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Research Article

Zidovudine Exposure during Pregnancy and Hypospadias in Infants: An Analysis of Data from the Antiretroviral Pregnancy Registry, 1989-2014

Jessica D. Albano[1]*, Susan Sinclair[2], Angela E. Scheuerle[3], D. Heather Watts[4], Nana Koram[5], Conway Gee[1], Hugh Tilson[6], and Vani Vannappagari[7]

[1]*Real World & Late Phase, INC Research, Raleigh, USA*
[2]*University of North Carolina Wilmington, USA*
[3]*Department of Pediatrics, University of Texas Southwestern, USA*
[4]*Office of the Global AIDS Coordinator and Health Diplomacy, U.S. Department of State, USA*
[5]*Epidemiology Consultant for Advanced Clinical, USA*
[6]*Gillings School of Global Public Health, University of North Carolina Chapel Hill, USA*
[7]*ViiV Healthcare, Research Triangle Park, Gillings School of Global Public Health, University of North Carolina, USA*

***Corresponding author**
Jessica Albano, Real World & Late Phase, INC Research, 3201 Beechleaf Court, Suite 600, Raleigh, NC 27604, USA, Tel: +919-257-6918; Email: jessica.albano@incresearch.com

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Abstract

Objective: To evaluate a potential increase in the number of hypospadias cases after *in utero* exposure to zidovudine (ZDV) reported to the Antiretroviral Pregnancy Registry (APR), a prospective cohort study of antiretroviral-exposed pregnancies.

Methods: The rate of hypospadias in male infants following first trimester exposure to ZDV-containing regimens was compared to three internal unexposed groups.

Results: Of 7,643 prospective pregnancies, 6,504 (85%) were exposed and 1,139 (15%) were unexposed to ZDV during pregnancy. Among the 7,812 male birth outcomes resulting from these pregnancies (including multiple births), the earliest exposure to ZDV was during 1st trimester in 1,969 infants; during 2nd/3rd trimester in 4,662 infants (Group 1), 1,169 infants had no ZDV exposure (Group 2), and 1,424 had exposure to antiretrovirals (ARV) other than ZDV in the 1st trimester (Group 3). In total, 22 hypospadias cases were reported. The odds ratio of 1st trimester ZDV exposed cases compared to the three unexposed groups were 3.74 (95% CI 1.45, 9.66), 1.63 (95% CI 0.52, 5.12), and 2.00 (95%CI 0.63, 3.28).

Conclusion: The increased rate of hypospadias in the primary screening analysis for 1st trimester ZDV-exposed infants compared to ZDV exposures in 2nd/3rd trimester did not persist when compared to those without any ZDV exposure and those with 1st trimester exposures to non-ZDV ARVs. The data do not support a causal relationship between zidovudine exposure and hypospadias. The disappearance of the possible signal in more sophisticated analyses suggests that the increase may be related to other factors.

ABBREVIATIONS

APR: Antiretroviral Pregnancy Registry; ARV: anti retro viral; CDC: Centers for Disease Control and Prevention; CI: confidence interval; EUROCAT: European Surveillance of Congenital Anomalies; IRB: institutional review board; MACDP: Metropolitan Atlanta Congenital Defects Program; NICHD: National Institute of Child Health and Human Development; NISDI: International Site Development Initiative; NOS: not otherwise specified; OR: odds ratio; TBDR: The Texas Birth Defect Registry; WIRB: Western IRB; WITS: The Women and Infants Transmission Study; ZDV: zidovudine

INTRODUCTION

Hypospadias, a condition in which the urethral meatus is displaced along the underside of the penis, is one of the most common congenital malformations in males. Hypospadias affects approximately four to six males per 1000 male births [1-5]. The etiology of hypospadias is multifactorial being found as an isolated anomaly as well as part of genetic, metabolic, and chromosomal

syndromes. Regarding potential association with environmental exposures, the timing of the development of hypospadias suggests that first trimester exposures are most relevant [2,6-8]. Hypospadias severity is most commonly classified as first-, second- or third-degree, based on the position of the urethral meatus. First-degree hypospadias is the least severe form, with the urethral opening on the distal one-third of the penis. Second-degree hypospadias occurs when the urinary meatus is located along the proximal two-thirds of the penis to the penoscrotal junction. Third-degree hypospadias involves the urethral opening on the scrotum or perineum. Hypospadias is typically diagnosed at birth; however mild, first-degree hypospadias may not be detected until a circumcision procedure has begun [9].

