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ORIGINAL ARTICLE

The impact of low-dose aspirin on preterm birth: secondary analysis of a randomized controlled trial

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OBJECTIVE: The objective of this study is to determine whether low-dose aspirin (LDA) reduced the rate of preterm birth (PTB) in a cohort of women at high risk for preeclampsia.
STUDY DESIGN: Secondary analysis of the Maternal-Fetal Medicine Units High-Risk Aspirin trial. Preterm births were categorized by phenotype: indicated, spontaneous or due to preterm premature rupture of membranes (PPROMs).
RESULTS: Of 1789 randomized women, 30.5% delivered before 37 weeks (18.5% indicated, 5.8% spontaneous and 6.2% following preterm PPROMs). Among women randomized to LDA, we observed a trend favoring fewer PTBs due to spontaneous preterm labor and preterm PPROMs, odds ratio (OR: 0.826 (0.620, 1.099)); the incidence of indicated PTBs appeared unchanged, OR: 0.999 (0.787, 1.268).
CONCLUSION: Although not reaching significance, we observed an effect size similar to other studies of both low- and high-risk women. These results support findings from other studies assessing LDA as a PTB prevention strategy.

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INTRODUCTION

Given the enormous adverse public health implications of preterm birth (PTB), ongoing research into preventative strategies remains critical.[1–3] Low-dose aspirin (LDA) has been studied extensively for over 30 years as a strategy for the prevention of preeclampsia. Meta-analyses and a systematic review have confirmed modest but consistent reductions in the incidence of preeclampsia.[4–6] A second, perhaps somewhat unexpected observation has been a consistent reduction in the incidence of PTB in women randomized to LDA.[4,5,6] PTB prevention is part of the rationale given in the 2014 United States Preventive Services Task Force recommendations that LDA be administered to women at high risk of preeclampsia.[4] A recent secondary analysis of the Effects of Aspirin in Gestation and Reproduction (EAGeR) trial, a randomized trial of women with prior pregnancy loss, found similar effects.[7]

Although some of the reduction in PTB presumably results from a reduction in indicated PTB (iPTB) related to preeclampsia, growth restriction or other placentally mediated disease processes, the magnitude of the reduction in PTB seems too large to attribute to this alone, as LDA in general reduces PTB and preeclampsia by similar magnitudes. As the majority of preeclampsia occurs at term, preventing preeclampsia would not translate into PTB prevention in many cases. Accordingly, it seems possible that LDA may have an impact on other mechanisms of PTB including prevention of spontaneous PTB (sPTB) or PTB following premature rupture of membranes (PPROM-PTB). Unfortunately, although most LDA preeclampsia prevention trials have reported PTB rates in LDA and placebo-randomized women, most have not reported PTB phenotype in those women that delivered prematurely, making this question difficult to directly address from published studies. To understand the potential role of LDA in PTB prevention, it is critical to understand patients that might benefit and PTB phenotypes that might be impacted.

The Maternal-Fetal Medicine Units High-Risk Aspirin trial did not show a reduction in preeclampsia in women at high-risk, owing to multiple gestation, chronic hypertension (HTN), previous preeclampsia or preexisting diabetes.[8] However, even in this overall negative trial, there was a near significant trend toward a reduction in PTB (odds ratio (OR): 0.9, 95% confidence interval (CI): 0.8 to 1.0). Furthermore, this trial did report PTB phenotype, making it amenable to addressing LDA's effect on sPTB and PPROM-PTB. Here, in a secondary analysis, we further investigate the effect of LDA on PTB as characterized by PTB phenotype (iPTB, PPROM-PTB and sPTB). We hypothesized that LDA would decrease the incidence of sPTB and/or PPROM-PTB.

