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USE OF PRAVASTATIN FOR PREVENTION AND TREATMENT OF PREECLAMPSIA IN HIGH RISK PREGNANCIES IN PAKISTANI WOMEN: RANDOMIZED CONTROLLED TRIAL STUDY

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Abstract:

Objective*: To compare the effects of pravastatin and control group for prevention of Preeclampsia in high risk pregnancies in Pakistani women.*

Design: *double-blind randomization, placebo-controlled trial*

Patient(s): *The study comprised a total of 400 singleton pregnant women with high risk of preeclampsia*

Intervention(s): *Pravastatin was given once daily for 4 weeks starting from the 13th week to the 16th week of gestation.*

Main Outcome Measure(s): *incidence of preeclampsia*

Result(s): *16 cases developed preeclampsia in the control group (11 cases were severe and the remaining 5 were mild) with a percentage of 8% instead of 6 cases in the study group (4 cases were severe and 2 were mild) with a percentage of 3%.*

Conclusion: *Pravastatin can be used as an effective agent in the prevention and treatment of preeclampsia in pregnant women.*

Key words: *pravastatin, placebo, pregnancy, preterm preeclampsia.*

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INTRODUCTION:

Preeclampsia is a multisystem disorder that complicates 3%–5% of pregnancies and remains a major cause of maternal, fetal, and neonatal morbidity and mortality [1]. It is characterized by angiogenic imbalance, exaggerated inflammation, and endothelial dysfunction, which ultimately lead to the clinical manifestations of hypertension, proteinuria, and end organ damage [1,2]. Preeclampsia is associated with serious short- and long-term maternal and neonatal morbidities [1,3], and its recurrence in subsequent pregnancies depends on the presence of risk factors (e.g., diabetes, hypertension, and multifetal gestation) and the severity and time of onset of preeclampsia in a prior pregnancy [4,5]. Despite being unique to pregnancy, preeclampsia shares pathogenic similarities and many risk factors with adult cardiovascular disease [4]. Endothelial dysfunction and inflammation are fundamental for the initiation and progression of both atherosclerosis and preeclampsia [2,6,7,8].

Numerous attempts at primary and secondary prevention of preeclampsia, using various supplements and medications, have had limited success. [4] Only low-dose aspirin was found to have a modest benefit in reducing the rate of preeclampsia in an individual patient meta-analysis, [9] and that benefit was only achieved if the drug was started before 16 weeks gestational age. On the contrary, inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme-A (HMG-CoA) reductase (statins) are effective in primary and secondary prevention of cardiovascular mortality and morbidity [10,11] fig 1. Moreover, statins have been in animal models of preeclampsia to revert the angiogenic imbalance, a hallmark of preeclampsia, and restore endothelial dysfunction. This biological plausibility and data from preclinical animal studies support a role for statins in preeclampsia prevention [12-15]. Use of antihypertensive medications in women with chronic hypertension, who are at higher risk of preeclampsia, was found to better control severe hypertension, without decreasing the risk of preeclampsia. [16] Supplementation with fish oil, calcium, or antioxidant vitamins C and E did not show any benefit in reducing the rate of recurrence or severity of preeclampsia. [17,18] Low-dose aspirin, by selectively inhibiting the production of the vasocontractile thromboxane A2 without affecting the vasorelaxant prostacyclin, was thought to protect the vasculature and prevent preeclampsia. However, the benefits of low-dose aspirin in preeclampsia prevention were not supported by multiple large randomized studies that included both high-risk and low-risk women. Recently, the Perinatal Antiplatelet Review of International Studies Collaborative Group performed an individual patient meta-analysis of the effectiveness of antiplatelet agents (predominantly aspirin) for the prevention of preeclampsia. [19] They included 31 randomized trials involving 32,217 women, and found a small benefit in reducing the rate of preeclampsia [RR of developing preeclampsia 0.90 (95% CI 0.84-0.96)]. When the effect of aspirin was evaluated according to when it was started, a meta-analysis found that the benefit from low-dose aspirin was achieved only when it was started before 16 weeks gestational age, with no benefit if aspirin was started after that. [20] Overall, the trials regarding preeclampsia prevention have been negative, contradictory, or not convincing enough to lead to widespread adoption of any particular strategy.

