The impact of HIV and ART exposure during pregnancy on fetal growth: a prospective study in a South African Cohort

HIV and ART-exposed but uninfected infants continue to be at risk of adverse birth outcomes such as stillbirth, preterm birth, low birth weight, or microcephaly. These adverse birth outcomes may increase the risk of developing metabolic, cardiovascular, and neurological disorders across the life course.

The Eastern and Southern Africa region has the highest proportion of people (20.6 million) living with human immunodeficiency virus (HIV) in the world (1). Specifically, 7.5 million adults in South Africa (SA) were living with HIV in 2021 (1). Unfortunately, girls and women of reproductive age (aged 15 to 49 years) remain the most vulnerable group to HIV infections (24.5%) compared to their counterparts (13.5%) (1). However, the expansion of HIV treatment known as antiretroviral therapy (ART) has enabled people living with HIV to live longer and healthier lives. Additionally, ART has also assisted in reducing and preventing the risk of transmitting HIV to those who are not living with HIV, including unborn children. In 2021, more than 96% of South African women who were pregnant and living with HIV had access to ART to prevent mother-to-child transmission (PMTCT), resulting in a vertical transmission rate of 3.5 % (1). Despite these satisfactory results and the benefits of ART initiation before and during pregnancy, several HIV and ART-exposed but uninfected infants continue to be at risk of adverse birth outcomes such as stillbirth (death shortly before or shortly after birth), being born too early (preterm birth), weighing less than 2500 grams at birth (low birth weight), or having a smaller-than-normal head (e.g., reduced head circumference or microcephaly) (2,3). These adverse birth outcomes may increase the risk of developing metabolic, cardiovascular, and neurological disorders across the life course (3,4). Emerging research from high-income countries (e.g., Canada) and low- and other middle-income countries (e.g., Uganda, Kenya, and Brazil) suggest that the negative effects of HIV and ART on placental and umbilical cord function and morphology (e.g., shape/structure) might be the cause of these adverse birth outcomes. (5,6). In brief, the placenta and umbilical cord transport nutrients, and the placenta also acts as a barrier that protects the fetus/unborn baby from harmful maternal toxins and infections (7,8). To achieve these functions, the placenta may change its size, shape, or efficiency to maintain appropriate fetal growth (9). To the best of our knowledge, no study has examined the mediating effects of placental morphology on the association between HIV and ART exposure, and longitudinal fetal growth parameters, thus requires further investigation.