METHODS

We performed a secondary analysis of the Maternal-Fetal Medicine Units Network randomized controlled trial of LDA (60 mg) for the prevention of preeclampsia in high-risk women.[8] The original inclusion criteria were pregnancies with at least one risk factor for preeclampsia: pre-existing insulin-dependent diabetes (IDDM), HTN, multiple gestation or preeclampsia in a previous pregnancy (PrePreE). Women were enrolled into one of four mutually exclusive high-risk groups defined as follows: (1) diabetes (IDDM with or without PrePreE or HTN), (2) HTN (HTN with or without PrePreE), (3) multifetal gestation (multiple gestation with or without PrePreE) and (4) previous preeclampsia (and no other risk factor). The protocol received institutional review board approval at each center and all participating women provided written informed consent.

Full details of the study design are available in the original manuscript.[8] Briefly, enrollment of eligible women occurred between calendar years 1991 and 1995 during the 13th through 26th week of pregnancy. Women were randomized 1:1 to receive LDA (60 mg of aspirin) or placebo in a double-blind, randomized, placebo-controlled trial design, to assess the impact on incidence of LDA on preeclampsia. Adherence to study drug regimen was measured by questioning of women, counting pills and measuring thromboxane in serum. PTB was one of six prespecified

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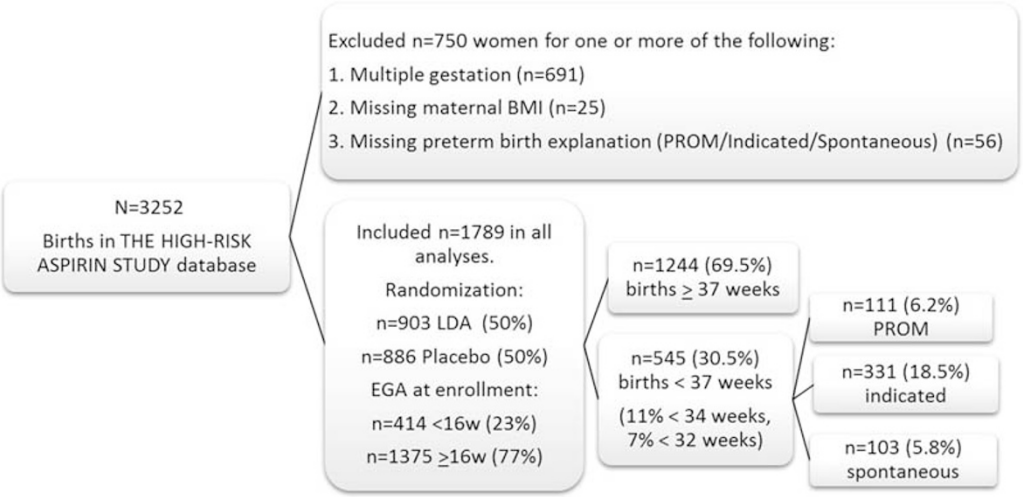

Figure 1. Population for analysis.

Table 1. Demographic comparisons by treatment randomization and randomization timing

Characteristic	*Treatment randomization*			*Randomization/enrollment timing*		
	LDA	*Placebo*		*⩽16 Weeks*	*>16 Weeks*	
	n = *903*	n = *886*	P-*values*	n = *414*	n = *1375*	P-*values*
Nulliparity *n (%)*	207 (22.92)	205 (23.14)	0.914	107 (25.85)	305 (22.18)	0.121
Primigravida *n (%)*	136 (15.06)	140 (15.80)	0.665	69 (16.67)	207 (15.05)	0.426
⩾1 previous miscarriage *n (%)*	270 (29.90)	223 (25.17)	0.025	130 (31.40)	363 (26.40)	0.046
Maternal age[a]	26.3 (25.92, 26.73)	26.4 (26.03, 26.84)	0.721	26.3 (25.68, 26.85)	26.4 (26.08, 26.74)	0.651
Black race *n (%)*	548 (60.69)	517 (58.35)	0.315	234 (56.52)	831 (60.44)	0.155
BMI						
Underweight *n (%)*	24 (2.66)	24 (2.71)	0.959	8 (1.93)	40 (2.91)	0.327
Normal/pre-obese	475 (52.60)	477 (53.84)		225 (54.35)	727 (52.87)	
Obese I, II	277 (30.68)	263 (29.68)		132 (31.88)	408 (29.67)	
Obese III	127 (14.06)	122 (13.77)		49 (11.84)	200 (14.55)	
GA randomization (w)[b]	19.6 (0.13)	19.6 (0.13)	0.891	14.5 (0.05)	21.1 (0.09)	x
GA at delivery (w)[b]	37.0 (0.11)	36.9 (0.13)	0.366	36.7 (0.19)	37.0 (0.10)	0.112
Risk Group IDDM *n (%)*	226 (25.03)	224 (25.28)	0.992	160 (38.65)	290 (21.09)	<0.001
HTN	376 (41.64)	368 (41.53)		136 (32.85)	608 (44.22)	
PrePreE	301 (33.33)	294 (33.18)		118 (28.50)	477 (34.69)	