Studies have explored the effect of exposure to several environmental factors, genetics, gene-environment interactions, maternal and paternal conditions, and pregnancy-related factors on the risk of hypospadias with varied results [10-19]. Increased risk has been associated with prematurity [12,13], multiple gestation [14], small size for gestational age [15], family history [16], maternal obesity [17], maternal hypertension [18], and exposure to insect repellant [19].

Data on the incidence of hypospadias among infants born to HIV-positive women exposed to antiretroviral (ARV) medication during pregnancy are limited. Nso Roca and colleagues (2009) reported a total of 28 birth defects among 206 Spanish children, the majority of whom were exposed *in utero* to zidovudine (ZDV) containing regimens; two were cases of hypospadias [20]. The Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) International Site Development Initiative (NISDI) Perinatal Study, a prospective cohort study conducted at Latin American and Caribbean clinical sites, reported no cases of isolated primary hypospadias but one case with congenital chordee with hypospadias out of 249 infants exposed to ARVs during the first trimester, and one case of primary hypospadias out of 746 infants exposed to ARVs during the second or third trimester [21]. The Women and Infants Transmission Study (WITS), a cohort study enrolling women during pregnancy and providing long-term infant follow-up, found seven cases of hypospadias among 382 live born male infants exposed to ARVs in the first trimester and two cases out of 892 live male infants exposed during the second or third trimesters [22]. In another study, 12 cases of hypospadias out of a total of 232 birth defects were reported, all in infants exposed to ZDV-containing regimens [23]. Both NISDI and WITS collaborated with the Antiretroviral Pregnancy Registry (APR) by submitting all eligible cases for inclusion in the Registry.

The APR detected an increase in the number of cases of hypospadias among male infants exposed *in utero* to ZDV. To examine this potential safety signal, we analyzed routinely collected Registry data to evaluate the relationship between *in utero* exposure to ZDV and hypospadias. Multiple internal comparison groups were used to determine the reproducibility of the findings.

MATERIALS AND METHODS

This study uses data from the APR, an ongoing, international pregnancy exposure registry established in January 1989 to detect any major teratogenic effects involving exposure to ARV medications during pregnancy. Detailed descriptions of APR's methodology are presented elsewhere [24-27]. Briefly, the APR is a prospective, exposure-registration cohort study that enrolls women following prenatal exposure to ARV medications and follows them until the end of pregnancy to capture data on birth defects and outcomes of pregnancy. Registration is voluntary and confidential. Health care providers prospectively register pregnant women (i.e., before the pregnancy outcome is known) with prenatal exposures to any ARV medication. At the end of pregnancy, the participants' health care providers send updated information to the APR about the pregnancy and pregnancy outcome with emphasis on birth defects. The APR is a collaborative of 24 manufacturers representing 38 ARV medications. The APR has received case reports from 67 countries; however, the majority of case reports are from the United States and its territories (77.6%) [24]. All women in the Registry are ARV-exposed, but may not necessarily be HIV-positive, as ARV medications may be taken for other indications such as hepatitis B infection or for HIV pre- and post-exposure prophylaxis.

Institutional review board (IRB) approval was obtained from the Western IRB (WIRB). The Registry was granted a waiver from obtaining patient informed consent. To preserve the patient's confidentiality, registration is conducted anonymously through the health care provider rather than the patient. Registry data are collected with no patient identifiers and follow up is managed through the use of Registry-assigned identification numbers maintained by the health care providers.

Exposure classification

Exposure is classified and analyzed by the earliest trimester of exposure to each individual ARV medication. The Registry defines first trimester from the beginning of pregnancy to gestational age less than 14 weeks; the second trimester ranges from 14 to 27 weeks; and the third trimester spans 28 gestational weeks until delivery. Gestational age is calculated from the first day of the last menstrual period, the estimated date of delivery, or the corrected estimated date of delivery by ultrasound, when available.

Outcome definitions

A "birth defect" in this Registry follows the Centers for Disease Control and Prevention's (CDC) guidelines and is defined as any major structural malformation or chromosomal defect diagnosed or with signs/symptoms before six years of age, and on a case-by-case basis, subject to independent review, any structural or chromosomal defect detected in the prenatal evaluation of a pregnancy or in the gross or pathologic examination of an abortus, fetus, or deceased infant. Additionally, on a case-by-case basis, subject to independent review, the APR includes cases with any cluster of two or more conditional abnormalities. The Registry excludes birth defects attributed to prematurity itself (e.g., patent ductus arteriosus, patent foramen ovale, and inguinal hernias).

