Sex- and gestational timing-specific associations between exposures of prenatal glucose intolerance and neurodevelopmental disorders

Kaiser Permanente Research

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Objective

To determine associations between prenatal glucose intolerance and risk of neurodevelopmental disorders and examine whether associations differ by child sex and gestational timing of exposure.

Background

- Gestational diabetes (GDM) has been associated with increased risk of neurodevelopmental disorders (NDD) including autism spectrum disorder (ASD) and developmental delay (DD).
- A handful of studies have examined effect modification by child sex or gestational timing of GDM with mixed findings; none to date have examined sub-clinical impaired glucose tolerance (IGT) as a separate risk factor for NDD.
- Knowledge of sex- and timing-specific associations can provide mechanistic insights and aid in identification of high-risk subgroups.

Methods

- **Design**: Retrospective case-control study
- **Setting**: Kaiser Permanente Northern California (KPNC), an integrated healthcare system with a diverse patient population
- **Participants:** 4,546 children who were born between January 1, 2011-December 31, 2018, and their mothers who received care at KPNC 2 years prior to delivery
- **Exposures**: GDM diagnoses were confirmed by lab results and extracted from ICD codes in maternal records. GDM diagnosis timing subgroups were defined as early (<22 weeks), standard (22-30) or late (≥30) gestation. Sub-clinical IGT was determined based on failure of 1-hour fasting screening and no GDM diagnosis nor treatment with any antidiabetic medication.
- **Outcomes**: Diagnosis of ASD or DD recorded in the child medical record on or prior to December 31, 2023
- **Statistical Approach**: Odds ratios for ASD and DD were estimated separately from logistic regression models, and stratified models used to evaluate effect modification by sex and gestational timing. The final covariate set included maternal age at delivery, race/ethnicity, education, parity, gestational age at first prenatal visit, pre-pregnancy body mass index, child sex and birth year.

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Conclusions and Implications

Gestational diabetes (GDM) was associated with increased risk of ASD in females only, and only among those exposed to GDM early in gestation (diagnosis <22 weeks).

Prenatal impaired glucose tolerance (IGT), separate from GDM, was associated with increased risk of DD also in females only.

Associations of prenatal hyperglycemia with NDDs may be fetal sex-specific and occur at subclinical thresholds, warranting further research in larger samples.

Discussion

- GDM earlier in pregnancy may represent prolonged exposure of the fetus, occurring during critical periods of brain development.
- Despite not receiving a GDM diagnosis, pregnant individuals with sub-clinical indicators of hyperglycemia may still experience metabolic dysregulation with implications for fetal development and may therefore benefit from treatment recommendations similar to GDM.

Limitations

- Timing of GDM diagnosis derived from prenatal test results can at best be considered a proxy for hyperglycemia onset.
- Exposures were ascertained at a single timepoint and therefore fail to consider trajectories of hyperglycemia throughout pregnancy.
- We were unable to disaggregate the DD group into specific outcomes (e.g., motor delay) due to small sample size.

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Results

Table. Baseline sociodemographic and health characteristics

Characteristic	Overall (N=4,546)	ASD (N=683)	DD (N=2,054)	GP (N=1,809)
Age at Delivery, N (%)	31.2 (5.1)	31.3 (5.2)	31.3 (5.1)	31.0 (5.1)
Race/Ethnicity, N (%)				
Asian	948 (20.9)	153 (22.4)	428 (20.8)	367 (20.3)
Black	243 (5.3)	47 (6.9)	107 (5.2)	89 (4.9)
Hispanic	1088 (23.9)	143 (20.9)	502 (24.4)	443 (24.5)
Unknown	217 (4.8)	40 (5.9)	87 (4.2)	90 (5.0)
White	2050 (45.1)	300 (43.9)	930 (45.3)	820 (45.3)
Pre-pregnancy BMI, M (SD)	27.1 (6.5)	28.3 (7.2)	27.0 (6.3)	26.9 (6.3)
Child Sex Male	2697 (59.3)	522 (76.4)	1306 (63.6)	869 (48.0)

- GDM prevalence was 10.3% in ASD, 9.6% DD, and 7.5% in GP; IGT prevalence was 2.0% in ASD, 1.6% DD and 1.0% in GP.
- **Overall**, GDM was not associated with a change in the odds of ASD (OR=1.15 (0.83-1.60)) or DD (OR=1.24 (0.98-1.57)) (**Figures 1 & 2**)
- **By sex and timing**, GDM was associated with increased risk of ASD in females only ($OR_{Females}$=2.05 (1.15-3.56); OR_{Males}=0.93 (0.62-1.37)) and only in the early GDM diagnosis group (OR=3.13 (1.08-8.47)) (**Figure 1**)
- **Prenatal IGT** was associated with increased risk of DD in females only ($OR_{Females}$=3.25 (1.34-8.68); OR_{Males}=1.07 (0.50-2.39)) (**Figure 2**)

Figure 1. Associations between prenatal glucose intolerance and **ASD**

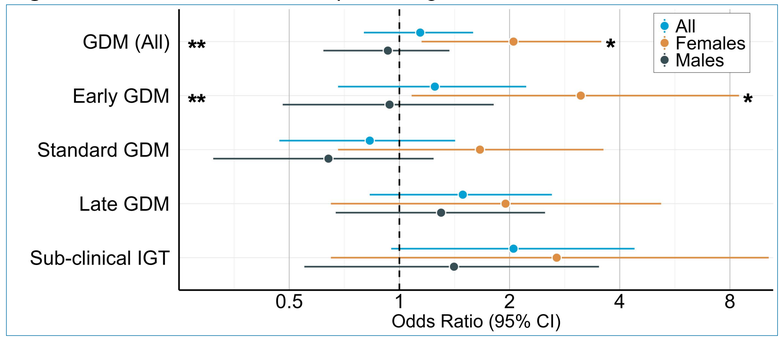

Figure 2. Associations between prenatal glucose intolerance and **DD**