Abbreviations: BMI, body mass index; CI, confidence interval; GA, gestational age; GMCI, geometric mean CI; GMean, geometric mean; HTN, chronic hypertension; IDDM, pre-existing insulin-dependent diabetes; LDA, low-dose aspirin; PrePreE, preeclampsia in a previous pregnancy. [a]GMean and GMCI. [b]Mean (s.e.).

secondary outcome variables included in the original analysis; the years of study enrollment predated the era of prophylactic 17-αhydroxyprogesterone caproate.

For this study we chose *a priori* to exclude 691 women (1404 births) with multiple gestations due both to the intrinsic high rate of PTB and possible different underlying mechanisms in this group. We also excluded 81 women missing key measures for our analysis: type of PTB (spontaneous, PROM or indicated) or maternal body mass index (BMI) (Figure 1). This secondary analysis was considered exempt by the Colorado Multiple Institutional Review Board.

PTB was defined as delivery before the completion of 37 weeks gestation. From the original trial, PTB was further categorized by PTB phenotype: iPTB related to intrauterine fetal demise, hypertension, preeclampsia, oligohydramnios, suspected intrauterine growth restriction or fetal distress (iPTB); sPTB; and PTB due to PPROM-PTB. In our analyses, we considered all PTB and each of these phenotypes separately. We also considered a group consisting of women with sPTB or PPROM-PTB combined.

Recorded adverse neonatal events included small for gestational age (GA), perinatal death and neonatal intraventricular hemorrhage.

BMI was calculated and patients placed into one of six standard BMI categories (underweight (< 18.5), normal (18.5 to 24.9), pre-obese (25 to 29.9), obese class I (30 to 34.9), obese class II (35 to 39.9) and obese class III (> 40). For analysis, BMI categories were combined if similar PTB rates were observed, resulting in four BMI groups (underweight, normal/pre-obese, obese I/II and obese III).

Statistical methods

To compare the impact of LDA administration (including GA at which randomization occurred) on the incidence of PTB, categorical measures were summarized as frequency and percentage, continuous variables were summarized with mean and s.e. and demographics were compared between groups by LDA randomization, randomization timing and PTB outcome using χ^2- and two-sample *t*-tests. For skewed measures, comparisons were made on the log-scale and back transformed for reporting as geometric mean and 95% CI. *P*-values < 0.05 were considered statistically significant; all tests were two sided. As no adjustments were made for multiple comparisons, results of this analysis should be interpreted as hypothesis generating.

