Stillbirth rate by maternal HIV serostatus and antiretroviral use in pregnancy in South Africa: An audit

The global perinatal mortality burden is high, with over 2.6 million stillbirths annually.[1] The plurality (41%) of stillbirths occur in sub-Saharan Africa, which also has the highest HIV burden (20% prevalence) in the world.[1,2] The extent to which these two phenomena are related has not been fully characterised.

In 2003, South Africa (SA) introduced a national HIV prevention of mother-to-child transmission (PMTCT) programme,[2] and by 2017 over 90% of all pregnant SA women living with HIV (WLWH) were receiving antiretroviral therapy (ART).[3] As a result, the proportion of HIV-exposed children who acquired HIV perinatally in SA declined from 18.0% in 2010 to 2.7% by 2017.[4,5] Despite this impressive accomplishment, *in utero* and perinatal HIV transmission still occurs too frequently, and has been linked to a variety of poor fetal and neonatal outcomes, including stillbirth, preterm delivery, intrauterine growth restriction, low birthweight and mortality.[6] Although there are tremendous benefits to ART, there is also concern that combination ART (cART; use of three antiretroviral medications simultaneously) may alter fetal and placental development. Some studies suggest cART is associated with a higher risk of stillbirth, preterm delivery and low birthweight compared with prophylactic (i.e. single or dual drug) ART for PMTCT.[6-8]

To address the gap in knowledge of the effects of ART on the developing fetus, we analysed outcome data for all deliveries captured in the SA Perinatal Problem Identification Programme (PPIP) database, a quality-of-care audit system developed in 1995 to improve perinatal outcomes in SA.[9] Our analysis of PPIP data from 2008 to 2017 represents 80% of the 9 million births in SA over that 10-year period. Our objectives were to report the prevalence of stillbirths in WLWH, and explore differences in stillbirth rates based on maternal HIV serostatus and prophylactic v. combination ART.

Methods

Setting

SA national ART regimens for PMTCT have changed over time. Before 2010, single-dose nevirapine was given in labour. In 2010, dual ART, combining single-dose nevirapine and zidovudine, was introduced in labour. From 2011 to 2013, the PMTCT regimen included zidovudine from 14 weeks' gestation through delivery, and nevirapine, lamivudine and tenofovir in labour. In 2014, lifelong cART was rolled out for pregnant women, with fixed drug combinations of as first-line regimens. Currently, lifelong cART is recommended at the time of HIV diagnosis regardless of pregnancy status. We extracted ART usage in pregnant WLWH from the PPIP database. However, details on ART usage in neonates or in women after birth were unavailable.

Analysis

Stillbirth was defined as a previously viable fetus born dead at 28 or more weeks of gestation, or a birth weight of at least 500 g. We used χ^2 tests to compare demographic characteristics and pregnancy outcomes by maternal HIV serostatus and between ART regimens. The PPIP received ethical approval from the University of Pretoria in 1995, and was subsequently adopted as a nationally approved programme. The National Perinatal Morbidity and Mortality Committee granted permission to carry out this secondary analysis.

Results

Between January 2008 and December 2017, 7 454 172 deliveries were recorded in the PPIP database: 1 607 757 (22%) to WLWH, 4 321 619 (58%) to HIV-uninfected women and 1 524 796 (20%) to women with unknown HIV serostatus. Over this 10-year period, 150 682 stillbirths were recorded, which equates to a stillbirth rate (SBR) of 20/1 000 pregnancies. Among all women with a stillbirth, HIV testing increased from 68% in 2008 to 98% in 2017. Of the 150 682 stillbirths, 40 177 (26%, SBR= 25/1000) were delivered by WLWH, 94 305 (63%, SBR = 22/1 000) by HIV-uninfected women and 16 200 (11%, SBR = 11/1 000) by HIV-unknown women. The SBRs between these three groups were significantly different ($p<0.001$).

Of the 40 177 WLWH who had stillbirths, 22 954 (57%) received some form of ART during pregnancy; the proportion of WLWH with a stillbirth receiving ART rose from 11% in 2008 to 86% in 2017. The SBR was highest among WLWH not on ART (SBR = 48/100). Among WLWH on some form of ART, the percentage of stillbirths was significantly higher in those taking lifelong cART than those taking prophylactic ART (2.3% v. 1.7%, $p<0.001$).

Discussion

In this study of stillbirths over a 10-year period in SA, SBRs were similar for WLWH and HIV-uninfected women. Women with untreated HIV had the highest SBRs. Our analysis demonstrates a marked increase in HIV testing and cART use over this decade, further highlighting the success of the PMTCT programme. However, among WLWH, those receiving cART had a higher SBR than those on prophylactic ART. This was a small but significant difference.

The primary strength of our study is the large sample size, which captured 80% of 9 million births over a 10-year period in SA. The limitations of the study include a high proportion (11%) of women with unknown HIV status among whom the SBR was low; the reason for this latter finding is unclear. Our study also had no data on duration or adherence to prescribed ART regimens, and unaccounted-for changes in pregnancy care might have affected SBRs over time.

In summary, the effects of HIV and ART on the fetus and placenta are poorly understood. Future studies should include surveillance of WLWH on cART for adverse fetal outcomes, including unexplained stillbirth, preterm birth, low birthweight and other effects of fetal inflammation which may be triggered by maternal HIV infection, cART use, or both.[10,11] Future analyses should also be stratified by timing of cART initiation (pre v. post conception), and specific cART regimen.

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