Birth defect cases are reviewed and defects classified by a medical geneticist using the CDC's Metropolitan Atlanta Congenital Defects Program (MACDP) definition of defects and an

organ system classification of the defects is based on the ICD-9-CM and public health 6-digit-code terminology [26,27]. All types of hypospadias are classified as a major birth defect regardless of severity; hypospadias severity was not consistently available for the reported cases. For all cases with birth defects reported to the APR, the medical geneticist evaluates the timing of ARV exposure(s) alongside the probable timing of the embryological development of the defect. All defects are reviewed by the APR's Scientific Advisory Committee for consensus.

Statistical methods

The APR patterns analysis of the birth defect data after the CDC population-based birth defects surveillance system, which includes all major defects meeting the MACDP case definition for a defect occurring in infants/fetuses of at least 20 weeks gestational age at birth [31]. Registry enrollment and pregnancy outcome must have occurred from the initiation of the APR on January 1, 1989 through January 31, 2014.

The primary exposure group included all male birth outcomes whose mothers took ZDV during the first trimester of pregnancy. To evaluate the potential signal of hypospadias, three internal comparison groups were used in separate analyses (Figure 1). All three comparison groups were restricted to male birth outcomes that occurred at 20 weeks gestation or greater and are not mutually exclusive. The analytical comparisons were as follows:

- ZDV exposure in the 1st trimester vs. ZDV in the 2nd/3rd trimester (Group 1)
- ZDV exposure in the 1st trimester vs. no ZDV in any trimester (Group 2)
- ZDV exposure in the 1st trimester vs. any non-ZDV ARV in the 1st trimester (Group 3)

The comparison described for Group 1 mimics the approach used in APR for its primary analysis [24-26]. The analyses comparing the exposure group (first trimester ZDV exposure) to Groups 2 and 3 serve as confirmatory comparison groups.

Descriptive analyses were conducted using frequencies and percentages for categorical data; and means, standard deviations, medians and inter-quartile ranges for continuous data. Statistical comparisons were done using the Chi-square test (or Fisher's exact test where appropriate) for categorical data and the independent t-test for continuous data.

The incidence of hypospadias was defined as the number of birth outcomes with hypospadias (at least 20 weeks of gestation) divided by the number of live born male infants within the group. Spontaneous losses and induced abortions with or without birth defects are excluded from the denominator to be consistent with the calculation used by the MACDP, which is the primary comparator for the APR.

The risk of hypospadias among first trimester ZDV-exposed male birth outcomes was compared to the risk of hypospadias among each of three unexposed, internal comparison groups, through the estimation of odds ratios (OR), 95% confidence intervals (CI) based on the exact binomial method, and p-values. Due to the small number of outcomes with hypospadias, Fisher's exact test was used to determine relevant p-values.

RESULTS AND DISCUSSION

From inception (January 1, 1989) through January 31, 2014, the APR has prospectively enrolled and completed follow-up on 16,646 pregnant women with ARV exposure. Of these, 7,643 (45.9%) resulted in 7,812 male birth outcomes (singleton and multiple births) that were 20 weeks of gestation or older (Tables 1 and 2). Among the 7,643 pregnancies, 6,504 (85.1%) were exposed to ZDV-containing regimens at sometime during the pregnancy; the earliest exposure to ZDV occurred in the first trimester for 1,922 (29.6%) women and in the second or third trimester in the remaining 4,570 (70.3%) women. Of the 7,643