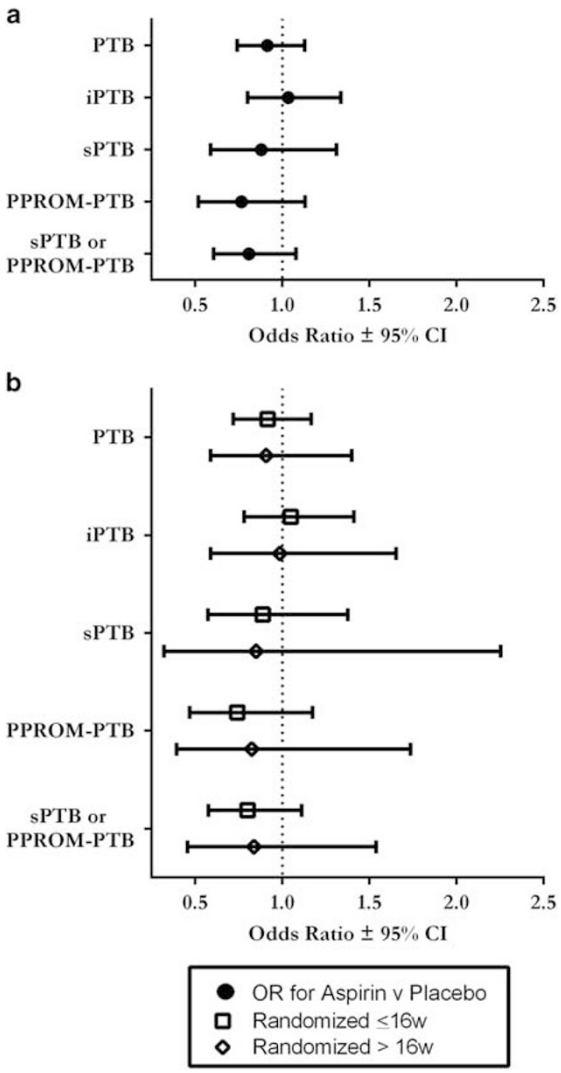

Figure 2. (**a** and **b**) ORs of PTB for LDA versus placebo from 10 logistic regression models (definition of PTB for each model outcome indicated on *y* axis), adjusted for preeclampsia risk group, history of $\geqslant 1$ miscarriage, and 4-group BMI and Black race and their interactions. (**b**) GA at randomization as an effect modifier for LDA.

Rates of each the PTB phenotypes (all PTB, iPTB, sPTB, PPROM-PTB, sPTB and PPROM-PTB combined) were summarized and compared between groups randomized to LDA and placebo. To estimate the adjusted OR of PTB for women randomized to LDA versus placebo, five multivariable logistic regression models (one for each PTB outcome) were estimated with covariates including the following: nulliparity, 1 or more previous miscarriage, maternal age, BMI category, risk group (IDDM, HTN and PrePreE) and race (Black vs otherwise). Potential covariates were excluded if not significant in any model; a covariate significant in at least one model was included in all models.

In a secondary analysis, timing of randomization ($\leqslant$16 weeks vs later than 16 weeks GA) was assessed as an effect modifier of the relationship between LDA and PTB. Sixteen weeks was chosen, as other studies have suggested this to be an important determinant of LDA's benefit.[9] In sensitivity analysis, women with medically indicated preterm deliveries were excluded from analyses and sPTB, PPROM-PTB and combined sPTB/PPROM-PTB endpoints were reanalyzed on the subset of nonmedical iPTBs. Rates of protocol compliance and neonate adverse events were compared by LDA randomization.

Code availability

All analyses were performed in SAS 9.4 (SAS Institute, Cary, NC, USA). Code for the creation of any derived variables, or for statistical methods employed to generate results, will be available on email request to the corresponding author.

RESULTS

The racial and ethnic distribution of the 1789 patients that satisfied the inclusion criteria for this study was 59% Black, 32% White, 7% Hispanic and 0.5% other races or ethnicities. Randomization to LDA or placebo occurred at 19.6 ± 4 weeks. Risk group enrollment included 450 IDDM, 744 HTN and 595 PrePreE. The overall rate of PTB (< 37 weeks) was 30.5% (95% CI: 28.3%, 32.7%), with 11% (9.6%, 12.5%) births occurring before 34 weeks and 7.7% (6.5%, 9.1%) births occurring before 32 weeks. Among PTBs, the median GA at birth was 35 weeks (P25 to P75: 31 to 36 weeks). Phenotype of PTB included: 331 (18.5%) iPTB, 103 (5.8%) sPTB and 111(6.2%) PPROM-PTB (Figure 1). Among all women with PTB ($n = 545$), Black women (57%) appeared marginally less among iPTB (53%) than in PROM (66%) or sPTB (60%) births ($P = 0.06$).