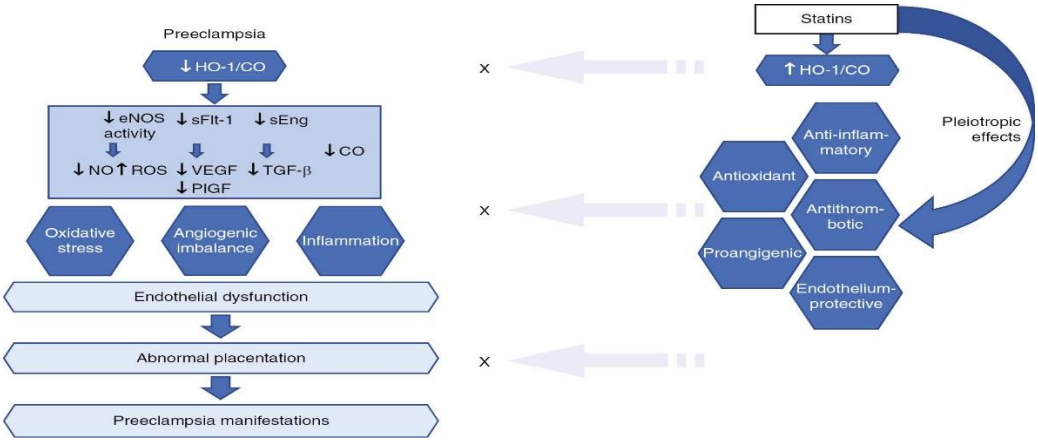

Figure 1: Schematic diagram of preeclampsia pathomechanism model and pleiotropic effects of statins which contribute to their therapeutic effect on preeclampsia.
HO-1/CO=Heme oxygenase-1/carbon monoxide, eNOS=nitric oxide synthase, ROS=reactive oxygen species, sFlt=soluble fms-like tyrosine kinase-1, sEng=soluble endoglin, VEGF=vascular endothelial growth factor, PlGF=placental growth factor, TGF-β=transforming growth factor-β.

METHOD:

We conducted a multicenter, double-blind, placebo-controlled randomized trial involving 400 pregnant women at high risk for preeclampsia. 400 pregnant females attending the antenatal care clinics between August 2015 to June 2019 according to the following inclusion and exclusion criteria.

Inclusion criteria: these include the following: female age: ranges from 20 to 35 years, singleton, viable pregnancy morphologically normal by ultrasound, gestational duration: from 13th weeks to 16 weeks of gestation.

Exclusion criteria: the following cases were excluded: Pregnancy duration less than 13 weeks, or more than 16 weeks, Cases with major fetal anomalies, Women with chronic hypertension evidenced by : Blood pressure ≥ 140/90 mmHg on two different occasions at least 4 hours apart. Those taking anti-hypertensive drugs, Women with history of recurrent early pregnancy loss. , Women with proteinuria discovered by urine dipstick test done at first visit. Women with contraindication to pravastatin (e.g. hypersensitivity to the active substance or to any of the excipients or active liver disease including unexplained persistent elevations of serum transaminase elevation exceeding 3 x the upper limit of normal) Women with known medical conditions: - Diabetes mellitus - Sickle cell disease - Thrombophilias - Connective tissue diseases - Anti-phospholipid antibody syndrome

Procedure:

All the patients were submitted to the following steps
1-Informed consent was taken from each patient
2-Full history
3-Blood pressure measurement
4-Albumin in urine test
5-Height and weight measurement for estimation of BMI (Body mass index)
6-General examination
7-Abdominal examination
8-Obstetric ultrasound for checking the number of fetuses, viability, gestational age, placental location and congenital fetal malformations

The present study includes 400 cases have been randomly divided into two groups (randomization has been done by sealed envelope): I. Group A (The study group): (200 case) In this group Pravaststin was given once daily for 4 weeks starting from the 13th week to the 16th week of gestation. II. Group B (The control group): (200 cases) In this group placebo was given once daily for 4 weeks starting from the 13th week to the 16th week of gestation Collected data: Patients were asked to complete a questionnaire on maternal age, cigarette smoking during pregnancy (yes or no), method of conception (spontaneous or assisted), medical history (including chronic hypertension, diabetes mellitus, anti-phospholipid syndrome, thrombophilia, and sickle cell disease), medication (including antihypertensive, antidepressant, antiepileptic, aspirin, steroids, betamimetics, insulin and thyroxin), parity (parous or nulliparous if no delivery beyond 24 weeks), obstetric history (including previous pregnancy with preeclampsia), and family history of preeclampsia (mother). The questionnaire was reviewed by a doctor together with the patient. The maternal weight and height were measured, and the BMI was calculated in kilograms per meter squared. The baseline blood pressure was measured and documented and an initial urine dipstick test was done to exclude proteinuria. Follow up: All cases were followed regularly once monthly for the first six months of pregnancy, twice monthly during the seventh and eighth month and then once weekly till delivery. In follow up visits, the blood pressure was taken by mercurial sphygmomanometers which were calibrated before and at regular intervals during the study. Recordings were taken with the women in the seating position, and 24-h collection of urine was analysed for proteinuria or dipstick analysis of midstream urine specimens was done if 24-h collection of urine was not available.

