Protease Inhibitors and Adverse Birth Outcomes: Is Progesterone the Missing Piece to the Puzzle?

Kathleen M. Powis1,2 and Roger L. Shapiro2,3

1Departments of Internal Medicine and Pediatrics, Massachusetts General Hospital, 2Department of Immunology and Infectious Diseases, Harvard School of Public Health, and 3Division of Infectious Diseases, Beth Israel Deaconess Medical Center, Boston, Massachusetts

(See the major article by Papp et al on pages 10–8.)

Keywords. HIV; protease inhibitors; progesterone; pregnancy outcomes.

The ability to prevent mother-to-child transmission (MTCT) of human immunodeficiency virus (HIV) with combination antiretroviral (ARV) treatment or prophylaxis represents one of the greatest success stories of the HIV epidemic [1–6]. Virtually all national and international guidelines now call for maternal combination ARV prophylaxis or antiretroviral treatment (ART) during pregnancy [7–10], and MTCT has been nearly eliminated in regions of the world where women have access to ART in pregnancy. But has this success come with a cost? In addition to our ongoing efforts to treat women and protect children, we need to understand the consequences of using 3 potent medications throughout pregnancy and to explore mechanisms for making ART use in pregnancy safer for women and children.

At least a decade of studies have alerted the medical and public health communities to associations between ART and adverse birth outcomes, including pre eclampsia, stillbirth, preterm delivery, small-for-gestational-age births, and lower birth weight [11–22]. Protease inhibitors (PIs), which remain a mainstay for ART among pregnant women in the developed world, are the most common specific class of ARVs associated with preterm delivery [17–22], and low birth weight (or small for gestational age) may be common to all ART regimens [12–15, 17]. Particularly among women on ART from conception, more severe events, such as stillbirths, have been reported at 2–3 times that for women receiving monotherapy or dual ARV prophylaxis [12, 17]. Is there a unifying mechanism for these adverse outcomes? Unfortunately, few studies have explored possible mechanisms beyond those suggested by basic epidemiologic findings. While we have known since the pre-ART era that adverse birth outcomes are associated with maternal HIV infection alone [23–26], more-recent associations with ART appear independent of CD4+ T-cell count [12, 17–19] and suggest a complex picture with more than one pathway to these adverse events. Fiore et al demonstrated that ART in pregnancy shifts the normal T-helper type 2 (Th2) cytokine–predominant environment, permissive to the fetal allograft, to a Th1 cytokine–predominant environment, with increased levels of interleukin 2, a cytokine associated with preterm delivery in pregnancy [27]. In a study of stillbirths in Botswana, placental examination demonstrated a surprisingly high amount of chronic placental insufficiency among women receiving ART in pregnancy, compared with HIV-infected women not receiving ART [28]. Other studies have found possible associations between preeclampsia and ART [11, 29] and between preeclampsia and baseline HIV RNA level prior to starting ART [30], suggesting a relationship between ART and this immune-mediated complication of pregnancy [31–33]. Thus, it appears that ART may reduce some adverse birth outcomes by improving the overall health of pregnant women, while possibly increasing the risk for adverse outcomes that may be related to direct placental damage or immune-mediated fetal allograft intolerance. The complexity of these associations may explain why the scientific community has been slow to agree on the basic epidemiologic findings associating ART with adverse birth outcomes and why few mechanistic studies have been performed to date.

In this issue of the Journal, Papp et al present an elegant and important study investigating the association between antiretrovirals in pregnancy, alterations in progesterone levels, and adverse birth outcomes [34]. To evaluate the effect of ART on progesterone production in late pregnancy, the authors performed 3 separate experiments: (1) an in vitro study, in
which a third-trimester cytotrophoblast cell-line capable of sex steroid production was exposed to ARVs; (2) study of mouse models to evaluate pregnancy outcomes with different ART exposures and with progesterone administration; and (3) a comparison of progesterone levels in the third trimester among HIV-infected women receiving ART with those of HIV-uninfected women. In vivo, 3 PIs (atazanavir, lopinavir, and ritonavir) were associated with significantly lower release of progesterone from trophoblast cells, whereas 1 PI (darunavir) and ARVs from the nucleoside reverse transcriptase inhibitor (NRTI) class and the non-NRTI class were not. Similarly, trophoblast cells treated with the combination of a dual NRTI backbone and ritonavir-boosted lopinavir or atazanavir were found to release significantly lower levels of progesterone, compared with controls. In vivo studies demonstrated that pregnant mice treated with ritonavir-boosted lopinavir with a dual NRTI backbone experienced significantly higher prevalence of fetal resorption, lower fetal viability, and lower mean fetal and placental weights, compared with controls, a finding that was not observed when pregnant mice were treated with the combination of zidovudine and lamivudine. Plasma progesterone levels in the PI-treated mice were significantly lower than those in controls and correlated with fetal weight. Progesterone supplementation of PI-treated mice was partially protective against fetal growth restriction. Finally, among a small group of HIV-infected and HIV-uninfected women, significantly lower mean progesterone levels early in the third trimester of pregnancy were noted among HIV-infected women receiving a PI-based triple ART regimen, and the progesterone level was correlated with birth weight percentile.

