The Antiretroviral Pregnancy Registry: 30 years of Monitoring for Congenital Anomalies

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The Antiretroviral Pregnancy Registry

- The Antiretroviral Pregnancy Registry (APR) is a voluntary, international, prospective exposure-registration cohort study
  - Started as Zidovudine in Pregnancy Registry in 1989; became APR in 1993
  - Currently 29 sponsoring ARV manufacturers
  - Overseen by an independent Advisory Committee
  - As of July 31, 2020, include >20,437 live births with antiretroviral (ARV) exposure

- Designed to assist clinicians and patients in weighing potential risks and benefits of HIV treatment used during pregnancy
  - Monitors prenatal exposures to ARV drugs to detect a potential increase in the risk of birth defects
  - 150 ARV drugs: 57 brand-name single-entity drugs or fixed-dose combinations; 94 generic versions

- APR Objectives:
  - Provide early warning signals of major teratogenicity
  - Estimate prevalence of major birth defects and compare to the general population
  - Supplement animal toxicology, clinical, and epidemiological study data
Antiretroviral Pregnancy Registry Analysis

1. Prospective
   - Reported during pregnancy before delivery, follow-up for outcome
   - Primary Analysis
     - Prevalence = \( \frac{\text{number of defects}^\wedge}{\text{number of live births}} \)
     - Compared to:
       - MACDP* 3/100 live births
       - TBDR* 4/100 live births
     - 1st trimester vs. 2nd & 3rd trimester

2. Retrospective
   - Secondary Review for Clusters and Patterns
   - Reported after birth, no denominator
   - Secondary Analyses

3. Clinical Studies
   - Timing, Dosage, Type of Antiretroviral Drug Use, Concomitant Exposures, and Pregnancy Outcome/Birth Defect at Time of Delivery

^ defects counted among all outcomes >20 wks gestation including stillbirth, induced abortion & live births
* MACDP = Metropolitan Atlanta Congenital Defects Program; TBDR = Texas Birth Defects Registry
## Overall Birth Defect Rate

### Confidence Intervals for Birth Defects – All Prospective Registry Cases with Follow-up Data Closed Through 31 July 2020

<table>
<thead>
<tr>
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<th>Number of Live Births</th>
<th>Number of Live Births with at least one defect</th>
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<tbody>
<tr>
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<td>20,437</td>
<td>580 (2.8%)</td>
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95% Confidence Intervals for % of Birth Defects for exposures in:

- **First Trimester**: 304/10,754 (2.8%) (95% CI: 2.5–3.2%)
- **Second/Third Trimester**: 274/9,680 (2.8%) (95% CI: 2.5–3.2%)
- **Any Trimester**: 580/20,437 (2.8%) (95% CI: 2.6–3.1%)

Relative Risk (first vs second/third trimester): 1.00 (95% CI: 0.85, 1.17)

*Due to unknown trimester of exposure data for 2 case(s) with birth defects, specific counts may not sum to the overall total.*
APR Drug-Specific Birth Defect Rates*

Prevalence of Birth Defects (95% CI): 1 January 1989 – 31 July 2020
First Trimester Exposure

*For drugs meeting threshold of ≥ 200 1st trimester exposed pregnancies
MACDP: Vertical solid line = upper 95% CI, 2.76%
TBDR: Vertical dashed line = upper 95% CI, 4.19%

2.8% (CI 2.5-3.2%)
Conclusions

- The APR has not found a significant difference in CA prevalence overall or by trimester of exposure compared to population based surveillance systems.

- A detailed review of cases for DDI, NFV, and TAF did not identify a pattern of CAs. The relevance of the statistical findings for DDI and NFV are unclear.

ADVISORY COMMITTEE CONSENSUS Statement (Precis)

- The Antiretroviral Pregnancy Registry finds no apparent increases in frequency of defects with first trimester exposures compared to exposures starting later in pregnancy and no pattern to suggest a common cause; however, potential limitations of registries should be recognized.

- Providers are strongly encouraged to report eligible patients to SM_APR@APRegistry.com or visit www.APRegistry.com
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