

Placental histopathology and long-term outcomes of children with antenatal Zika virus exposure

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Children's National

Background

Zika virus (ZIKV) is a teratogenic flavivirus that can be vertically transmitted from mother to fetus.¹ Since the ZIKV epidemic of 2015-2017, studies have documented the ZIKV invasion of the placenta and subsequent placental damage.² However, it is unclear whether placental changes in ZIKV infection influence short- and long-term child outcomes.

Project Objectives

To determine if placental histopathology findings in ZIKV correlate with offspring outcomes at birth and age 3-4 years for children with in utero ZIKV exposure without congenital Zika syndrome.

Methods

- In 2016, 24 placentas were collected from 24 pregnant women with symptomatic ZIKV enrolled in a prospective ZIKV study in Colombia^{3,4}
- Placentas were formalin fixed and reviewed by a placental pathologist, blinded to child outcome
- Children from ZIKV-exposed pregnancies had neuroimaging during the fetal and neonatal periods, and were longitudinally evaluated to age 3-4 years^{4,5}

Standardized child development measures

- BSRA: Bracken School Readiness Assessment
- PEDI-CAT: Pediatric Evaluation of Disability Inventory – Computer Automated Test
- MABC-2: Movement Assessment Battery for Children – Second Edition
- BRIEF-P: Behavioral Rating Inventory of Executive Function – Preschool

Analysis

- Aggregate scores for standard assessment measures compared by presence or absence of placental perivillous fibrin deposition, calcifications, and increased syncytial knotting.
- T-test, Fisher's Exact, and one way ANOVA were used for statistical analysis
- Significance considered $p < 0.05$

Table 1: Maternal and neonatal characteristics of ZIKV-exposed mothers and infants

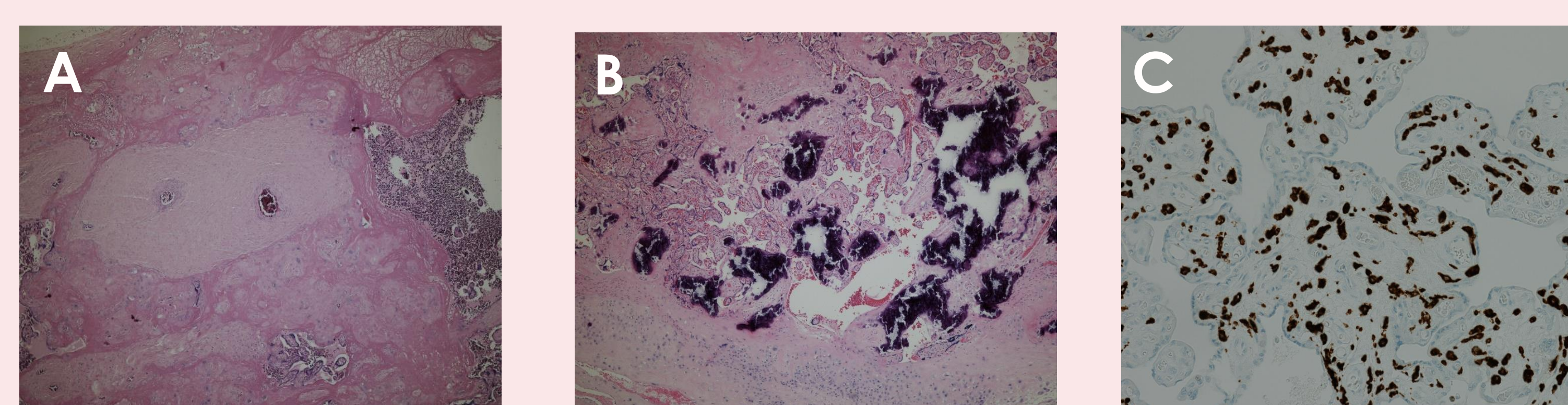
Characteristic	ZIKV-exposed dyads (n = 24)
Maternal age, years (mean [SD])	24.4 (5.8)
Gestational age at exposure, weeks (mean [SD])	8.3 (4.2)
Trimester of exposure (n [%])	
Trimester 1	18 (75)
Trimester 2	6 (25)
Trimester 3	0 (0)
Gestational age at birth, weeks (mean [SD])	39 (1.5)
Infant male sex (n [%])	10 (42)
Birth weight, grams (mean [SD])	3,219 (376)
Birth head circumference, cm (mean [SD])	34 (1.7)
Birth length, cm (mean [SD])	49.8 (3.9)
Ponderal index (mean [SD])	2.51 (.3)

