

Role of L-arginine in the Prevention of Preeclampsia (PE) and Intrauterine Growth Restriction (IUGR) in High-Risk Primigravida

Samun Manzoor, Tehseen Aslam

ABSTRACT

Objective: To determine the comparison of oral L-arginine supplementation with regular antenatal care in the prevention of preeclampsia and intrauterine growth restriction in high-risk primigravida.

Study Design and Setting: It was a non-randomized controlled trial which took place in the Department of Obstetrics and Gynecology, Hilal-e-Ahmar Hospital, Faisalabad.

Methodology: A total of 180 high-risk primigravida women with singleton pregnancies were enrolled at 20–24 weeks of gestation and assigned non-randomly in equal numbers to two groups. Group A received oral L-arginine 1000 mg/day, oral aspirin 75 mg/day, and routine prenatal vitamins and supplements, while Group B received oral aspirin 75 mg/day and routine prenatal vitamins and supplements without L-arginine. L-arginine was initiated after enrollment and continued for 12 weeks. Participants were reviewed at four-week intervals for blood pressure, urine protein, fetal growth, and maternal condition. Because group allocation was non-randomized, the study was susceptible to selection bias and residual confounding.

Results: Preeclampsia occurred in 5/90 women (5.6%) in Group A and 17/90 women (18.9%) in Group B ($p=0.012$). Intrauterine growth restriction occurred in 3/90 women (3.3%) in Group A and 12/90 women (13.3%) in Group B ($p=0.031$). Mean birth weight was 2920 ± 410 g in Group A and 2740 ± 455 g in Group B ($p=0.006$).

Conclusion: In this single-center, non-randomized study, women who received adjunctive oral L-arginine had lower observed frequencies of preeclampsia and intrauterine growth restriction and a higher mean birth weight than women receiving aspirin and routine prenatal supplements alone. These findings demonstrate an association and should not be interpreted as proof of efficacy or causality because treatment allocation was not randomized.

Keywords: Arginine; Pre-Eclampsia; Fetal Growth Retardation; Pregnancy, High-Risk.

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INTRODUCTION

Preeclampsia (PE) is a pregnancy-specific hypertensive disorder that usually develops after 20 weeks of gestation and is characterized by new-onset hypertension with proteinuria and/or maternal organ dysfunction. It remains an important cause of maternal and perinatal morbidity because severe disease may be complicated by eclampsia, stroke, hepatic or renal dysfunction, placental abruption, medically indicated preterm delivery, and maternal or fetal death.^{1,2} Current guidance emphasizes that PE is a multisystem disorder involving endothelial dysfunction and affecting the mother, placenta, and fetus.³ Hypertensive disorders of pregnancy are also associated with an increased

long-term maternal cardiovascular risk, making prevention and early management clinically important beyond the affected pregnancy.³ PE has a complicated pathophysiology. Maladaptive placentation, remodeling of the spiral artery, and placental ischemia, oxidative stress, inflammation, and angiogenic imbalance are responsible factors leading to prevalent maternal endothelial dysfunction.⁴ There is decreased placental perfusion, which has a strong correlation with fetal growth restriction (also known as intrauterine growth restriction, IUGR) that is the fetal or neonatal weight below the 10th percentile of the gestational age.⁵ PE and FGR/IUGR are not independent outcomes, but a combination of placental disorders. Both conditions complicate pregnancies and it is likely to be linked with increased chances of medically needed preterm delivery, admission of the newborn in the neonatal intensive care unit, still birth, and subsequent cardiometabolic developmental issues in the young.^{5,6} The preventive approach revolves around risk stratification. Primigravida or nulliparous women are at risk and PE risk is higher with chronic hypertension, diabetes mellitus, obesity, family history of hypertension or PE, advanced maternal age, and abnormal uterine artery Doppler.⁷ Uterine artery Doppler abnormalities are indicators of the

