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Original Article

Compliance with Low-Dose Aspirin and Outcomes in High-Risk Pregnant Women in Guna District of Central India

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Abstract

Aim This article determines the compliance rates with low-dose aspirin (LDA) and outcomes in a group of pregnant women identified at high risk for preeclampsia (PE) and fetal growth restriction (FGR) at 11 to 14 gestational weeks (GWs) in a rural district of central India.

Methods A single, experienced fetal radiologist assessed all enrolled pregnant women using trimester-specific antenatal screening protocols that included mean arterial blood pressure assessment, and fetal ultrasound and Doppler studies. A trimester-specific individualized risk for preterm PE and FGR was estimated for each woman. Pregnant women categorized as high risk for preterm PE or FGR based on a 1 in 150 criteria at 11 to 14 GW were recommended LDA 150 mg once daily at bedtime. Outcome measures included compliance with LDA assessed, incidence of PE and FGR, preterm delivery (< 37 GW), birth weight, stillbirths, and perinatal mortality.

Results The data of 488 pregnant women with longitudinal trimester-specific assessments from 11 to 14 GW till childbirth was analyzed. At the 3rd trimester assessment, 215 (80.83%) of the high-risk women were compliant with LDA. The incidence of PE, FGR, and preterm births was significantly higher in LDA noncompliant women, and the mean birth weight was significantly higher in LDA-compliant high-risk women.

Conclusion Good compliance for LDA is possible in rural populations with adequate counseling. Starting LDA at 11 to 14 GW for high-risk pregnant women lowered the incidence of PE, FGR, and preterm birth rates and improved birth weight in the study population.

Keywords
- compliance
- fetal growth restriction
- low-dose aspirin
- preeclampsia
- preterm births

Introduction

Evidence generated from the ASPRE trial regarding the effectiveness of low-dose aspirin (LDA) in the prevention of preterm preeclampsia (PE) has been integrated into several international guidelines on the screening of PE.[1–4] Samrakshan is an ongoing national program of the Indian Radiological and Imaging Association that aims to reduce perinatal mortality in India through trimester-specific antenatal screening protocols.[5–7] Consistent with the international guidelines,

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the Samrakshan program recommends starting LDA 150 mg once daily at bedtime from 11 to 14 gestational weeks (GWs) for pregnant women who are at high risk for preterm PE.[5–7] The effectiveness of preventative interventions is dependent on the compliance of the patient with the recommendations. In this article, we report on compliance with LDA and pregnancy outcomes in a rural population of high-risk pregnant women in the community-integrated Samrakshan program in the central Indian district of Guna in Madhya Pradesh, India.

Methods

The community-integrated Samrakshan model in the Guna district of central India was described previously.[7] Briefly, all enrolled pregnant women were assessed through trimester-specific antenatal screening protocols that included clinical and demographic details, prior obstetric history, mean arterial blood pressure (MAP) assessment, fetal Doppler studies, assessment of fetal biometry, growth, and environment and fetal anomalies.[5–7] The Bayesian algorithm of the Fetal Medicine Foundation was used to ascertain trimester-specific individualized risk for preterm PE and fetal growth restriction (FGR).[5–7] The study included high-risk pregnant women with live singleton fetuses who were advised LDA at 11 to 14 GW and followed up with 2nd and 3rd trimester assessments using the Samrakshan protocols. Pregnant women categorized at high risk for preterm PE or FGR based on a 1 in 150 criteria at 11 to 14 GW were recommended LDA 150 mg once daily at bedtime till 37 weeks, or development of preterm PE or childbirth, whichever was earlier.[5–7] Pregnant women for whom details of any of the 1st, 2nd, or 3rd trimester assessments or of childbirth were unavailable, or with multifetal gestation, fetal anomalies, or nonviable fetus at $<$ 24 GW were excluded from the study. The 2nd and 3rd trimester assessments were performed at 18 to 24 gestation weeks and 28 gestation weeks upwards. These include the targeted imaging for fetal anomalies, assessment of the mean uterine artery pulsatility index (UtA PI), umbilical artery PI, middle cerebral artery PI, and estimation of the cerebroplacental ratio and ductus venosus assessments. The single deepest vertical pocket and amniotic fluid index, fetal biometry, and growth velocity were assessed. PE was defined based on the International Society for the Study of Hypertension in Pregnancy criteria[8] and FGR was staged in the 3rd trimester using the protocol proposed by Figueras and Gratacós.[9] All fetal ultrasound and Doppler assessments were done by a single fetal radiologist with over 30 years of experience in sonography.