Table 2: Neuroimaging & Placental Findings in ZIKV-exposed cases

Findings	ZIKV-exposed dyads (n=24)
Completed head ultrasound (n [%])	17 (71)
Completed brain MRI (n [%])	15 (63)
Non-specific brain imaging findings (n [%])*	6 (40)
Placental perivillous fibrin deposition (n [%])	21 (88)
≥30%	14 (58)
<30%	7 (29)
None	3 (13)
Placental calcifications (n [%])	17 (71)
≥10	10 (42)
1-9	7 (29)
None	7 (29)
Increased placental syncytial knotting (n [%])	14 (58)

Note: * n=15 children had neonatal neuroimaging; all children did not have birth defects of congenital Zika syndrome. Neuroimaging findings were only non-specific, or results were considered normal.⁴

Figure 1: Placental histopathology findings in ZIKV



Placental histopathology images of A.) massive perivillous fibrin deposition on H&E at 40 power, B.) multiple calcifications on H&E at 40 power, and C.) CD163 immunostain showing proliferation of Hofbauer cells at 200 power

Results- continued

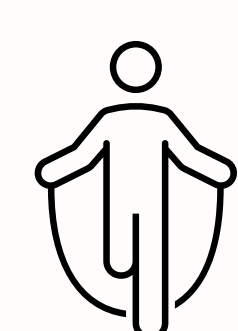
Children with ≥10 placental calcifications had lower composite school readiness scores on BSRA ($p=0.031$)



Children with increased syncytial knotting had lower scores on parent report (PEDI-CAT) of social/cognitive ability ($p=0.024$)