Outcome measures:

The primary outcome:

Incidence of preeclampsia

T **secondary outcome**

1-Getational age at time of delivery
2-Type of delivery
3-Fetal birth weight
4-Fetal birth defects
5-NICU admission and Neonatal mortality

Statistical Analysis:

Results have been statistically described in terms of mean ±standard deviation (mean ±SD), number of cases and relative frequencies (percentages). Comparison of quantitative variables between the study groups was done using Student t-test for independent samples. Statistical significance was evaluated using the Chi-square test for differences in qualitative variables. A probability value (p value) less than 0.05 was considered statistically significant, P-value 0.05 was considered insignificant.

RESULTS:

At study entry, there were no differences in baseline characteristics such as gestational age at delivery in prior qualifying pregnancy and the percent of subjects receiving low dose aspirin. Although statistically non-significant, more subjects in the pravastatin group were obese. The rates and types of side effects and AEs, irrespective of relation to study medication, were not different between the 2 groups (Table 2). The most common side effects reported by subjects who received pravastatin were musculoskeletal pain and heartburn. There were no reports of myopathy/rhabdomyolysis or liver injury. None of the participants discontinued their study medication. In addition, there were no maternal, fetal, or infant deaths in either group. One fetus in the pravastatin group had hypospadias and another had coarctation of the aorta (diagnosed postnatal), whereas in the placebo group one fetus had polydactyly and another had ventriculomegaly. One subject in the placebo group underwent postpartum hysterectomy secondary to hemorrhage from placenta previa and uterine atony.

In our study, in the group supplemented with pravastatin, 6 of them developed preeclampsia; 4 of them showed severe disease. On the other hand 16 women in the placebo group developed preeclampsia; 11 of them showed severe disease compared to the pravastatin group, suggesting a beneficial effect of pravastatin in preventing the onset of preeclampsia.

Table 1. Baseline characteristics of subjects who participated in the study. Data are reported as median [interquartile range], or n (%)

Characteristic	Placebo Group [#] (N= 200)	Pravastatin Group[#] (N= 200)
Age—years	30 [27 ,34]	27 [21 , 34]
Body mass index—Kg/m^2	29.6 [27 , 32.3]	36 [26 , 38.2]
C Systolic blood pressure at entry to care, mm Hg c Diastolic blood pressure at entry to care, mm Hg	115 [110 , 122] 68 [64 , 72]	109 [107 , 131] 64 [55 , 77]
D Parity	2 [2 , 3]	1 [1 , 2]
Gestational age at randomization—weeks	14.9 [13.4 , 16.4]	13.9 [13.3 , 16.1]
Gestational age at delivery in prior pregnancy—	30.7 [29.4 , 32.0]	32.0 [30.7 , 33.0]

Independent Sample t-test and chi- square does not show statistically significant difference between groups. None of the comparisons between the two groups is statistically significant (P > 0.05)

Blood pressure at entry to care, measured in clinic after a 10-minute rest period, in seating position with the right arm in a roughly horizontal position at heart level, supported on a desk. [D] Parity is any pregnancy that lasted >20 weeks

Table 2. Adverse and serious adverse events experienced by subjects, irrespective of association with study medications. Data are reported as n (%).

Condition	Placebo Group[#] (N= 200)	Pravastatin Group[#] (N= 200)
Adverse events		
Heartburn	30 (15)	40(20)
Musculoskeletal pain	10(5)	40 (36)
Dizziness	20 (10)	3 (27)
Chest Pain	0	20 (10)
Diarrhea	1 (10)	2 0(10)
Headache	3 (30)	20 (10)
Cough	1 (10)	20 (10)
Swelling	0	20 (10)
Nausea	10 (5)	11 (5)
Fever	20(10)	10 (5)
Flatulence	0	30(15)
Fatigue	0	10 (5)
Wheezing	0	10(5)
Vomiting	15 (7.5)	0
Influenza-like symptoms	20 (10)	0
Serious Adverse Events		
Maternal, fetal, or infant death	0	0
a Rhabdomyolysis	0	0

None of the comparisons between the two groups is statistically significant (P > 0.05).For all variables t-Independent Sample t-test and chi- square does not show statistically significant difference between groups

[a]Rhabdomyolysis was defined as muscle pain or muscle weakness in conjunction with increase in creatinine kinase (CK) values to greater than 10 times the upper limit of normal. Liver injury was diagnosed with elevation of transaminases (AST or ALT) values greater than three times the upper limit of normal.