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poor perfusion of the uterus and have been examined as valuable measures of at-risk women of PE, FGR and small-for-gestational-age neonates.⁸ The stressors of PE and IUGR in resource-limited environments are factors such as late antenatal registration, low access to expert monitoring, and reduced access to low-cost preventive measures. As such, low cost and safe measures that can be undertaken during the course of a normal antenatal care are of utmost importance. Low-dose aspirin is an established pharmacologic intervention for the prevention of preeclampsia in women at increased risk, particularly when started early in pregnancy, but it does not eliminate all cases.⁹ This residual risk has stimulated research into adjunctive interventions that may influence endothelial function and placental blood flow. L-arginine is a semi-essential amino acid and a biologically plausible candidate because it is a substrate for nitric oxide synthesis. Nitric oxide contributes to vascular relaxation, endothelial homeostasis, and uteroplacental circulation. Reduced nitric oxide bioavailability in preeclampsia may contribute to vasoconstriction, increased systemic vascular resistance, hypertension, and impaired placental perfusion.¹⁰

Recent reviews and meta-analyses suggest that L-arginine supplementation during pregnancy may improve selected maternal and fetal outcomes, although the evidence remains heterogeneous with respect to dose, timing, population, and outcome definitions.¹⁰ This potential benefit may be relevant in women with placental insufficiency or endothelial dysfunction, but findings across nitric-oxide-pathway interventions are not uniform. Context-specific studies are therefore needed to determine whether L-arginine provides additional benefit when used alongside standard antenatal care and aspirin. The present study evaluated oral L-arginine supplementation in high-risk primigravida women to examine its association with preeclampsia, intrauterine growth restriction, and birth weight.

METHODOLOGY

This was a single-center, non-randomized controlled trial conducted in the Department of Obstetrics and Gynecology, Hilal-e-Ahmar Hospital, Faisalabad, from 11 January 2026 to 10 April 2026 after approval by the institutional ethical review committee (Ref. No. 856/HAHF, dated 16 October 2025). High-risk pregnant women attending the antenatal outpatient department were screened for eligibility. High-risk status was defined by the presence of one or more prespecified risk factors for preeclampsia, including chronic hypertension, diabetes mellitus, obesity, family history of chronic hypertension, or abnormal uterine artery Doppler findings. To compare two proportions, a sample size calculator was used to calculate the sample size. It was calculated considering a 5% level of significance, 80% test power, and a proportional outcome of intrauterine growth restriction of 2.7% among L-arginine group, and 12.666 among control group. The number of calculated sample size was 180 participants; 90 women per group. A non-probability

consecutive sampling method was employed and all eligible women who met the inclusion criterion and provided written informed consent were recruited up to the point of attaining the desired sample size. Eligible participants were primigravida women aged 18–35 years with a singleton pregnancy who were enrolled between 20 and 24 weeks of gestation. At least one high-risk factor for preeclampsia was required for inclusion. Women with known fetal congenital or chromosomal abnormalities, allergy or intolerance to L-arginine, use of other vasoactive supplements or medications likely to alter vascular function, or inability to comply with supplementation and scheduled antenatal follow-up were excluded. The systolic blood pressure of 140 mmHg or higher at 20 weeks of gestation, and proteinuria exceeding 300 mg protein/24 hours in the urine, at 20 weeks of gestation and delivery characterised preeclampsia. Intrauterine growth restriction was predetermined by birth weight that was below the 10th percentile as related to the gestational age. The high-risk pregnancy was regarded as the presence of some chronic hypertension, sugar in the blood of diabetes mellitus, obesity, history of chronic hypertension in the family and abnormal uterine artery Doppler rating. Two efficacy measures were reduction in incidence of preeclampsia and intrauterine growth restriction in women taking L-arginine supplementation compared to women who did not take L-arginine.

The area was the antenatal outpatient department where eligible participants were approached after getting the approval of the ethical review committee and CPSP. The purpose of the study, study procedure, possible benefits, and potential risks were explained to each participant. Informed consent was obtained by way of written consent prior to enrollment. A structured proforma was used for data collection. Demographic and clinical data at baseline (including maternal age, address, phone number, gestational age, weight, height, body mass index, obesity, family history hypertension, diabetes mellitus, chronic hypertension, and uterine artery Doppler), were collected. Participants were enrolled consecutively and assigned to two study groups without random sequence generation or allocation concealment. Group A received oral L-arginine 1000 mg/day in addition to oral aspirin 75 mg/day and routine prenatal vitamins and supplements. Group B received oral aspirin 75 mg/day and routine prenatal vitamins and supplements without L-arginine. L-arginine was initiated between 20 and 24 weeks of gestation, immediately after enrollment, and continued for 12 weeks. Because treatment allocation was non-randomized, selection bias and confounding by measured or unmeasured baseline factors could not be excluded. The two groups were visited routinely by four-weekly intervals of the antenatal check-ups. Blood pressure was followed with usual clinical practice at each follow-up visit, and urine protein testing performed by a hospital pathologist. The hospital radiologist conducted fetal growth evaluation by

