Risk Factors for Low Birth Weight and Preterm Delivery in the PROMISE Trial

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ABSTRACT

Background: Although antiretroviral therapy (ART) in pregnancy can reduce vertical HIV transmission to <1%, it may also increase the risk of low birth weight (<2500 g), LBW, and preterm delivery (<37 weeks, PTD), conditions that confer significant morbidity and mortality to newborns in resource-limited settings. In the multi-site PROMISE trial, we previously reported an increased risk of LBW and PTD among women initiating (PI)-based ART during pregnancy, when compared to ZDV alone. We further describe obstetrical and clinical risk factors for LBW and PTD in our study population.

Methods and Materials: Within the antepartum component of PROMISE, we assessed baseline clinical and obstetrical risk factors associated with LBW and PTD. Risk factors with a p-value <0.15 in univariate analysis were included in multivariable backward logistic regression models. We also adjusted for treatment arm, gestational age (GA) at entry, and country.

Results: Birth outcomes were available for 3425 HIV infected women delivering between 4/2011-11/2014 across 14 sites in Africa and Asia. Among the 3333 women delivering at least one live born infant, median maternal age at enrollment was 26 years (IQR 22-35) and 110 (3.3%) reported to be less than 18 years of age. Median birth weight was 2900g (IQR 2600-3200), and 558 (17%) infants weighed <2500g. Median GA at birth was 39 weeks (IQR 38-40). 557 (17%, 95%CI: 16.1%-18.9%) were born before 37 weeks. In univariate analyses, clinical factors including maternal age, year and entry RNA ≥200,000 copies were significant for PTD but not LBW. Obstetrical risk factors such as maternal age, entry GA, or obstetrical risk factors for LBW and/or PTD included BMI, multiple gestation, prior PTD, pregnancy or chronic hypertension, oligohydramnios, placental abruption, urinary tract infection, preterm labor, and maternal BMI at entry. Clinical factors were entered into multivariable logistic regression analyses with backward selection.

Conclusion: Besides receipt of antenatal PI-based ART, a number of obstetrical risk factors contributed to LBW and PTD for HIV-infected pregnant women in PROMISE. Along with optimization of ART regimens, public health interventions are needed to address modifiable obstetrical risk factors, including education of pregnant women and clinicians on early warning signs and management of pregnancy-associated complications.

BACKGROUND

- PMTCT (Prevention of Mother to Child Transmission of HIV) is a major component in the global struggle against HIV/AIDS with ARV prophylaxis being one of the major components.
- The effectiveness and efficacy of maternal antiretroviral therapy (ART) given for PMTCT has been shown in several studies; and can reduce transmission to <1%.
- Maternal ART may also increase the risk of low birth weight (<2500 g), LBW, and preterm delivery (<37 weeks, PTD), conditions that confer significant morbidity and mortality to newborns.
- Several studies done in developed and developing countries showed evidence of adverse outcomes in HIV pregnant women on ART including LBW, PTD, HIV birth, and associated maternal neonatal death.
- We previously reported an increased risk of LBW and PTD among women initiating protease inhibitor (PI)-based ART during pregnancy, when compared to ZDV alone in the PROMISE trial.

METHODS

The PROMISE 1077BF and 1077F trials were multi-center studies conducted at 14 sites in seven countries: India, Malawi, South Africa, Tanzania, Uganda, Zambia, and Zimbabwe.

Pregnant women enrolled into the antepartum component of PROMISE were randomized to receive one of the three regimens:

- Arm A: ZDV + NVP at delivery + tenofovir (TDF)cocktail
- Arm B: ZDV/lamivudine (3TC) + lopinavir/ritonavir (LPVr)
- Arm C: TDF/FTC + LPVr

This secondary analyses study the potential risk factors for LBW (<2500g) and PTD (<37wks gestation). Women with these outcomes were compared with those who had term infants and those who had infants with normal birth weight.

Potential risk factors consisted of baseline clinical and demographic factors, along with maternal obstetrical risk factors identified throughout the pregnancy. Treatment was also included as a predictor in the analyses. Risk factors with a p-value <0.15 in univariate analysis were entered into multivariable logistic regression analyses with backward selection.

RESULTS

Birth outcomes were available for 3425 HIV infected women delivering between 4/2011-11/2014 across 14 sites in Africa and Asia. 90 women had either stillbirths or spontaneous abortions and not included in the analyses presented below. Among the 3333 women delivering at least one live born infant, median maternal age at enrollment was 26 years (IQR 22–38).

Maternal HIV RNA at baseline by MI pair outcomes (PTD and LBW)

Maternal age by MI pair outcomes (PTD and LBW)

Risk factors significant in the univariate analysis:

- Maternal clinical, baseline and demographic factors including: study treatment, country, age, BMI, baseline RNA and CD4, multiple gestation, # of prior prematures births, history of alcohol use, chronic hypertension

- Obstetrical factors, including:
  - Gestational age at study entry, UTI, pregnancy induced hypertension, oligohydramnios, intravenous growth restriction, abrupt placenta, prematurity labor, premature rupture of membranes, vaginal bleeding

- The following univariate results were specific to one outcome:
  - Maternal age and baseline RNA were significant risk factors for PTD, but not LBW
  - Oligohydramnios and vaginal bleeding were significant risk factors for LBW, but not PTD
  - Baseline adherence to ART C and UTI were marginally significant risk factors for PTD, but not LBW

Table 1: Multivariate Analyses Results for Obstetrical Complications and Clinical Factors Associated with Preterm Delivery (<37 weeks). Reference category

Table 2: Multivariate Analyses Results for Obstetrical Complications and Clinical Factors Associated with Low Birth Weight (<2500 gram). Reference category

CONCLUSION

We identified a variety of obstetrical and clinical risk factors related to LBW and/or PTD among PROMISE HIV + women in the multivariable analyses, including:

- Several common complications of pregnancy: Pregnancy-induced hypertension, chronic hypertension, intravenous growth restriction, abrupt placenta, oligohydramnios, prematurity labor, premature rupture of membranes and vaginal bleeding (PTD only).
- Other clinical risk factors: Maternal BMI at entry, multiple gestation, # of prior prematures births, maternal age (PTD only) and baseline RNA (PTD only).
- Maternal age and baseline RNA were significant risk factors for PTD, but not LBW from the univariate analysis.

ART (Triple Antiretroviral regimen) was also associated with elevated risk for LBW and PTD, compared to antiretroviral zidovudine alone.

Potential obstetrical risk factors will be carefully evaluated as part of comprehensive antenatal care for HIV-infected women.

Pregnant clients need education about early warning signs of adverse pregnancy so they can seek immediate medical care.

DISCUSSION

Strengths

Data from randomized clinical trial. Large sample size representing multiple international sites. Limitations

Some potential obstetrical risk factors were too rare for inclusion in the multivariate analysis.

Our findings on risk factors for LBW and PTD may or may not be generalizable to settings other than those included in PROMISE study.

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