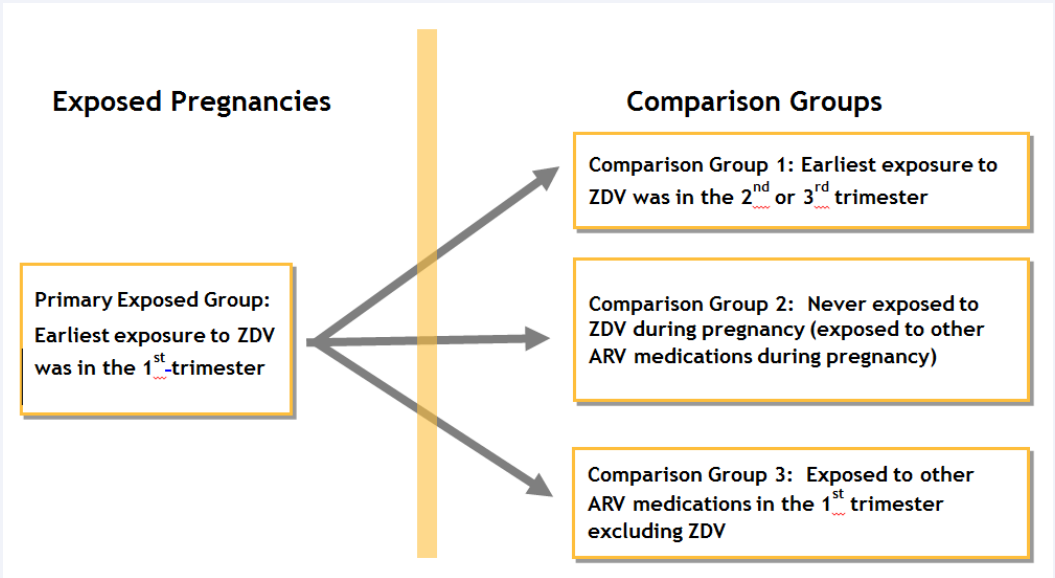

Figure 1 Schematic of the comparisons between the ZDV-exposed group and the 3 internal comparison groups.

Table 1: Maternal demographics of enrolled pregnancies resulting in male outcomes.

		Exposed Group	Comparison Groups[1]		
Characteristic	**Overall (n = 7643) n (%)**	**First Trimester ZDV (n = 1922) n (%)**	**1. Second/Third Trimester ZDV (n = 4570) n (%)**	**2. No ZDV in Any Trimester (n = 1139) n (%)**	**3. Other ARV in First Trimester (n = 1387) n (%)**
Median age in years (IQR)	28.0 (8.0)	29.0 (8.0)	27.0 (9.0)	30.0 (9.0)	30.0 (8.0)
Race					
White	1205 (15.8)	335 (17.4)	694 (15.2)	175 (15.4)	216 (15.6)
Black	4320 (56.5)	963 (50.1)	2769 (60.6)	588 (51.6)	745 (53.7)
Hispanic	1459 (19.1)	459 (23.9)	866 (18.9)	131 (11.5)	222 (16.0)
Asian	167 (2.2)	28 (1.5)	26 (0.6)	113 (9.9)	78 (5.6)
Other	246 (3.2)	61 (3.2)	124 (2.7)	60 (5.3)	54 (3.9)
Missing	246 (3.2)	76 (4.0)	91 (2.0)	72 (6.3)	72 (5.2)
CD4+ T-cell categories					
>=500 cells/µL	2350 (30.7)	610 (31.7)	1439 (31.5)	301 (26.4)	415 (29.9)
200-499 cells/µL	3198 (41.8)	821 (42.7)	1969 (43.1)	408 (35.8)	548 (39.5)
<200 cells/µL	1170 (15.3)	314 (16.3)	715 (15.6)	139 (12.2)	198 (14.3)
Unknown	173 (2.3)	23 (1.2)	50 (1.1)	97 (8.5)	98 (7.1)
Not applicable	111 (1.5)	6 (0.3)	13 (0.3)	92 (8.1)	54 (3.9)
Missing	641 (8.4)	148 (7.7)	384 (8.4)	102 (9.0)	74 (5.3)
Country of Report Origin					
United States	6139 (80.3)	1625 (84.5)	3866 (84.6)	644 (56.5)	955 (68.9)
Other	1502 (19.7)	297 (15.5)	702 (15.4)	495 (43.5)	432 (31.1)
Missing	2 (0.0)	0	2 (0.0)	0	0

Note: Table excludes unknown/missing data and hence the numbers do not add up to the total number for the column.
[1]The three comparison groups are not mutually exclusive
Abbreviations: IQR: inter quartile range; ZDV: zidovudine; ARV: antiretroviral

Table 2: Counts of pregnancies and birth outcomes by analysis grouping.