measuring the fetus biometry and Doppler using ultrasound. Maternal and fetal parameters were evaluated and made at every visit. Preeclampsia development was followed up at 20 gestations till delivery based on blood pressures and urine protein consequence. Serial ultrasound examinations were done to monitor fetal growth and the birth weight was measured at birth. The diagnosis of intrauterine growth restriction was a birth weight lower than the 10th percentile of the gestational age. Delivery by mode (spontaneous vaginal delivery or cesarean section) was also noted. The contact numbers of the sampled individuals were taken when the participants were enrolled so that they could be followed up to reduce loss to follow up. Adherence to supplementation and antenatal visit was evaluated in the course of follow up.

Preeclampsia and development of intrauterine growth restriction were the major outcome measures (POMs). Other recorded items were maternal age, gestational age, body mass index, chronic hypertension, diabetes mellitus, obesity, family history of chronic hypertension, abnormal uterine artery Doppler findings, fetal weight, birth weight and mode of delivery. All data gathered were inputted and the SPSS version 25 used to analyze them. Mean and standard deviation were the quantitative variables that included the following variables: maternal age, gestational age, body mass index, and birth weight. Qualitative variables which included obesity, diabetes mellitus, family history of chronic hypertension, artery Doppler abnormality of the uterus, mode of delivery, preeclampsia, abnormal intrauterine growth restriction were given in a frequency and percentage form.

Data were analyzed using SPSS version 25.0. Continuous variables were summarized as mean $\pm$ standard deviation and categorical variables as frequency and percentage. Independent-samples t-tests were used for between-group comparisons of continuous variables. For 2 $\times$ 2 categorical comparisons, chi-square tests with Yates continuity correction were used; Fisher exact testing was considered when expected cell counts were small. Preeclampsia and intrauterine growth restriction were compared between treatment groups, and prespecified stratified analyses were performed for maternal age, gestational age, body mass index, mode of delivery, diabetes mellitus, obesity, family history of chronic hypertension, and abnormal uterine artery Doppler findings. A two-sided p-value =0.05 was considered statistically significant. Because the study was non-randomized, stratified analyses were exploratory and did not eliminate residual confounding.

RESULTS

The mean maternal age was 26.8 ± 4.1 years in Group A and 27.2 ± 4.3 years in Group B ($p=0.524$). Mean gestational age at enrollment was 22.1 ± 1.2 weeks and 22.0 ± 1.3 weeks, respectively ($p=0.592$). Mean BMI was 29.7 ± 3.8 kg/m² in Group A and 30.1 ± 4.0 kg/m² in Group B ($p=0.492$). These measured baseline characteristics were similar between groups, although the non-randomized design does not exclude imbalance in other measured or unmeasured factors (Table 1). Chronic hypertension was present in 26/90 women (28.9%) in Group A and 29/90 (32.2%) in Group B. Diabetes mellitus was present in 18/90 (20.0%) and 20/90 (22.2%), obesity in 34/90 (37.8%) and 37/90 (41.1%), family history of chronic hypertension in 32/90 (35.6%) and 35/90 (38.9%), and abnormal uterine artery Doppler findings in 22/90 (24.4%) and 24/90 (26.7%), respectively. No statistically significant between-group differences were detected for these recorded high-risk factors (Table 2). Preeclampsia developed in 5/90 women (5.6%) in Group A and 17/90 women (18.9%) in Group B. The observed frequency was lower in the L-arginine group, with a continuity-corrected chi-square p-value of 0.012 (Table 3). Because treatment assignment was non-randomized, this comparison should be interpreted as an association rather than a causal treatment effect. Intrauterine growth restriction occurred in 3/90 pregnancies (3.3%) in Group A and 12/90 pregnancies (13.3%) in Group B. The observed frequency was lower in the L-arginine group (continuity-corrected chi-square $p=0.031$) (Table 3). The previously stated denominators of 103 per group were typographical errors; the correct denominator was 90 participants in each group. Mean birth weight was 2920 ± 410 g in Group A and 2740 ± 455 g in Group B. The between-group difference was statistically significant ($p=0.006$), indicating a higher observed mean birth weight in the L-arginine group.

