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Prenatal exposure to zidovudine and risk for ventricular septal defects and congenital heart defects: data from the Antiretroviral Pregnancy Registry☆

Vani Vannappagari [a,b,*], Jessica D. Albano [c], Nana Koram [d], Hugh Tilson [b], Angela E. Scheuerle [e], Melanie D. Napier [b]

[a] Epidemiology and Real World Evidence, ViiV Healthcare, Research Triangle Park, NC, United States
[b] Gillings School of Global Public Health, University of North Carolina at Chapel Hill, NC, United States
[c] INC Research, Post Approval and Strategic Services, Raleigh, NC, United States
[d] Worldwide Epidemiology, GlaxoSmithKline, Research Triangle Park, NC, United States
[e] Department of Pediatrics, University of Texas Southwestern Medical Center, Dallas, TX, United States

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ABSTRACT

Objective: To assess the risk for ventricular septal defects and congenital heart defects following zidovudine exposure during pregnancy using data from the Antiretroviral Pregnancy Registry.

Study design: Data on 16,304 prospectively reported pregnancies were analyzed to estimate the frequency and risk of ventricular septal defects and congenital heart defects, comparing exposure between zidovudine-containing regimens and non-zidovudine antiretroviral regimens. The numerator includes defect cases in outcomes at ≥20 weeks of gestational age. The denominator includes live birth outcomes. Infants with chromosomal anomalies were excluded.

Results: There were 15,451 live birth outcomes; 13,073 were prenatally exposed to zidovudine-containing regimens and 2378 to non-zidovudine containing regimens. There were 36 ventricular septal defect cases: 31 exposed to prenatal zidovudine and 5 unexposed. Nine of the zidovudine-exposed cases had earliest exposure in the first trimester; 22 had second/third trimester exposure. Of the 5 ventricular septal defect cases not exposed to zidovudine, 2 had earliest exposure to non-zidovudine antiretroviral regimens in the first trimester, and 3 had exposure in the second/third trimester. The prevalence of ventricular septal defect was 0.24% (95% confidence interval: 0.16, 0.34) for infants exposed to zidovudine-containing regimens and 0.21% (95% confidence interval: 0.07, 0.49) for non-zidovudine regimens. The relative risk comparing the 2 was 1.13 (95% confidence interval: 0.44, 2.90).

There were a total of 90 congenital heart defect cases; 78 were exposed prenatally to zidovudine-containing regimens, and 12 were unexposed. Twenty-six of the zidovudine-exposed cases had earliest exposure in the first trimester and 52 had second/third trimester exposure. Six congenital heart defect cases with non-zidovudine antiretroviral regimens had earliest exposure in the first trimester and 6 had exposure in the second/third trimester. The prevalence of congenital heart defects was 0.60% (95% confidence interval: 0.47, 0.74) for infants exposed to zidovudine-containing regimens and 0.50% (95% confidence interval: 0.26, 0.88) for non-zidovudine regimens. The relative risk comparing the 2 was 1.18 (95% confidence interval: 0.64, 2.17).

Conclusions: The prevalence and risk of ventricular septal defects and congenital heart defects among infants exposed to zidovudine-containing regimens is not significantly different from the prevalence and risk in infants exposed to non-zidovudine containing regimens.

Clinical Trial Registration: ClinicalTrials.gov identifier: NCT01137981.

Introduction

Zidovudine (ZDV), a nucleoside reverse transcriptase inhibitor (NRTI), is used in combination with other antiretroviral (ARV) drugs for the treatment of HIV infection and is also indicated for the prevention of mother-to-child transmission of HIV [1]. The US Food

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* Corresponding author at: 5 Moore Drive, Mail Stop: A.2412, PO Box 13398, Research Triangle Park, NC 27709-3398, United States. Tel.: +1 919 483 7046.
E-mail address: vani.x.vannappagari@viivhealthcare.com (V. Vannappagari).

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and Drug Administration labels it as a Pregnancy Category C drug, meaning that teratogenic effects have been observed in animal studies, but no human studies are available [1], and ZDV is to be given only if the potential benefit justifies the potential risk to the fetus. The World Health Organization guidance suggests that ZDV is well tolerated by both pregnant women and their neonates, and the recommended first-line ARV regimens for pregnant women include ZDV [2].

In published literature, there are limited data on prenatal ARV exposure and congenital anomalies. In a US prospective cohort of 2580 HIV-exposed uninfected children (SMARTT study), Williams et al. examined first trimester exposure to ARVs and found that the prevalence of congenital anomalies was 6.8% (95% confidence interval [CI]: 5.9%, 7.8%), including 55 cardiovascular congenital anomalies [3]. There was no significant association with ZDV exposure (odds ratio [OR] = 1.10; 95% CI: 0.78, 1.56) or ZDV plus lamivudine (OR = 1.19; 95% CI: 0.84, 1.69) [3]. In a US Medicaid study population of 1932 ZDV-exposed infants, Newschaffer et al. found that ZDV use was associated with an increased risk of congenital abnormalities (OR = 1.55; 95% CI: 1.01, 2.29) [4]. A second, larger study of 7573 singleton births by Tariq et al. found no significant difference in the risk of congenital anomalies when comparing highly active antiretroviral therapy (HAART) with ZDV to HAART without ZDV [5]. The French perinatal multicenter cohort study of 13,124 live births from HIV-infected pregnant women with HAART exposure reported a significant association between first trimester ZDV exposure and congenital heart defects (CHDs) with a prevalence of 2.3% (74/3267), 58% being ventricular septal defect (VSD) cases and 18% being atrial septal defects. The adjusted OR for ZDV exposure was 2.2 (95% CI: 1.3, 3.7; $P = 0.003$). The absolute risk difference attributed to ZDV was estimated at +1.2% (95% CI: +0.5, +1.9%) [6]. A more recent analysis of the same study cohort reported a similar association with first trimester ZDV for non-VSD non-atrial septal defect CHD (OR = 2.4; 95% CI: 1.0, 5.9), as well as for VSDs (OR = 2.2; 95% CI: 1.4, 3.5) [7]. Two smaller studies have also reported an association between first trimester ZDV exposure and CHD [8]. One was a 6-year study evaluating a cohort of 248 infants in Spain that found that isolated VSD was the most common CHD [9], and the second was a study of 2202 HIV-exposed children enrolled in the Pediatric AIDS Clinical Trials Group before one year of age that reported a 2 times higher risk of heart defects associated with first trimester ZDV exposure (adjusted OR = 2.04; 95% CI: 1.03, 4.05) [10]. According to data from the Texas Birth Defects Registry, the prevalence of VSD among 1999 to 2011 Texas deliveries was 0.56% (95% CI: 0.55%, 0.57%) [11].