Outcome measures included compliance with LDA assessed through an in-person interview at follow-up visits, the incidence of PE and FGR, preterm delivery ($<$ 37 GW), birth weight, stillbirths, and perinatal mortality. Poor compliance with LDA was defined as irregular or nonuse of LDA in any trimester of pregnancy.

Data were entered into MS Excel and exported to STATA v14.0 (College Station, Texas, United States) for analysis. Categorical variables are expressed as proportions and continuous variables as mean $\pm$ standard deviation (SD). A Student's *t*-test and one-way analysis of variance test were used to compare means and the Fisher's exact test was used to compare categorical variables. A *p*-value of $<$ 0.05 was considered statistically significant.

Results

The data of 488 pregnant women with longitudinal trimester-specific assessments from 11 to 14 GW till childbirth was analyzed. The mean age $\pm$ SD of women was 26.89 $\pm$ 4.98 (range 19–43) years, 258 (52.87%) were nulliparous and 33 (6.76%) women had a body mass index $>$ 30 kg/m^2. Eleven (2.25%) women had chronic hypertension. At the 11 to 14 GW assessment, 76 (15.57%) women were categorized as high risk for both preterm PE and FGR, 38 (7.79%) at high risk for preterm PE alone, and 153 (31.35%) at high risk for FGR alone, and 266 (54.51%) women were recommended LDA. Three (1.13%) and 9 (3.38%) of the 266 high-risk women developed PE and FGR in the 2nd trimester assessments. Forty (15.04%) of these 266 women were noncompliant with LDA in the 18 to 24 GW assessment. Early PE and early FGR (20–24 GW) were significantly higher in high-risk women who were noncompliant compared with women compliant with LDA (►**Table 1**). At the 3rd trimester assessment, 215 (80.83%) of the high-risk women were compliant with LDA. The incidence of PE, FGR, and preterm births was significantly higher and the mean birth weight was significantly lower in LDA noncompliant women (►**Table 1**). The mean MAP and mean UtA PI were higher in noncompliant women compared with compliant women, but the difference was not statistically

Table 1 Compliance and pregnancy outcomes in the 266 high-risk pregnant women advised low-dose aspirin at 11 to 14 gestational weeks

	Compliant with low-dose aspirin	Noncompliant with low-dose aspirin	*p*-Value
Early PE (20–24 wk)	1 (0.44%)	2 (6.06%)	$<$ 0.001
Early FGR (20–24 wk)	4 (1.77%)	5 (15.15%)	$<$ 0.001
PE in 3rd trimester	3 (1.40%)	3 (5.88%)	$<$ 0.001
Stage 1 FGR in 3rd trimester	21 (9.77%)	18 (36.00%)	$<$ 0.001
Preterm births	17 (9.09%)	9 (23.68%)	0.01
Mean birth weight $\pm$ SD (kg)	2.69 $\pm$ 0.47	2.48 $\pm$ 0.50	0.01

Abbreviations: FGR, fetal growth restriction; PE, preeclampsia; SD, standard deviation.

significant (both $p = 0.52$). The MAP and mean UtA PI in the 3rd trimester were significantly higher in the women identified at high risk in the 11 to 14 GW assessment compared with the low-risk women (< 0.001). There was one stillbirth and two early neonatal deaths in this study. The three perinatal deaths occurred in women who had a high risk for PE in the 3rd trimester and developed severe PE. These women were compliant with LDA but did not follow the therapeutic recommendations by the treating obstetrician for the management of PE.

Only 1 (0.45%) of the 222 low-risk women developed PE in the early 2nd trimester and 7.66% developed stage 1 FGR in the 3rd trimester.

Discussion

The lower incidence of PE and FGR and better outcomes of pregnancy in high-risk women compliant with LDA provide evidence of the effectiveness of early initiation of LDA and a protocol-based antenatal screening that integrates fetal Doppler assessments. The 80.83% compliance with LDA suggests that good compliance is possible in rural, vulnerable populations with appropriate counseling using an integrated approach with multiple health care workers. The rate of compliance in this study population is similar to a recent study by Olson et al, that reported 81.7 and 76.9% compliance in high-risk and moderate-risk pregnant women based on the American College of Obstetricians and Gynecologists criteria for PE.[10] The study by Olson et al highlighted the importance of adequate and appropriate counseling as they reported that 42.3% of high-risk women did not recall the recommendations for LDA and that nearly 30% of women reported adherence with $< 90\%$ of the doses.[10] The fetal radiologist and the community-integrated team of health workers in this study provided constant reinforcement of the message to use LDA, which might explain the good compliance rates with LDA in this study. Regular reminders by the treating obstetrician will also help to improve compliance. The assessment of compliance through a self-reporting recall can lead to a potential bias and overreporting of compliance by the women. However, biochemical assessment of aspirin compliance is not feasible for reasons of availability, affordability, and accessibility and is not a pragmatic possibility in this population. Nearly 1 in 5 high-risk women who were recommended LDA did not use it regularly even after counseling. The parameters of irregularity are subjective even though we set the parameters of irregular use as two or more breaks of 2 to 3 days between daily LDA use. Most of the self-reported reasons for noncompliance were personal, family, and cultural preferences against medications during pregnancy and were not reported as related to side effects or associated medical complications. The proportion of noncompliance may reduce with sustained health education in community and family settings especially as community and family members witness or experience the beneficial outcomes.