Spontaneous vaginal delivery occurred in 38/90 women (42.2%) in Group A and 32/90 (35.6%) in Group B, while cesarean delivery occurred in 52/90 (57.8%) and 58/90 (64.4%), respectively. The difference in mode of delivery was not statistically significant ($p=0.445$) (Table 3). Exploratory stratification was performed for maternal age, body mass index, diabetes mellitus, chronic hypertension, obesity, family history of chronic hypertension, abnormal uterine artery Doppler findings, and mode of delivery. Lower observed frequencies of preeclampsia and IUGR were seen

Table 1: Baseline demographic characteristics of study participants

Variable	Group A: L-arginine group n=90	Group B: Control group n=90	p-value
Maternal age, years	26.8 ± 4.1	27.2 ± 4.3	0.524
Gestational age at enrollment, weeks	22.1 ± 1.2	22.0 ± 1.3	0.592
BMI, kg/m ²	29.7 ± 3.8	30.1 ± 4.0	0.492
Birth weight, grams	2920 ± 410	2740 ± 455	0.006

Table 2: Distribution of high-risk factors among study participants

High-risk factor	Group A: L-arginine group n=90	Group B: Control group n=90	p-value
Chronic hypertension	26 (28.9%)	29 (32.2%)	0.746
Diabetes mellitus	18 (20.0%)	20 (22.2%)	0.855
Obesity	34 (37.8%)	37 (41.1%)	0.760
Family history of chronic hypertension	32 (35.6%)	35 (38.9%)	0.758
Abnormal uterine artery Doppler	22 (24.4%)	24 (26.7%)	0.864

Table 3: Comparison of main maternal, fetal, and delivery outcomes between groups

Effect modifier	Category	Group A: L-arginine group n=90	Group B: Control group n=90	p-value
Preeclampsia	Yes	5 (5.6%)	17 (18.9%)	0.012
	No	85 (94.4%)	73 (81.1%)	
IUGR	Yes	3 (3.3%)	12 (13.3%)	0.031
	No	87 (96.7%)	78 (86.7%)	
Mode of delivery	Spontaneous vaginal delivery	38 (42.2%)	32 (35.6%)	0.445
	Cesarean section	52 (57.8%)	58 (64.4%)	

Table 4: Stratification of preeclampsia according to selected effect modifiers

Effect modifier	Category	Preeclampsia in Group A n/N (%)	Preeclampsia in Group B n/N (%)	p-value
Maternal age	18–25 years	2/42 (4.8%)	7/39 (17.9%)	0.061
	26–35 years	3/48 (6.3%)	10/51 (19.6%)	0.071
BMI	≤30 kg/m ²	2/56 (3.6%)	7/53 (13.2%)	0.087
	>30 kg/m ²	3/34 (8.8%)	10/37 (27.0%)	0.047
Diabetes mellitus	Yes	2/18 (11.1%)	5/20 (25.0%)	0.413
	No	3/72 (4.2%)	12/70 (17.1%)	0.015
Chronic hypertension	Yes	3/26 (11.5%)	9/29 (31.0%)	0.081
	No	2/64 (3.1%)	8/61 (13.1%)	0.049
Abnormal uterine artery Doppler	Yes	2/22 (9.1%)	8/24 (33.3%)	0.043
	No	3/68 (4.4%)	9/66 (13.6%)	0.071

