Timing of initiation of antiretroviral therapy and adverse pregnancy outcomes: a systematic review and meta-analysis


Summary

Background Although lifelong combination antiretroviral therapy (ART) is recommended for all individuals with HIV, few data exist for pregnancy outcomes associated with ART initiation before conception. We assessed adverse pregnancy outcomes associated with ART initiated before conception compared with that of ART started after conception.

Methods We did a systematic review of studies from low-income, middle-income, and high-income countries by searching the Cochrane Central Register of Controlled Trials, Embase, LILACS, MEDLINE, Toxline, Web of Knowledge, and WHO Global Index Medicus and trials in progress (International Clinical Trials Registry Platform) for randomised trials, quasi-randomised trials, and prospective cohort studies done between Jan 1, 1980, and June 1, 2016, in which timing of ART initiation in pregnant women living with HIV was reported. We used the risk ratio (RR) and corresponding 95% CIs as the primary measure to assess the association between the selected outcomes and ART initiation before conception versus after conception. We used a random-effects model to pool risk ratios.

Findings We included 11 studies with 19 189 mother–infant pairs. Women who started ART before conception were significantly more likely to deliver preterm (pooled RR 1·20, 95% CI 1·04–1·44) or very preterm (1·53, 1·22–1·92), or to have low-birthweight infants (1·30, 1·04–1·62) than were those who began ART after conception. Few data exist for neonatal mortality. The risk of very low birthweight, small for gestational age, severe small for gestational age, stillbirth, and congenital anomalies did not differ significantly between women who were taking ART before conception and those who began ART after conception.

Interpretation The benefits of ART for maternal health and prevention of perinatal transmission outweigh risks, but data for the extent and severity of these risks are scarce and of low quality. As use of ART before conception rapidly increases globally, monitoring for potential adverse pregnancy outcomes will be crucial.

Funding WHO.

Introduction

In 2013, WHO recommended that all pregnant and breastfeeding women with HIV infection should initiate combination antiretroviral therapy (ART) irrespective of clinical or immune status, and that ART be continued at least for the duration of mother-to-child transmission risk, with the option of continuing lifelong ART—an approach adopted by many low-income countries as a result of its programmatic and clinical benefits. After the results of the TEMPRANO and START trials showed that beginning ART at higher CD4 cell counts (>500 cells per μL) was associated with significant clinical benefits, in 2015, WHO recommended immediate initiation of lifelong ART for all HIV-infected individuals, including pregnant women. Thus, an increasing proportion of HIV-infected women will become pregnant while receiving ART.

ART started before conception and continued throughout pregnancy is associated with extremely low rates of mother-to-child transmission of HIV. In a report from the UK and Ireland on 5652 deliveries between 2007 and 2011, only four (0·19%) of 2105 women on ART before conception transmitted HIV to their infant. In the French Perinatal Cohort, no cases of mother-to-child transmission were noted among 2651 women who started ART before conception and had achieved viral suppression at delivery.

Lifelong ART for all HIV-infected pregnant women will not only contribute substantially to the global elimination of new paediatric HIV infections and improve maternal health and survival, but will also lead to a rapid rise in fetal exposure to antiretrovirals as pregnant and breastfeeding women started on ART have subsequent pregnancies. Despite nearly two decades of ART use during pregnancy, evidence for safety is scarce and conflicting. ART use during pregnancy has been associated with increased risk of adverse birth outcomes, such as preterm delivery and low birthweight, in reports...
Evidence before this study

We did a systematic literature review of the Cochrane Central Register of Controlled Trials, Embase, LILACS, MEDLINE, TOXLINE, Web of Knowledge, and WHO Global Index Medicus and trials in progress (International Clinical Trials Registry Platform) to identify studies published between Jan 1, 1980, and June 1, 2016, in which pregnancy outcomes in pregnant women with HIV initiating antiretroviral therapy (ART) before conception were compared with those in women beginning ART after conception. We found 11 studies including 19,189 women with HIV; 10,232 of whom started ART before conception and 8957 of whom started ART after conception. ART use during pregnancy has been associated with increased risk of adverse birth outcomes, such as preterm delivery and low birthweight, when compared with use of less complex regimens such as zidovudine prophylaxis in some studies in both low-income and high-income countries. The results of some studies have suggested that adverse pregnancy outcomes could be specifically associated with protease inhibitor use during pregnancy, but data from large studies in Botswana and Tanzania suggest such outcomes could also be linked to nevirapine-based or efavirenz-based ART. Very few data are available to allow comparison of pregnancy outcomes in women initiating ART before conception with outcomes in those beginning ART after conception. Until 2013, in low-income settings, where the largest proportion of women living with HIV are, WHO guidelines recommended use of lifelong ART during pregnancy only for pregnant women with low CD4 cell counts or advanced disease. Thus, the number of women who conceived while taking ART was low. In high-income settings, ART was recommended for all pregnant women, but until 2015, many women with high CD4 cell counts (&gt;500 cells per μL) stopped ART after delivery. In some studies, use of ART before conception was compared with use of any regimen during pregnancy, including zidovudine alone, whereas in other studies ART use before conception was combined with first trimester use, without accounting for timing of first trimester initiation.

Added value of this study

To our knowledge, ours is the first systematic review that has specifically assessed adverse pregnancy outcome risks by timing of initiation of ART (ie, before conception vs after conception). Although, reassuringly, many adverse outcomes, such as stillbirth, small for gestational age, and congenital abnormalities did not seem to differ by timing of ART initiation, we found that preterm delivery and low birthweight were significantly more likely in women who began ART before conception than in those who began ART after conception. However, data are sparse and of low to very low quality, and correlation with infant mortality or morbidity was not shown.

Implications of all available evidence

Although the clear benefits of ART for maternal health and prevention of perinatal transmission outweigh potential risks, data for the extent or severity of these risks remain few and of poor quality. We showed an increased risk of preterm delivery and low birthweight associated with pre-conception initiation of ART, but there are potential confounders, because ART was used before conception primarily by women with low CD4 cell counts who were felt to require treatment for their health. In view of new guidelines for immediate ART in all individuals with HIV, use of ART before conception can be expected to increase rapidly worldwide, and will be crucial to monitor for potential adverse pregnancy outcomes.

Methods

Inclusion criteria

We specified in advance the study background, rationale, and methods and documented them in a protocol to be published at the international prospective register of systematic reviews (PROSPERO number CRD42015025189). To be eligible for inclusion in our review, studies had to contain information about pregnancy outcomes after exposure to ART. The selection criteria we used to identify potential studies were study design (randomised trials, quasi-randomised trials, and prospective cohort studies), study population (pregnant women living with HIV and receiving ART), intervention (ART initiation before conception), comparator (ART initiation after conception), and outcomes (prematurity, defined as livebirth at &lt;37 weeks' gestation; very preterm delivery, defined as livebirth at &lt;34 weeks' gestation; low birthweight &lt;2500 g; very low birthweight &lt;1500 g; small for gestational age, defined as birthweight &lt;10th centile for gestational age; severe small for gestational age, defined as birthweight &lt;3rd centile for gestational age; stillbirth, defined as infant born with no signs of life &ge;28 weeks' gestation; maternal mortality;
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