Randomization assignment was successful in creating two groups not significantly different by basic demographics (Table 1). Demographic characteristics of women according to GA at randomization were similar; however, risk category for preeclampsia differed by randomization timing, with more women with IDDM randomized early. Similar to the parent study, 79 to 80% of women took at least 80% of pills and an additional 13 to 14% took at least 50% of pills; there were no significant differences by LDA randomization or timing of randomization. No significant difference was detected in the rate of any neonate adverse event between women randomized to LDA versus placebo.

The rates of PTB overall and by phenotype are summarized and compared by LDA randomization in Figure 2a. LDA did not significantly reduce the incidence of PTB in the overall study cohort (OR: 0.91, 95% CI: 0.74 to 1.11). When categorized by PTB phenotype, trends were noted favoring a reduction in sPTB, PPROM-PTB and the two combined, but not in iPTB. Point estimates and CIs of the unadjusted ORs of PTB associated with LDA randomization are tabulated in Table 2. The effect of LDA was not significantly altered by risk group (IDDM, HTN and PrePreE; data not shown).

In adjusted modeling, maternal age and parity were considered for inclusion in each of five logistic regression models but were not significant. Final adjusted models included the same covariates in all models, with covariates included if they were significant in at least one model. These covariates are LDA, risk group, 1 or more previous miscarriage, Black race, BMI and the interaction of Black race and BMI. LDA was forced to remain in all models.

When we assessed GA at randomization as an effect modifier of LDA, no apparent additional benefit was seen for women randomized before 16 weeks as compared with those randomized later in unadjusted (Table 2) or adjusted (Figure 2b) analyses. Parameter estimates of ORs changed by $< 5\%$ for PTB, iPTB, sPTB and sPTB or PPROM-PTB in adjusted models; however, the OR of PPROM-PTB decreased by 7% (from 0.79 to 0.74) in the adjusted model overall and by 9% (from 0.89 to 0.81) among patients randomized at or before 16 weeks.

Results were similar to the unadjusted results and not significantly different in sensitivity analysis when sPTB, PPROM-PTB and sPTB/PPROM-PTB combined models were re-estimated on the subgroup excluding iPTB from the denominator (data not shown).

Table 2. Unadjusted PTB ORs by treatment randomization and randomization timing

Description	*LDA*	*Placebo*	P-*value*	*OR (95% CI)*
Whole cohort	*N* = 903 (%)	*N* = 886 (%)		
PTB	266 (29.46)	279 (31.49)	0.356	0.909 (0.743, 1.111)
iPTB	167 (18.49)	164 (18.51)	>0.99	0.999 (0.787, 1.268)
sPTB	49 (5.43)	54 (6.09)	0.612	0.884 (0.594, 1.317)
PPROM-PTB	50 (5.54)	61 (6.88)	0.241	0.793 (0.539, 1.166)
sPTB or PPROM-PTB	99 (10.96)	115 (12.98)	0.191	0.826 (0.620, 1.099)
Randomized ≤16 weeks	*N* = 211	*N* = 203		
PTB	64 (30.33)	68 (33.50)	0.527	0.864 (0.572, 1.307)
iPTB	41 (19.43)	43 (21.18)	0.714	0.897 (0.556, 1.449)
sPTB	8 (3.79)	9 (4.43)	0.808	0.849 (0.321, 2.246)
PPROM-PTB	15 (7.11)	16 (7.88)	0.853	0.894 (0.430, 1.860)
sPTB or PPROM-PTB	23 (10.90)	25 (12.32)	0.759	0.871 (0.477, 1.591)
Randomized >16 weeks	*N* = 692	*N* = 683		
PTB	202 (29.19)	211 (30.89)	0.518	0.922 (0.732, 1.161)
iPTB	126 (18.21)	121 (17.72)	0.833	1.034 (0.785, 1.362)
sPTB	41 (5.92)	45 (6.59)	0.657	0.893 (0.577, 1.382)
PPROM-PTB	35 (5.06)	45 (6.59)	0.250	0.755 (0.479, 1.190)
sPTB or PPROM-PTB	76 (10.98)	90 (13.18)	0.216	0.813 (0.587, 1.126)