The proportion of women who were recommended LDA in the 11 to 14 GW assessment is large in this study. The high proportion is influenced by the high estimated risk for FGR in this population with 1 in 3 pregnant women at high risk for FGR without an accompanying high risk for PE. The current risk estimates for FGR use the Hadlock III formula which may overestimate the number of "small" babies in India.[11] The estimated risk for FGR in the population might differ if locally relevant growth and biometry charts are used. However, India is a large diverse country with great intracountry and even intrastate variations in growth estimates between existing charts that were developed for regional populations.

Samrakshan recommends initiating LDA 150 mg once daily at bedtime even if the 11 to 14 GW assessment shows only a high risk for FGR and this approach has significantly increased the pool of pregnant women that are advised LDA. If we exclude this subgroup, the pool recommended LDA will reduce from just over 1 in 2 to 1 in 4 pregnant women in the study population. However, the inclusion of the subgroup of only at high risk for FGR is vindicated by the significantly lower and comparable rates of FGR in the compliant with LDA group (9.77%) and the low-risk group (7.66%) ($p = 0.4$), and the significantly higher rates of FGR in the noncompliant group (36.00%). The huge difference in the FGR rates between groups is suggestive of a beneficial effect for LDA in the subgroup of women at high risk for FGR alone. India has a high background risk and incidence of FGR and the significant reduction in rates of FGR will translate to a large change in the absolute number of growth-restricted fetuses.

The improvement in the preterm birth rates can be partly attributed to the lowered incidence of PE and FGR due to LDA and antenatal screening protocols, early identification of signs of PE and FGR, and optimal management resulting from sustained surveillance. All the FGR were stage 1 FGR, which can be carried till term if there are no associated maternal or fetal comorbidity. The lowered preterm birth rates lead to an increase in birth weight as more babies are born at term. The significant improvement in preterm birth rates, birth weight, and reduction in the incidence of PE and FGR in the study area, after starting Samrakshan, has been reported previously.[7]

The MAP, mean UtA PI measures, and the incidence of PE and FGR were compared in the groups identified as high-risk and low-risk in the 1st trimester assessment to assess the effectiveness of the risk categorization and potential misclassification. The comparative MAP and mean UtA PI measures were higher for the high-risk group compared with low-risk women at 11 to 14 GW and remained higher at the 3rd trimester assessment. The incidence of PE and FGR was significantly higher in the high-risk group in the 3rd trimester assessment. These results suggest that the risk of misclassification by the algorithm at 11 to 14 GW is low.

The study was conducted in a single community area of a single district of central India and the results may not be representative of the entire population of pregnant women in India. The strengths of the study are the longitudinal ultrasound and Doppler assessments and protocol-based assessments by an experienced fetal radiologist. Many subjects present for cross-sectional assessments without preceding assessments and may not return for subsequent

assessments. Exclusion of such subjects without longitudinal assessments through all trimesters of pregnancy can cause a selection bias and is a limitation. However, longitudinal assessment by the same practitioner is difficult in rural India with in-and-out migration a pragmatic reality as the pregnant woman shifts residence to their parents' home for social and cultural reasons or to be closer to higher medical centers for medical and accessibility reasons. The exclusion of women with fetal loss before 24 gestation weeks from the study is a possible selection bias that can lead to a potential underreporting of cases where LDA may not have been effective like severe early-onset PE or severe early FGR or severe systemic lupus erythematosus, antiphospholipid antibody, and other autoimmune diseases.

In conclusion, this study provides evidence that good compliance for LDA is possible in rural populations with adequate counseling through an integrated network of health care workers. Starting LDA at 11 to 14 GW for high-risk pregnant women lowered the incidence of PE and FGR and improved preterm birth rates and birth weight in the study population.

Note

This work is attributed to Indian Radiological & Imaging Association, IRIA House, C-5, Qutab Institutional Area, New Delhi 110016, India.

Conflict of Interest

None declared.

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