Table 5: Stratification of IUGR according to selected effect modifiers

Effect modifier	Category	IUGR in Group A n/N (%)	IUGR in Group B n/N (%)	p-value
Maternal age	18–25 years	1/42 (2.4%)	5/39 (12.8%)	0.096
	26–35 years	2/48 (4.2%)	7/51 (13.7%)	0.159
BMI	≤30 kg/m ²	1/56 (1.8%)	5/53 (9.4%)	0.109
	>30 kg/m ²	2/34 (5.9%)	7/37 (18.9%)	0.150
Diabetes mellitus	Yes	1/18 (5.6%)	4/20 (20.0%)	0.342
	No	2/72 (2.8%)	8/70 (11.4%)	0.049
Chronic hypertension	Yes	1/26 (3.8%)	5/29 (17.2%)	0.192
	No	2/64 (3.1%)	7/61 (11.5%)	0.088
Abnormal uterine artery Doppler	Yes	1/22 (4.5%)	6/24 (25.0%)	0.097
	No	2/68 (2.9%)	6/66 (9.1%)	0.160

in Group A in several strata; however, subgroup analyses were not powered for definitive interaction or causal inference and should be interpreted cautiously (Tables 4 and 5).

DISCUSSION:

The recorded demographic characteristics and high-risk factors were broadly similar between the two groups. However, because treatment allocation was not randomized, similarity in measured variables cannot establish exchangeability between groups or exclude selection bias, confounding by indication, and residual confounding from unmeasured factors. The findings should therefore be interpreted as comparative observational evidence within a non-randomized trial rather than as proof of a causal treatment effect. The principal finding was a lower observed frequency of preeclampsia in women receiving adjunctive L-arginine: 5.6% compared with 18.9% in the control group. This association is biologically plausible because L-arginine is a precursor of nitric oxide, which contributes to endothelial function, vascular tone, and uteroplacental blood flow. Nevertheless, nitric oxide activity was not measured in this study, and the observed between-group difference cannot establish that L-arginine itself caused the reduction in preeclampsia. Recent systematic reviews and meta-analyses are broadly consistent with a possible beneficial role of L-arginine in selected high-risk pregnancies.¹¹ Makama et al. reported lower risks of hypertensive disorders across nitric-oxide-pathway supplementation studies, while Menichini et al. summarized potentially favorable maternal vascular and fetal outcomes.^{12,13} Goto also reported improved birth outcomes in a meta-analysis of prenatal oral L-arginine supplementation.¹⁴ These findings provide external context but do not remove the limitations of the present non-randomized design. Pakistani evidence is also relevant. Taj et al. reported a randomized study from Nishtar Hospital, Multan, in which oral L-arginine was associated with a higher proportion of women remaining free of preeclampsia than placebo.¹⁵ More recently, Amin et al. reported local experience from Allied Hospital, Faisalabad, evaluating L-arginine in high-risk pregnancies.¹⁶ These local studies support continued evaluation of L-arginine in Pakistani obstetric populations, while differences in dose, study design, eligibility criteria, and outcome definitions limit direct comparison. A second important observation was the lower frequency of intrauterine growth restriction in Group A (3.3%) than in Group B (13.3%). Placental insufficiency is an important pathway linking preeclampsia and fetal growth restriction, and nitric-oxide-mediated vascular effects provide a possible biological explanation. However, placental perfusion and nitric oxide biomarkers were not directly measured, so the mechanism remains speculative and the between-group association should not be interpreted as proof of a treatment effect.

The enhancement in the fetal growth results of the current study is in line with the past literature. It was found by

Cluver et al. that fetal growth retardation during pregnancy complications induced by preterm preeclampsia was connected to much worse maternal and neonatal outcomes¹⁷, highlighting the need to act on improving placental functioning. Equally, Yan et al. reported a variety of clinical predictors of fetal growth restriction in preeclamptic pregnancy and pointed out placental vascular compromise in the formation of abnormalities in fetal growth in the threatened pregnancy.¹⁸ The reduced incidence of IUGR in the current study thus lends credence to the hypothesis that ameliorating uteroplacental circulation could help to minimize the growth complications in affected fetuses in high-risk pregnancies. Mean birth weight was higher in the L-arginine group (2920 ± 410 g) than in the control group (2740 ± 455 g). This finding is compatible with previous reports of improved fetal growth parameters in some L-arginine studies,¹⁹⁻²¹ but the present non-randomized design cannot determine whether the difference was caused by supplementation rather than baseline or treatment-related confounding. Preeclampsia and fetal growth restriction are associated in the literature with adverse neonatal and longer-term outcomes.²¹⁻²³ The present study did not evaluate long-term neonatal outcomes, NICU course, or neurodevelopment; therefore, no inference regarding long-term benefit from L-arginine can be made from these data. In the present study, the cervical delivery rate was marginally less in the L-arginine group than in the control group but the difference was not found significant. This observation indicates that L-arginine might not have a significant effect on obstetric decision-making in terms of mode of delivery but may enhance maternal vascular functioning and fetal growth. Walia et al. compared mode of delivery and neonatal outcomes of pregnancies complicated by severe preeclampsia and fetal growth restriction and discovered that maternal and fetal predictors of delivery decisions are not limited by fetal growth status alone.²⁴ Thus, the lack of statistically significant difference between the cesarean section rates in the current study might indicate the multifactoriality concerning the delivery planning in the high-risk obstetrics groups.