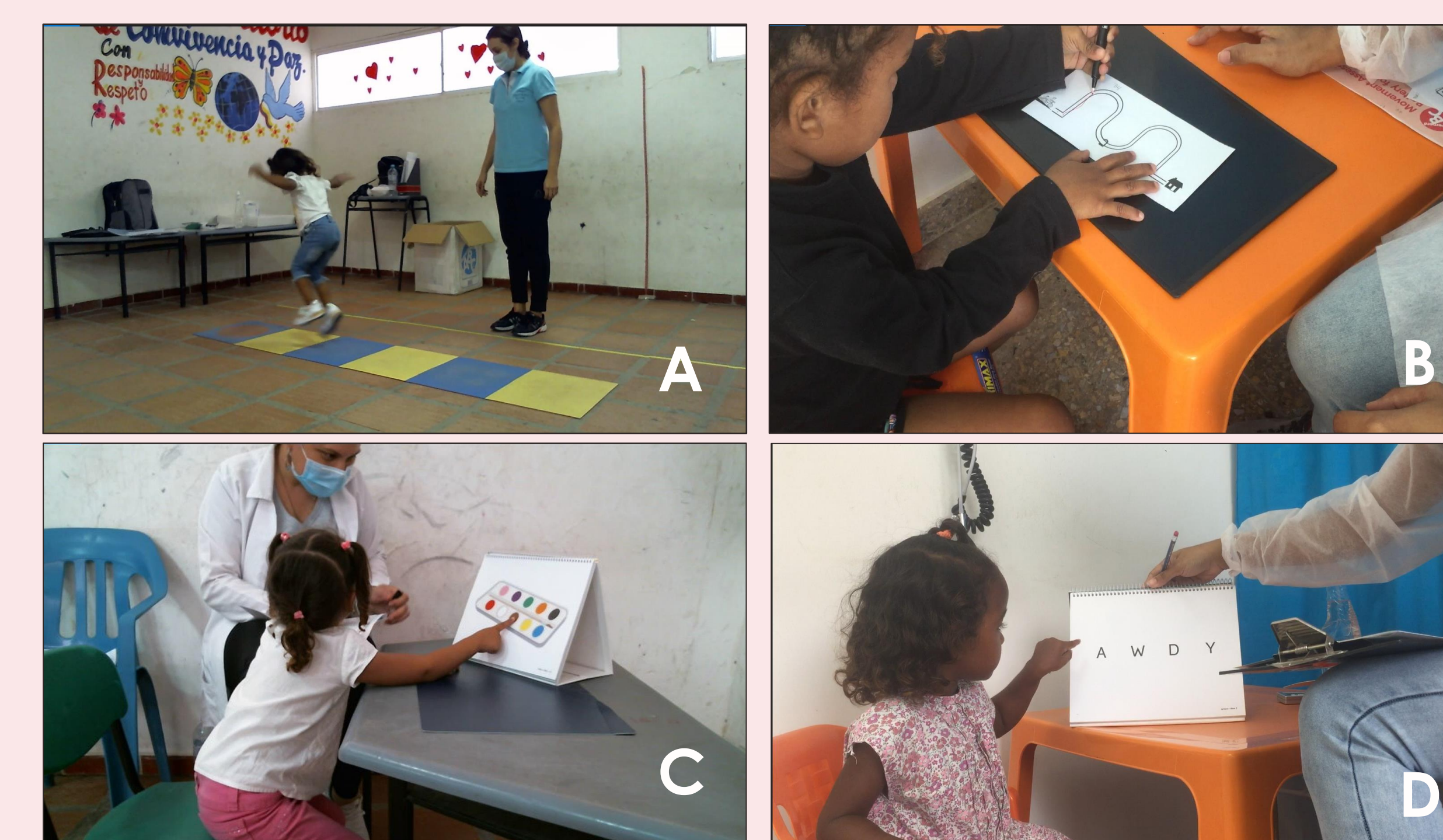
Children with moderate (1-9) placental calcifications had lower parent report (PEDI-CAT) of mobility than those with none or many (≥10) ($p=0.025$)



MABC total movement scores trended in a similar direction by placental calcifications, though did not reach significance ($p=0.127$)

- There was no relationship between any of the placental findings and non-specific brain imaging findings in the infants
- There was no correlation between the presence of each of the placental findings
- Massive (≥30% coverage) perivillous fibrin deposition was not associated with birth measurements or long-term neurodevelopmental outcomes at age 3-4 years.

Neurodevelopmental assessments



Early preschool neurodevelopmental evaluations at age 3-4 years A.) MABC balance (jumping on mats) B.) MABC manual dexterity (drawing trail) C.) BSRA colors D.) BSRA letters

Discussion and limitations

- Small sample size of case placentas
- Not all infants had postnatal neuroimaging; all had normal fetal brain on MRI and antenatal US⁴
- We did not compare ZIKV-exposed placentas to placentas without ZIKV exposure. None of the cases had congenital Zika syndrome or adverse pregnancy outcomes due to ZIKV.
- Increased syncytial knotting & calcifications are non-specific placental findings and are not uncommon in mature term placentas
- Though the patterns observed in some of the categories align with our hypothesis, it is unclear why the moderate calcification group had the lowest PEDI-CAT mobility score

Conclusions

- Placentas from ZIKV-infected pregnancies have pathological findings that indicate risk of impaired fetal perfusion, but these were not associated with preterm birth or small size.
- There may be associations between placental findings and long-term neurodevelopment in ZIKV-exposed children requiring additional studies.

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