CS 5020 :Low Dose Aspirin for Prevention of Preterm Birth In Women Living With HIV

Proposing Investigators

- Protocol Chair: Adriana Weinberg, MD
- Protocol Vice-Chairs: Benjamin H. Chi, MD
  Jeffrey A.S. Stringer, MD
  International TBD
- Statistician: Camlin Tierney, PhD
- Team Members: Mark J. Abzug, MD; Lynda Stranix-Chibanda, MBChB, MMED; Geraldo Duarte, MD, PhD; Dwight J. Rouse, MD, MSPH; Matthew K. Hoffman, MD, MPH; Linda Aurpibul, MD, MPH; and Marisa M. Mussi-Pinhata, MD, DSc.

Rationale

- Preterm birth (PTB) is the most important cause of neonatal morbidity and mortality in the general population.
- PTB has increased incidence in pregnancies complicated by HIV infection.
- PTB is associated with increased inflammation during pregnancy.
  - Similar associations were shown for intrauterine growth restriction (IUGR) and preeclampsia.
- Aspirin (ASA) has anti-inflammatory and other immune suppressive properties and inhibits platelet aggregation, which makes low dose aspirin (LDA) an excellent candidate to prevent adverse pregnancy outcomes associated with inflammation.
- **LDA may be particularly successful in preventing PTB in women with HIV due to the increased inflammation and immune activation characteristic of HIV infection.**

Prior experience with LDA in pregnancy

- **LDA at 60 to 150 mg ASA has been safe for mothers and infants (multiple studies with >22,000 mother-infant pairs including ≥4721 mother-infant pairs on 150 mg ASA qd).**
- LDA initiated in early pregnancy effectively prevents preeclampsia, which is the basis for the current ACOG recommendation to use LDA in high risk pregnancies beginning at 6 $^{0}/_{7}$ and 15 $^{6}/_{7}$ weeks gestation through 36 $^{0}/_{7}$ weeks.
- Small studies and metanalyses indicate that LDA may prevent PTB.
  - ASPIRIN, a study of LDA prevention of PTB in ~12,000 pregnant women, has been recently completed and is currently under analysis.
- Small studies and metanalyses indicate that LDA may also prevent IUGR, but not early pregnancy loss.

Primary objectives

- To evaluate the effect of LDA administered to women with HIV beginning between $6\,^{0}/_{7}$ and $15\,^{6}/_{7}$ weeks of gestation and continuing through $37\,^{0}/_{7}$ weeks on the probability of successful pregnancy outcome, defined as a live infant delivered at ≥37 weeks gestation.
- To evaluate the safety of LDA administered to women with HIV during pregnancy in mothers and newborns.

Secondary objectives

- To evaluate the effect of LDA on the risk of the following pregnancy outcomes:
  - Preterm birth (<37 weeks) from any cause among pregnancies with a viable fetus at ≥ 20 weeks gestation (matches the ASPIRIN primary analysis population).
  - Spontaneous abortion, defined as pregnancy loss prior to 20 weeks gestation
  - Stillbirth, defined as fetal death at ≥20 weeks
  - Spontaneous preterm birth (<37 weeks) including those prior to 20 weeks gestation
  - Iatrogenic preterm birth (<37 weeks GA) including those prior to 20 weeks gestation
  - Small-for-gestational age (SGA) defined as newborn weight-for-age at birth <10^{th} centile in a fetus surviving to at least 24 weeks
  - Eclampsia, preeclampsia, or severe gestational hypertension
  - Neonatal mortality, defined as death of a liveborn fetus within the first 28 days of life.
- **To evaluate the effect of LDA on plasma levels of sIL2Ra, PGF2a, 5-HEPE, PlGF and sEng.**
- **To assess the association between LDA adherence and successful pregnancy outcome among women randomized to the LDA arm.**

Hypotheses

- LDA administered to women with HIV beginning between 6 $^{0}/_{7}$ and 15 $^{6}/_{7}$ weeks of gestation and continuing through 37 $^{0}/_{7}$ weeks will increase the probability of a successful pregnancy outcome.
- LDA administration to women with HIV is safe for mothers and fetuses/newborns.

Schema

- **Design**: double-blind, placebo-controlled, randomized 1:1.
  - Randomization stratified by use of PI or not.
- **Population**: women with HIV, ≥18 years of age, with singleton pregnancy between $6\ ^{0}/_{7}$ and $15\ ^{6}/_{7}$ weeks (documented by fetal US), on ART.
- **Intervention**: 150 mg ASA or placebo per day from entry to 37 weeks gestation.
- **Duration**: up to 44 weeks.
- **Sample size**: 906/arm for 80% power or 1212/arm for 90% power.

Sample size estimation

- Primary outcome measure is successful pregnancy outcome defined as live birth at ≥37 weeks gestation.
- Considerations and assumptions:
  - ASPIRIN primary analysis population was PTB with live fetus at 20 weeks gestation and assumed 20% decrease in PTB from 8% with placebo to 6.4% with 81 mg ASA per day.
  - ASPRE showed 62% decrease in PTB due to preeclampsia from 4.3% with placebo to 1.6% with 150 mg ASA per day.
  - Current rate of PTB in women with HIV is ~16% and early pregnancy losses ~4%, which translates into 80% successful outcomes in the placebo group.
  - LDA will decrease PTB by ~30%, but it is not expected to affect early pregnancy losses, which translates into 85% probability of successful outcome in the LDA group.
- **An increase of 5 percentage points in successful pregnancy outcomes in women with HIV justifies a change in policy.**
  - 906 participants/arm are needed for 80% power; and 1212 for 90%

Key features of the schedule of evaluations

- Monthly visits during pregnancy alternating between physical and phone visits; delivery (+≤14 days) physical visit; and 6±2 weeks phone visit .
- Adverse events and adherence information are collected at each visit.
- Medication is dispensed at physical visits as appropriate.
- CBC; AST and ALT; and creatinine levels at entry to fulfill exclusion criteria.
- Maternal CD4 and plasma HIV RNA at entry and 34±2 weeks gestation.
- Neonatal plasma HIV DNA/RNA at delivery (+≤14 days).
- Plasma stored for PGF2a, 5-HEPE, sIL2Ra, PlGF, sEng and ASA levels at entry, 4 weeks after treatment initiation and 34±2 weeks gestation.

Significance and innovation

- An intervention that increases the number of successful pregnancy outcomes in women with HIV will have a great impact on infant morbidity and mortality and other beneficial long term effects on child development.
- May decrease the financial burden on public health.
- Examine for the first time the impact of LDA on plasma factors that are likely to be mechanistically associated with PTB.
- Examine for the first time the relationship between adherence to LDA, measured by self report and drug levels, with therapeutic success.

Questions and comments?