% incidence of diastolic notch in teenage pregnancies and a reduction of preeclampsia from 45% in the placebo group to 10% in the IMN group.

**Power of the study:** This pilot study is the first to use NO donors vaginally for prevention of preeclampsia. The NO molecule has a very short half-life of only few seconds; so, the vaginal route may has a more direct and rapid action on the utero-placental circulation besides being acceptable and tolerable by all women. Mild headache was reported in few cases that needs no special intervention or discontinuation of treatment.

**Disclosure of interest**

The authors declare no conflict of interest.

**References**