		Exposed Group	Comparison Groups[1]		
Characteristic	**Overall**	**First Trimester ZDV**	**1. Second/ Third Trimester ZDV**	**2. No ZDV in Any Trimester**	**3. Other ARV in First Trimester**
Pregnant women	7643	1922	4570	1139	1387
Birth Outcomes					
Male birth outcomes	7812	1969	4662	1169	1424
Live born male infants	7727	1948	4618	1149	1402
Birth outcomes with hypospadias	22	11	7	4[2]	4[2]

[1]The three comparison groups are not mutually exclusive.
[2]Birth outcomes with hypospadias in Comparison Groups 2 and 3 are the same 4 subjects.
Abbreviations: ZDV: zidovudine; ARV: antiretroviral

pregnancies with live-born male infants, 1,139 (14.9%) were exposed to other ARV medications and had no ZDV exposure (Group 2); and 1,387 (18.1%) had no ZDV during the first trimester but had other ARV medication exposure in the first trimester (Group 3); this group may have received ZDV in the second or third trimesters.

Maternal demographic characteristics

Maternal age distribution (median: 27-30 years) was similar among the exposed and three comparison groups (Table 1). Women in the primary exposure group had higher percentages of race identified as "White" (n=335, 17.4%) and ethnicity identified as "Hispanic" (n=459, 23.9%) compared to the women in the three internal comparison groups. The group of women receiving no ZDV throughout pregnancy (Group 2) had the highest rates of race identified as "Asian" (n=113, 9.9%) and more frequently, these reports originated from outside the United States (n=495, 43.5%) compared to the other groups.

Frequency of hypospadias cases and timing of exposure

The APR received reports of 22 cases of hypospadias, and all were among live born infants (Table 2). Among these, 18 infants had prenatal ZDV exposure; the earliest ZDV exposure was in the first trimester for 11 infants (exposed group) and in the second or third trimester for seven infants (Group 1). The remaining four infants with hypospadias had no ZDV exposure during pregnancy and had *in utero* exposures to other ARV medications in the first

trimester (Groups 2 and 3, respectively).

Table (3) provides the MACDP defect classifications for each of the 22 hypospadias cases. Six cases were reported to have primary hypospadias,

one had primary hypospadias with chordee, 13 had hypospadias not otherwise specified (NOS), and

two had hypospadias NOS with chordee.

Male birth outcomes with first trimester prenatal exposure to ZDV had a higher risk of hypospadias compared to those with earliest exposure to ZDV in the second or third trimester (OR: 3.74, 95% CI: 1.45, 9.66, p = 0.007;compared rate in exposed 0.56, 95% CI: 0.28, 1.00 to rate in Group 1 0.15, 95% CI: 0.06, 0.31) (Table 4). Comparisons with Groups 2 and 3, revealed no significant increased risk associated with first trimester ZDV exposure (Table 4).

Discussion

In this study, three different internal comparison groups were used to evaluate the potential safety signal of hypospadias associated with *in utero* first trimester ZDV exposure. Although the OR was elevated in all three comparisons suggesting an increased risk for first trimester use of ZDV; only the first comparison (first trimester ZDV vs. second/third trimester ZDV) was statistically significant. This study estimates that infants with first trimester ZDV exposure were 3.7 times more likely to have hypospadias compared to those with earliest ZDV exposure in the second or third trimester (OR 3.7, 95%CI 1.45, 9.66). The incidence rates between groups (0.56% vs. 0.15%) were statistically significant, (p = 0.007).

The results from the second and third internal comparison groups lacked precision due to small sample sizes; however the differences in hypospadias incidence between the exposed and unexposed groups were not statistically significant (Table 4). Using Group 2, we compared first trimester exposure to ZDV to no exposure to ZDV in any trimester. Using Group 3, we compared first trimester exposure to ZDV to first trimester exposure to other ARV medications excluding ZDV, and did not find a significant increase.

The inability to replicate the findings in the second and third internal comparison groups may be related to the small numbers of cases, a possible lack of power to detect a significant change, unidentified confounding from concurrent medications or other unmeasured risk factors, or to a true lack of effect of ZDV on risk of hypospadias. Some medications may interfere with testosterone and estrogen levels, thus affecting fetal organ development [22]. Monitoring of this signal will continue as the APR continues to register prospective pregnancies.

Birth defects due to drug exposure have been reported when the exposure occurs during the first trimester of pregnancy, the most critical period of organ development [28]. Thus,

Table 3: MACDP defect classification for hypospadias cases.