Table 3. Maternal and neonatal outcomes of participants in the study. Data are reported as n (%) mean±SD, or median [IQR]

Outcomes	Placebo Group[#] (N=10)	Pravastatin Group[#] (N=10)
Maternal Out comes		
Preeclampsia Mild preeclampsia Severe features	18 (8) 5 (31.2%) 11 (68.8%)	6 (3) 2 (33.3%) 4 (66.7%)
Postpartum preeclampsia	10 (5)[a]	0 (0)
Gestational hypertension	20(10)	20 (10)
Gestational age at delivery, weeks	36.7± 2.1	37.7± 0.9
Indicated preterm delivery less than 37 weeks	50 (25)[b]	10 (5) [c]
Indicated preterm delivery less than 34 weeks	15(7.5)	0 (0)
Blood transfusion	20 (10)	20 (10)
d Length of hospital stay (days)	4 [3-7], range 2-43	3 [3-4], range 1-6
Neonatal Out comes		
Birth weight, grams	2,877±630	3,018± 260
Highest level of care Well baby/routine Intermediate (Level 2) NICU	 100 (50) 40(20) 60(30)	 140 (70) 20 (10) 20 (10)
NICU length of stay ≥ 48 hours	60 (30)	0
Respiratory Distress Syndrome	40 (20)	20 (10)

x 2 -Chi-square test; p-value <0.05 for shows statistically significant difference between groups according to preeclampsia.

For other variables t-Independent Sample t-test and chi- square does not show statistically significant difference between groups.

DISCUSSION:

Hypertensive disorders are among the most common medical complications of pregnancy; the reported incidence is between 5% and 10% [21]. Preeclampsia is a pregnancy-specific hypertensive disease with multisystem involvement. It usually occurs after 20 weeks of gestation, most often near term, and can be superimposed on another hypertensive disorder. Preeclampsia, the most common form of high blood pressure (BP) that complicates pregnancy, is primarily defined by the occurrence of new-onset hypertension plus new-onset proteinuria. However, although these two criteria are considered the classic definition of preeclampsia, some women present with hypertension and multi systemic signs usually indicative of disease severity in the absence of proteinuria [22]. In the absence of proteinuria, preeclampsia is diagnosed as hypertension in association with thrombocytopenia (platelet count less than 100,000/microliter), impaired liver function (elevated blood levels of liver transaminases to twice the normal concentration), the new development of renal insufficiency (elevated serum creatinine greater than 1.1 mg/dl or a doubling of serum creatinine in the absence of other renal disease), pulmonary edema, or new-onset cerebral or visual disturbances [22]. Hypertensive disorders in pregnancy remain one of the leading cause of maternal death worldwide (about 20% to 25% of maternal deaths in developing as well as developed nations) [23].

Preeclampsia shares pathogenic similarities with adult cardiovascular diseases as well as many risk factors. Endothelial dysfunction and inflammation are fundamental for the initiation and progression of both. There is strong evidence that 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins) are beneficial in primary and secondary prevention of cardiovascular mortality and other cardiovascular events. Biological plausibility as well as animal data supports a similar role for statins in preeclampsia. Currently, there are no clinically available agents to prevent preeclampsia. However because of the below properties of statins, this class of medications could substantially contribute to preeclampsia prevention. [21] Statins pleiotropic actions on various mechanisms: reversing the angiogenic imbalance by upregulating vascular endothelial growth factor (VEGF) and placental growth factor (PlGF), and reducing the antiangiogenic factors such as soluble fms-like tyrosine kinase-1 (sFlt-1) and soluble endoglin (sEng). 2. Statins up regulation of endothelial nitric oxide synthase, leading to improved nitric oxide production in the vasculature and to activate the heme oxygenase-1/carbon monoxide (HO-1/CO) pathway, protecting the endothelium and reducing the inflammatory and oxidative insult. [24]

In humans, the first report to suggest the beneficial effects of pravastatin in preventing preeclampsia described a patient with antiphospholipid syndrome (APS). The APS patient, with a history of early preeclampsia leading to a still birth at week 26, developed preeclampsia in her second pregnancy, despite anticoagulant treatment. Uterine artery Dopplers showed increased resistance and bilateral notching. To prevent intrauterine fetal death as in the previous pregnancy, the patient was supplemented with pravastatin. Addition of pravastatin (20 mg/day) to standard of care therapy low molecular weight heparin (LMWH) plus low dose aspirin (LDA) normalized maternal disease, blood pressure and proteinuria and reversed abnormal uterine blood flow. A live and healthy baby girl weighing 2830 g was delivered vaginally at 38 weeks with no complications. The patient stopped taking pravastatin prior to delivery, in preparation for breastfeeding. Interestingly, preeclampsia relapsed shortly after delivery. Pravastatin therapy (20 mg/day) was started again and the preeclamptic features disappeared [25].

A pilot clinical study to examine the effects of pravastatin in women diagnosed with PE between 24 and 29 weeks was conducted in Australia [26].

CONCLUSION:

Pravastatin can be used as an effective agent in the prevention and treatment of preeclampsia in pregnant women.

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