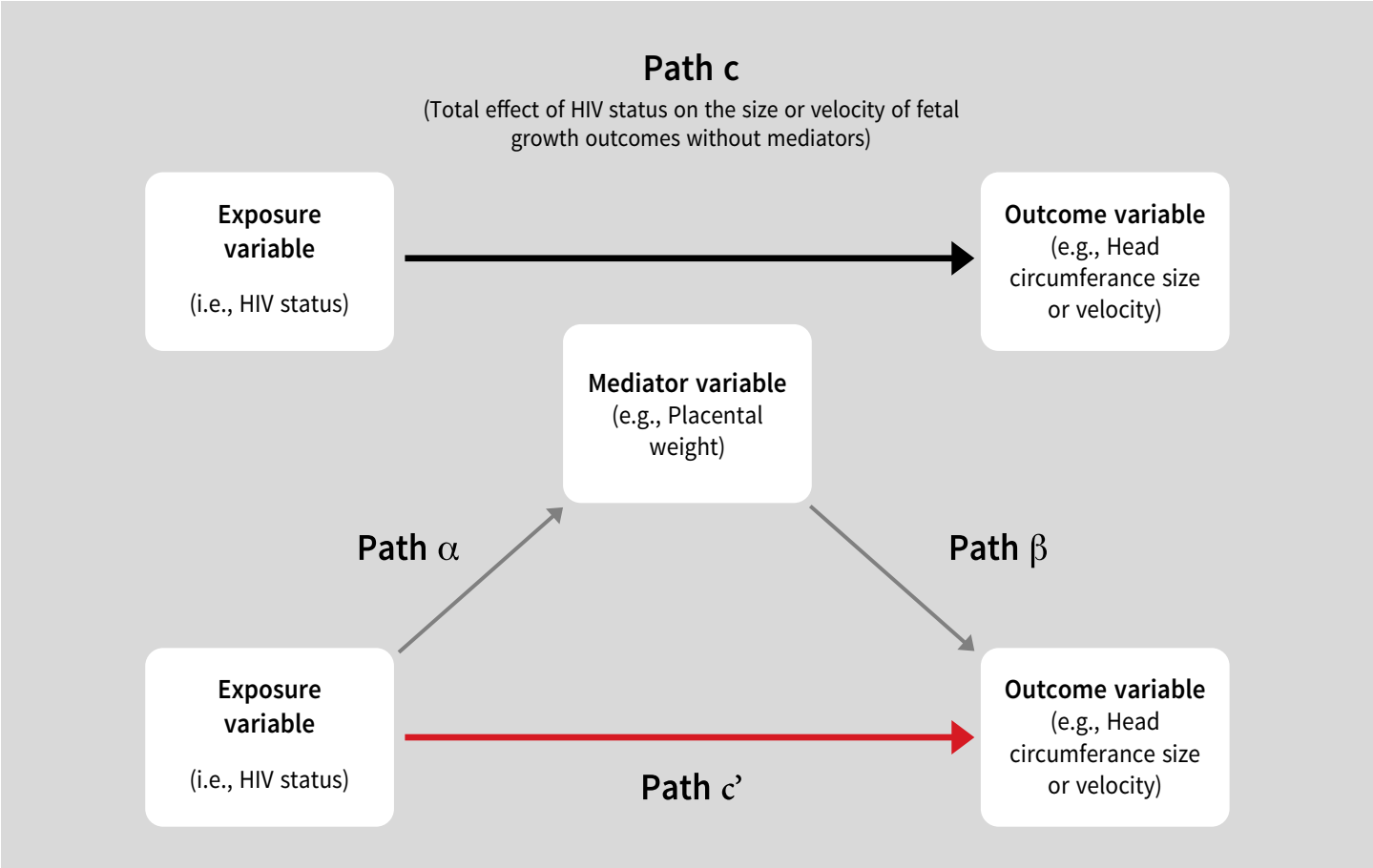

Figure 1: Represents a single SEM mediation analysis model

Methodology

To address the gaps in the literature, we conducted a prospective study and used structural equation models (SEMs) to explore the associations of HIV and its treatment on the size and the velocity of fetal growth measures, and whether these associations are mediated by placental morphology in an urban South African Cohort (Figure 1). A total of 372 pregnant women living with HIV (WLWH, n=122) and not living with HIV (SWNLWH, n=250) underwent repeated ultrasonography during pregnancy, and at delivery, to determine the size and velocity of longitudinal fetal growth parameters. For this study, fetal growth parameters refer to the size and velocity of the head and abdominal circumference, biparietal diameter, and femur length. These parameters were collected at six-time points during pregnancy (<14 weeks; 14–18 weeks; 19–23 weeks; 24–28 weeks; 29–33 weeks and 34–38 weeks), as well as at delivery. Thereafter, the Superimposition by Translation and Rotation was used to calculate the size and velocity of the fetal growth parameters. Placenta digital photographs taken at delivery were used to estimate morphometric parameters, and trimmed placental weight was measured. All WLWH were receiving an ART regimen consisting of efavirenz plus tenofovir plus emtricitabine provided as a fixed dose combination unless contraindicated according to PMTCT guidelines (10,11).

What the study found

A lower placental weight and significantly shorter umbilical cord length were reported in WLWH compared to their counterparts. After sex stratification, umbilical cord length was significantly shorter in males born to WLWH than in male fetuses born to WNLWH. In contrast, female fetuses born to WLWH had lower placental weight, birth weight, and head circumference than their counterparts. The SEM models showed an inverse association between HIV and ART and head circumference size and velocity in female fetuses. In contrast, HIV and ART exposure was positively associated with femur length growth (both size and velocity) and abdominal circumference velocity in male fetuses. None of these associations were mediated by placental morphology.

Conclusion and recommendations

In conclusion, our findings suggest that HIV and ART exposure during pregnancy in urban-dwelling Black South African women may directly impact head circumference growth in females and abdominal circumference velocity in male fetuses; but may improve femur length growth in male

fetuses only. Whether these associations are linked to adverse health outcomes across the life course, remains to be fully elucidated. Therefore, more prospective studies are needed to provide better insights into the risks and benefits of ART regimens, and the timing of ART initiation (pre-conception, early and late pregnancy), particularly in women of reproductive age in high-risk countries such as SA. This knowledge will help clinicians and policymakers in producing safer ART regimes and in formulating new guidelines that also consider fetal sex, types of ART regimens, and timing of ART initiation as important factors in determining the health status of the child. This is paramount since the current guidelines are favouring the use of dolutegravir-based regimens as first-line ART due to stronger viral suppression and higher genetic barrier to resistance compared to efavirenz-based regimens (12,13). Despite these benefits, there is limited knowledge about the effects of dolutegravir-based regimens and their associations with placental morphology, fetal growth parameters, and related developmental and functional implication across the life course, particularly in a South African population.

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Reference:

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