MACDP Defect Classification	Overall (n=22)	Exposed Group	Comparison Groups[1]		
		First Trimester ZDV (n=11)	1. Second/Third Trimester ZDV (n=7)	2. No ZDV in Any Trimester (n=4)[2]	3. Other ARV in First Trimester (n=4)[2]
Primary Hypospadias	6	3	1	2	2
Primary Hypospadias with Chordee	1	1	0	0	0
Hypospadias NOS	13	6	6	1	1
Hypospadias NOS with Chordee	2	1	0	1	1

[1]The three comparison groups are not mutually exclusive
[2]Birth outcomes with hypospadias in Comparison Groups 2 and 3 are the same 4 subjects.
Abbreviations: ARV: antiretroviral; MACDP: metropolitan atlanta congenital defects program; NOS: not otherwise specified; ZDV: zidovudine

Table 4: Hypospadias incidence in exposed and 3 comparison groups.

Earliest trimester of ARV exposure	Cases/ Population at risk	Hypospadias Rate (%) (95% CI)[1]	OR (95% CI)[2]	p-value[3]
Exposed Group				
1st trimester ZDV exposure	11/1948	0.56 (0.28, 1.00)	--	--
Comparison Groups[4]				
Group 1: 2nd/3rd trimester ZDV exposure	7/4618	0.15 (0.06, 0.31)	3.74 (1.45, 9.66)	0.007
Group 2: No ZDV in any trimester	4/1149	0.35 (0.09, 0.89)	1.63 (0.52, 5.12)	0.59
Group 3: Other ARV in 1st trimester	4/1402	0.28 (0.06, 0.72)	2.00 (0.63, 6.28)	0.30

[1]Hypospadias rate is calculated by dividing the number of male outcomes with hypospadias by the number of male live births in each exposure group. The 95% CIs are based on the Clopper-Pearson exact binomial method.
[2]Odds ratio compares the hypospadias risk among 1st trimester ZDV-exposed infants relative to each comparison group.
[3]P-value is based on the Fisher's Exact Test.
[4]The three comparison groups are not mutually exclusive.
Abbreviations: ZDV: zidovudine; ARV: antiretroviral; OR: odds ratio; CI: confidence interval

drug exposure during this time generally carries the highest risk of birth defects, in comparison to second/third trimester exposures [29]. In general, the use of ARV medications during pregnancy has been reported to be safe [29]. However, concerns have been raised about the use of specific ARV medications and fetal safety, particularly ZDV and other nucleoside reverse transcriptase inhibitors, as these drugs have been shown to become incorporated into human nuclear and mitochondrial DNA; results from animal research suggests that they can cause the depletion of mitochondrial DNA (30). The APR's Scientific Advisory Consensus statement reflecting the overall findings of the APR is included at the end of this manuscript.

In this analysis of a potential signal for hypospadias related to first trimester exposure to ZDV, we report hypospadias incidence rates ranging from 0.15% to 0.35% across the various subgroups analyzed and 0.56% among the exposure group. The MACDP reports a population estimate of hypospadias of 0.62% (793 cases per 127,167 male live births) [31]. The MACDP is a population-based registry that uses active case ascertainment in 22 hospitals and clinics in the Atlanta, Georgia area, and these data were collected from 1999 to 2003 [31]. The Texas Birth Defect Registry (TBDR) reports hypospadias rates from 2000 to 2009 of approximately 0.55% in live born males [32]. European Surveillance of Congenital Anomalies (EUROCAT) reports hypospadias rates that range from 0.06% to 0.31% across all member registries [33]. EUROCAT is a European network of population-based registries for the epidemiologic surveillance of congenital anomalies that includes 43 registries from 23 countries and covers more than 1.7 million births annually, representing 29% of European birth population [33].

Hypospadias is known to occur with other conditions. Micropenis has been reported to occur in isolation or in the presence of hypospadias [34]. The APR also reports three cases of isolated micropenis (1 with first trimester ZDV exposure, 1 with second trimester ZDV exposure and 1 with first trimester non-ZDV ARV exposure) among 7,643 male birth outcomes [24]. Yet, there were no reports of hypospadias among the three cases of micropenis. While the underlying mechanism for the occurrence of micropenis is not well defined, it has been suggested that the condition may result from insufficient gonadal androgens for penile growth stimulation, or as a result of a poor response of the penis to growth stimulation [34]. If insufficient levels of androgens are available during the critical period for penile development, micropenis with hypospadias is more likely to occur; however, if they occur after the critical period, then the risk of developing isolated micropenis is higher [34]. The lack of concurrent hypospadias in these three cases with micropenis may suggest that the mechanism for the development of micropenis differs from the mechanism(s) responsible for the development of the reported cases of hypospadias in this analysis.