This combination of experiments suggests that progesterone may, at least in part, mediate the relationship between PIs and fetal growth restriction. The placenta produces progesterone after about 12 weeks of pregnancy, and levels that maintain a healthy pregnancy as women approach term are more than 10–20 times greater than those following ovulation [35]. Low progesterone levels or decreased progesterone-induced blocking factor (PIBF), a protein produced by peripheral lymphocytes during pregnancy in the presence of progesterone, have been associated with several adverse pregnancy outcomes, including preterm birth [36], lower birth weight [37], and miscarriages [38], and progesterone supplementation has been shown to reduce the incidence of preterm delivery among high-risk women [39, 40]. Thus, low progesterone is a biologically plausible pathway by which PIs may lead to adverse birth outcomes. One of the most exciting possibilities in this research is the demonstration, through an animal model, that progesterone supplementation partially overcomes poor fetal growth observed in the pregnancies of mice treated with a PI-based ART regimen. Given the safety of intravaginal progesterone and its current use to prevent some adverse pregnancy outcomes, a clinical trial involving women receiving PI-containing ART should be considered in the near future. An additional finding of great interest is the difference between the effect of darunavir and other PIs on progesterone release from trophoblasts; as darunavir use in pregnancy increases, epidemiologic data for this agent will be welcome.

The study has a few limitations. Of importance, none of the experiments were able to assess whether low progesterone levels may explain the most specific concern for PIs, which is preterm delivery. The small number of outcomes in the study of pregnant women was underpowered to identify an ART effect (or a PI-specific effect) on preterm deliveries, and the in vivo mouse experiments were not designed to assess preterm delivery. Lacking data for this outcome, it is difficult to determine whether a low progesterone level is a final common pathway for several adverse outcomes (including preterm delivery and possibly stillbirths) or whether it is specific to fetal growth restriction. More generally, questions remain regarding whether PIs exert a specific effect on trophoblasts (as the in vitro experiment would suggest) or whether all ART can cause placental damage in some women that is mediated by immunologic intolerance of the fetal allograft (as might be expected if ART leads to a Th1 cytokine-dominated environment) [27]. Because progesterone helps to maintain an environment favoring Th2 cytokines in pregnancy [38], both mechanisms may be at work, as well as interconnected. Gaining a better understanding of the exact mechanism of placental damage has important implications for choosing ART regimens in pregnancy and for potential strategies (including the possibility of using intravaginal progesterone) to promote healthier pregnancies among women receiving ART.

In sum, Papp et al have provided an excellent model for the type of mechanistic research that is urgently needed with the global scale-up of ART use in pregnancy. As we reduce MTCT to low levels everywhere, the overarching goal to optimize pregnancy outcomes and protect infant health and development remains paramount. At present, we do not know whether specific ART regimens may offer safer pregnancy outcomes or whether interventions such as progesterone supplementation might be beneficial for women receiving either PI-based or non-PI-based ART. The research agenda will not be complete until a full understanding of the safety of the ARVs recommended for use during pregnancy has been explored. HIV-infected women should be able to enjoy a healthy pregnancy, and their children should have health outcomes comparable to those of all other children. The work of Papp et al brings us one step closer to that goal.

Notes
Financial support. This work was supported by the National Institute of Child Health and Human Development (1K23HD070774-01A1 to K. M. P.).
Potential conflicts of interest. Both authors: No reported conflicts.
Both authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.
References