Abbreviations: CI, confidence interval; iPTB, indicated PTB; OR, odds ratio; PPROM-PTB, preterm premature rupture of membrane; PTB, preterm birth; sPTB, spontaneous PTB. *P*-value from an exact Pearson's χ^2-test.

Table 3. Summary of risk reduction associated with LDA administration

Study	*Year*	*RR preeclampsia*	*RR (95% CI) PTB*
Cochrane Review[23]	2010	0.83	0.92 (0.88–0.97)
USPSTF[4]	2014	0.76	0.86 (0.76–0.98)
Coomarasamy[6]	2003	0.86	0.86 (0.79–0.94)
Askie[a,5]	2007	0.90	0.90[b] (0.83–0.98)

Abbreviations: CI, confidence interval; LDA, low-dose aspirin; PTB, preterm birth; RR, relative risk; USPSTF, United States Preventive Services Task Force. [a]LDA alone vs placebo in 27/31 trials. [b]PTB before 34 weeks.

DISCUSSION

We observed consistent trends in the reduction of PTB, especially for sPTB and/or PPROM-PTB, in women at high risk for preeclampsia and other pregnancy complications treated with LDA as compared with placebo. Although our results did not reach statistical significance, we believe that taken in the context of other trials,[7] meta-analyses[5,6] and systematic reviews,[4] our findings gain plausibility and add credence to the concept that LDA is worthy of investigation as a PTB prevention strategy. Further studies should be designed with adequate power to detect clinically meaningful reductions in PTB.

The United States Preventive Services Task Force recommends that LDA be administered to women at high risk for preeclampsia,[4] and PTB prevention is one of three listed rationale, with a number needed to treat of 65. The United States Preventive Services Task Force criteria for LDA administration are much more liberal than those specified by the American College of Obstetrics and Gynecology Hypertension in Pregnancy monograph.[10] Understanding the effect of LDA on both PTB (including PTB phenotype) and preeclampsia will be critical to help clinicians decide which recommendations to follow.

The trend in PTB reduction we observed was only present for sPTB and PPROM-PTB. In our analyses, we considered these two phenotypes individually and also grouped together as they may be different manifestations of common underlying processes.[11] Perhaps surprisingly, LDA did not appear to affect the occurrence of iPTB in this trial. As most LDA research has focused on the potential of LDA to improve placental function, one might have speculated that reductions in PTB would most strongly affect iPTB. Although caution is necessary in this interpretation, as a β-error is possible and the clear distinction of PTB phenotypes has recently been challenged to some extent,[12–14] the observed reduction in sPTB and/or PPROM-PTB is an important observation.

We also stratified our population on the basis of GA at which LDA was started based on multiple reports that LDA is more effective in preventing a variety of pregnancy complications if started early. The largest reported reduction in PTB in the literature is from a meta-analysis showing a relative risk for PTB of 0.35 if LDA is started before 16 weeks but only 0.9 if started after 16 weeks.[9] In this analysis, we found no indication that GA at LDA initiation is an important modifier of LDA's benefit. The importance of early administration of LDA to prevent preeclampsia has biologic plausibility if one assumes that LDA might improve placental invasion, a process that is largely complete by 16 weeks gestation. On the other hand, if LDA's purported effect on sPTB/PPROM-PTB is anti-prostaglandin and anti-inflammatory as discussed below, GA at onset of treatment might be less important. From a practical standpoint, pre-conceptual or early initiation of LDA is often not feasible.