Strengths and Limitations

The APR is multi-sponsor pregnancy registries that has been operating since 1989 and has completed follow up on 16,646 prospectively registered ARV-exposed, pregnant women as of January 31, 2014. The APR database provides an ideal platform to assess the effect of *in utero* exposure to ARV on birth outcomes due to the large sample size and the availability of high quality ARV exposure information throughout pregnancy. This design allows for the analysis of multiple ARV medications and all reported birth defects. However, this rich database is not without challenges. Pregnant women with HIV are often prescribed several ARV medications and multi-drug regimens throughout pregnancy. Some women receive ARV therapy later in pregnancy than others. Thus, dose-response relationships can be difficult to interpret in polypharmacy situations.

Due to the small number of hypospadias cases, multivariate logistic regression could not be conducted to evaluate additional risk factors for hypospadias in this population. Additionally, there are several limitations associated with the use of data from the APR, which is only designed to detect teratogenic effects of ARV medications used in pregnancy. The APR does not consistently obtain information on hypospadias severity or environmental (particularly exposure to non-ARV drugs) or genetic factors that could impact reporting, detection, and incidence.

Mild, or first-degree hypospadias, may be first detected during circumcision; however, only approximately 30% of males globally are circumcised [35]. Neonatal circumcision is common in some parts of the world (Israel, US, Canada, Australia, New Zealand, and much of the Middle East) but uncommon in Central Asia and West Africa, where circumcision occurs later in life (late boyhood to early twenties) [35]. Males who are not circumcised in the neonatal period may have undetected first-degree hypospadias from the Registry's perspective, and this may result in misclassification of cases as non-cases and thereby underestimate the risk associated with exposure. If additional information on the degree of hypospadias and circumcision (including timing of procedure) were available, it would be possible to evaluate rates of second- and third-degree hypospadias alone, and better determine risk and benefit associated with ZDV exposure during pregnancy.

CONCLUSION

The initial analysis of APR data suggested increased rates of hypospadias in infants exposed to zidovudine in the first trimester compared to those with only second/third trimester exposures, prompting a more detailed analysis. However, in the subsequent confirmatory analysis comparing ZDV exposure during pregnancy with non-ZDV ARV exposure during pregnancy and with other ARVs excluding ZDV during the first trimester, no statistically significant increases were observed. The rates were also not increased compared to the rates reported by the CDC's MACDP [31] or the TBDR [32]. The Advisory Committee to the APR concludes that the data do not support a causal relationship between ZDV exposure and hypospadias. The disappearance of the possible signal in more detailed analysis suggests that the increase may be related to other factors. Currently, the number of hypospadias cases reported does not provide a sufficient sample size for further investigation of these factors.

Scientific Advisory Committee Consensus Statement

In reviewing all reported defects from the prospective Registry, informed by clinical studies and retrospective reports of antiretroviral exposure, the Registry finds no apparent increases in frequency of specific defects with first trimester

exposures and no pattern to suggest a common cause. The Registry notes modest but statistically significant elevations of overall defect rates with didanosine and nelfinavir compared with its population based comparators, the MACDP, but not the TBDR. While the Registry population exposed and monitored to date is not sufficient to detect an increase in the risk of relatively rare defects, these findings should provide some assurance when counseling patients. However, potential limitations of registries such as this should be recognized. The Registry is ongoing. Given the emergence of new therapies about which data are still insufficient, health care providers are strongly encouraged to report eligible patients to the Registry at www.APRegistry.com.

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CONFLICT OF INTEREST

JA is and CG was (at the time of analysis) a salaried employee of INC Research LLC, which is contracted to manage the daily operations and conduct the statistical analyses of the Antiretroviral Pregnancy Registry.

SS is an employee of the University of North Carolina Wilmington and a consultant to INC Research LLC.

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VV is an employee of ViiV Healthcare, a joint venture between GlaxoSmithKline (GSK) and Pfizer and receives GSK company stock as part of her incentive package.

NK was a consultant at GSK at the time she worked on this manuscript.

HT and AS are contractors of INC Research LLC for their work on the Antiretroviral Pregnancy Registry.

AS is the birth defect evaluator and a member of the Scientific Advisory Committee.

HW has no conflicts of interest.

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DISCLOSURES

Preliminary analyses of these data were presented in 2012:

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