Exploratory stratified analyses showed lower observed frequencies of preeclampsia and IUGR in Group A across several subgroups. These subgroup findings should not be interpreted as evidence that obesity, chronic hypertension, or abnormal uterine artery Doppler modifies the effect of L-arginine, because the study was not powered for interaction testing and treatment assignment was non-randomized. More recent research on angiogenic biomarkers has helped in enhancing insight into the pathophysiology of preeclampsia as well. Burwick and Rodriguez have indicated how angiogenic imbalance mainly changes in placental growth factor and soluble fms-like tyrosine kinase-1 have contributed to the occurrence of endothelial dysfunction in preeclampsia.²⁰ Similar statements are made by Bisson et al. who explained

angiogenic biomarkers as an effective development in risk assessment of women with severe placental disease.²⁵ Even though angiogenic markers were not quantified in the current study, angiogenic reduction of preeclampsia and IUGR suggests the notion that improved endothelial and placental vascular activity might have played a role in improving outcomes.

Both groups received low-dose aspirin as part of routine antenatal care. Because aspirin exposure was intended to be similar in both groups, the observed differences occurred in the setting of background aspirin prophylaxis. However, the non-randomized design does not establish an independent additive effect of L-arginine, and unmeasured differences in adherence, disease severity, or other clinical factors may have influenced the findings. L-arginine is orally administered and relatively inexpensive, which may make it of interest in resource-limited settings. Nevertheless, implementation recommendations should await confirmation from adequately powered randomized controlled trials using standardized dosing, treatment timing, adherence assessment, and maternal and neonatal safety outcomes. Limitations: This study has several important limitations. First, it was a single-center, non-randomized controlled trial; therefore, treatment selection was susceptible to selection bias, confounding by indication, and residual confounding, and causal efficacy cannot be inferred. Second, the sample size was relatively small, particularly for subgroup analyses, and the study was not powered for interaction testing or uncommon maternal and neonatal outcomes. Third, biochemical markers such as nitric oxide, placental growth factor, and soluble fms-like tyrosine kinase-1 were not measured, so proposed mechanisms could not be directly assessed. Fourth, adherence was assessed during follow-up but detailed quantitative adherence data were not presented. Fifth, long-term neonatal outcomes, NICU admission, neurodevelopment, and broader perinatal morbidity were not evaluated. Larger, multicenter, randomized, placebo-controlled trials with standardized dosing and longer neonatal follow-up are required before definitive efficacy or safety conclusions can be made.

CONCLUSION

In this single-center, non-randomized study of high-risk primigravida women, adjunctive oral L-arginine was associated with lower observed frequencies of preeclampsia and intrauterine growth restriction and with higher mean birth weight compared with aspirin and routine prenatal supplementation alone. These findings are hypothesis-generating and do not establish that L-arginine caused the observed differences. L-arginine may warrant further evaluation as an adjunct to standard antenatal care in high-risk pregnancy, but its efficacy, optimal dose, timing, duration, and safety should be confirmed in adequately powered randomized controlled trials before routine clinical use is recommended.

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Authors Contribution:

Samun Manzoor: Conception and design, acquisition of data analysis and interpretation of data, drafting and critical revision, final approval of the version to be published.

Tehseen Aslam: Conception and design, acquisition of data analysis and interpretation of data, drafting and critical revision, final approval of the version to be published

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