The overall birth defect prevalence among outcomes of pregnancies with first trimester exposure to any ARV monitored by the Antiretroviral Pregnancy Registry (APR) is estimated to be 2.9% (95% CI: 2.5%, 3.3%) [12], which is similar to the birth defect prevalence of 2.72 per 100 live births reported by the Metropolitan Atlanta Congenital Defects Program (MACDP) [13]. For ZDV, sufficient numbers of first trimester exposures have been monitored by the APR to detect at least a 1.5-fold increase in risk of overall birth defects and a 2-fold increase in risk of birth defects in the more common classes of cardiovascular and genitourinary systems. The prevalence of birth defects with first trimester exposure to ZDV is estimated to be 3.2% (95% CI: 2.7%, 3.8%) [12].

The goal of this study was to assess the risk for VSD and CHD following ZDV exposure during pregnancy using APR data.

Materials and methods

Data from the APR, an international prospective pregnancy exposure registry established on January 1, 1989, to detect early signs of major teratogenic effects following exposure to ARV drugs during pregnancy, were analyzed for cases with follow-up through July 31, 2013. Registration is voluntary and confidential. Approximately 78% of case reports are from the United States and its territories; among the 66 other countries that have reported cases, 4.3% are from Brazil, 3.8% from the United Kingdom, 2.4% from Argentina, 3.2% from Uganda, 1.5% from South Africa, and 1.1% from France [12]. Each year the APR enrolls approximately 1300 pregnant women in the United States, representing approximately 15% of the HIV-infected women who give birth to live infants annually in the United States [14], and 200 pregnant women from other countries [12].

Healthcare providers register pregnant women with prenatal exposures to any ARV prior to knowing the pregnancy outcome (prospective enrollment). Patients are followed during pregnancy through healthcare providers who submit information on maternal risk factors and pregnancy outcomes. Institutional review board (IRB) approval was obtained from the Western IRB (IRB project number 20000469) for the protocol to establish the APR and the approval is renewed annually. The APR was granted a waiver for obtaining patient informed consent.

The APR defines pregnancy outcome as a spontaneous abortion (fetal loss at $<$20 weeks of gestation), still birth (fetal loss at $\geq$20 weeks of gestation), induced abortion, or live birth. The presence or absence of a birth defect is determined at the time of delivery or fetal loss or at enrollment when a defect has already been detected on a prenatal test. Ventricular septal defects and CHDs in birth outcomes prior to 20 weeks of gestation and those diagnosed in infants with a chromosomal anomaly (i.e., trisomy) were excluded due to the increased risk of other birth defects associated with such cases. In this analysis, VSD cases were separated into isolated (i.e., VSD was the only reported defect) and combined cases (i.e., VSD was reported in addition to one or more other defects of any type).

Statistical analysis

Using APR data through July 31, 2013, the rates of VSD and CHD per 100 live births were calculated for the following: (a) cases exposed to any ARV; (b) cases exposed to any regimen containing NRTIs; (c) cases exposed to any regimen excluding NRTIs; (d) cases exposed to any regimen containing ZDV; and (e) cases exposed to any regimen excluding ZDV. For regimens with and without ZDV exposure, the prevalence of VSD and CHD were estimated by trimester of earliest exposure, and corresponding 95% CI was calculated based on Clopper–Pearson exact binomial method [15,16]. Relative risks (RRs) were calculated comparing exposure groups with and without ZDV. The 95% CIs for the RRs were based on the normal asymptotic method. *P* values were based on the Fisher's exact test.

Results

Of 16,304 pregnancies, 13,437 were exposed to regimens containing ZDV in any trimester, and 2867 were exposed to regimens excluding ZDV. Pregnant women exposed to ZDV-containing regimens were younger than those exposed to non-ZDV ARV regimens. The majority of patients in both groups were black and had $CD4^+$ T-cell counts at enrollment ranging from 200 to 499 cells/μL (Table 1).

Table 2 presents the frequency of VSD and CHD cases by any ARV, NRTI, or ZDV exposure. There were a total of 15,451 live birth outcomes. Of these, 13,073 were prenatally exposed to ZDV-containing regimens, and 2378 to non-ZDV ARV regimens. There were a total of 36 VSD cases of varying subtypes, including transposition of the great vessels, double outlet right ventricle, tricuspid valve atresia, hypoplastic right ventricle, right ventricular