Two meta-analyses[5,6] and a systematic review[4] have shown reductions in the incidence of both preeclampsia and PTB with LDA use (Table 3). Unfortunately, these studies do not report in detail on the PTB phenotype, making it difficult to determine whether reductions were obtained in iPTB, sPTB and/or PPROM-PTB. The recently published Effects of Aspirin in Gestation and Reproduction secondary analysis also reported that LDA leads to a reduction in PTB in a cohort of women with a history of pregnancy loss.[7] In this trial, reductions in sPTB were as large as or larger than reductions in iPTB, consistent with our observations. Of note, although our findings occurred in a cohort of women with a very high rate of PTB, especially iPTB, other studies in Table 3 include mixtures of both high- and low-risk women.

There are limited other data to address the PTB phenotype issue. In a secondary analysis of the Hauth Low-Risk Aspirin trial, a biologic effect of LDA, as measured by a 50% or greater reduction in thromboxane A_2, was associated with not only a significant reduction in overall PTB (relative risk: 0.53, $P = 0.032$) but also a reduction in PPROM-PTB (relative risk: 0.22, $P = 0.046$) and a trend in the reduction of sPTB.[15] Although only a single report, these data lend credence to the concept that LDA might reduce PTB via multiple mechanisms.

The fact that aspirin can delay the onset of labor has been known for over 40 years, although this original report was related to aspirin in very high doses.[16] The presumed mechanism for the delay in labor was the anti-prostaglandin effect of aspirin. Inflammation in general and prostaglandins in particular are now well understood to be of central importance in the initiation of labor, both term and preterm.[17–19] Other anti-prostaglandin medications, most notably indomethacin, have been shown to effectively reduce the incidence of PTB in patients presenting with spontaneous preterm labor,[20] although safety concerns have limited their widespread use.[21] In contrast, LDA has a very favorable safety profile.[4] 17-Hydroxyprogesterone caproate, the most effective prematurity prevention tool currently at our disposal, is generally thought to mediate at least part of its effect as an anti-inflammatory.[22] Hence, the fact that LDA as an anti-prostaglandin, anti-inflammatory might shift the onset of parturition later in time has good biological plausibility. Comparisons with 17-hydroxyprogesterone caproate -C are premature, but it can be noted that costs and ease of administration would strongly favor LDA.

The strengths of this study are the prospective data collection that occurred at the time of the original trial by trained research nurses. PTB was a pre-specified secondary outcome of the original trial. PTB phenotype was carefully defined, unlike most other preeclampsia prevention trials, and was contemporaneously collected at delivery. The cohort is large and diverse, allowing generalizability of our findings. Our findings reinforce existing information on the ability of LDA to reduce PTB in women at high risk for preeclampsia and also remarkably extend these data by providing detailed, prospectively collected information on PTB phenotype. Together with the Effects of Aspirin in Gestation and Reproduction data, there is reason to hypothesize that LDA might benefit both high-risk and low-risk women.

Weaknesses of our study are the secondary nature of the analysis and a sample size too small for observed trends in sPTB and/or PPROM-PTB to be statistically significant. For example, our observed 17% reduction in the unadjusted rate of sPTB and/or PPROM-PTB between LDA and placebo randomized women would require similar results in a sample of 4152 in each group, for statistical significance to be achieved with a χ^2-test. Although requiring a large study to confirm, such a reduction in PTB would yield enormous public health benefits. Black women are significantly overrepresented in this cohort related to the centers participating in the Maternal-Fetal Medicine Units. As always, secondary analyses such as these should be viewed as hypothesis generating.

Although it remains a possibility that our conclusion is a true negative finding in which we have correctly failed to reject the null hypothesis of no effect of LDA on PTB, we believe that combined with other trials, ample data now exist to motivate a large randomized controlled trial. The population in this study comprises women with elevated preeclampsia risk, elevated PTB rate and proportionately more women of Black race. Given the enormous adverse public health burden of PTB, even a modest reduction in its incidence would be very important.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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