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PhD title: **'The development of children born to mothers with diabetes mellitus in pregnancy: growth, body composition, and cognitive and motor development'**

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Abstract

Background

Globally, the prevalence of hyperglycaemia in pregnancy is increasing, driven by risk factors associated with the nutrition transition and an increasingly sedentary lifestyle. In spite of this, little is known about the short or long-term outcomes of children exposed to hyperglycaemia in pregnancy in sub-Saharan Africa (SSA). The pregnancy factors associated with birth outcomes in pregnancies complicated by either pre-existing diabetes, or hyperglycaemia first detected in pregnancy (HFDP) are not thoroughly understood, particularly in light of context-relevant factors such as maternal HIV infection. In addition to these short-term obstetric consequences, HFDP may adversely impact early cognitive development and childhood body composition, contributing to an already high population level of childhood obesity. As a growing number of children are exposed to hyperglycaemia in utero, understanding its role as an early developmental determinant can contribute to improving the health and development of the next generation.

Aim

The overarching aim of the study was to assess the impact of diabetes in pregnancy on childhood outcomes in an urban African setting. Objectives included investigating outcomes of pregnancies complicated by pre-gestational diabetes or HFDP, the impact of HIV-infection on these outcomes, and assessing the association between HFDP and childhood body composition and cognitive and motor development at preschool age.

Methods

Firstly, a retrospective analysis of the hospital records of 1071 women with hyperglycaemia in pregnancy at a large tertiary hospital in Soweto, Johannesburg was undertaken, with data of interest including pregnancy characteristics, comorbidities, and obstetric and neonatal outcomes. Secondly, a comparative study was performed in 3–6-year-old children born to mothers with HFDP, subdivided into gestational diabetes mellitus (GDM) and 'overt' diabetes in pregnancy (DIP), versus a group of HFDP-unexposed children, to examine the association

with: 1) childhood overweight, adiposity and growth, and 2) cognitive and motor development. Inclusion criteria were met by 204 mother/child pairs. Children's anthropometry was measured, and the deuterium dilution method was used to determine fat mass index (FMI). The Herbst Early Childhood Development Criteria test was performed to assess cognitive, fine motor, and gross motor development, completed in 194 of the children. Hierarchical regression analyses were performed to assess the association between HFDP exposure and childhood outcomes. Generalized structural equation modelling (GSEM) was performed to explore the direct and indirect effects of maternal BMI on childhood BMI and adiposity in the context of HFDP.

Results

The rate of adverse obstetric and neonatal outcomes, including macrosomia (8.4%), caesarean section (72.2%), perinatal mortality (PNM) (3.7%), and prematurity (30.9%), were significant despite management of hyperglycaemia during pregnancy. HbA1c at the initial visit, maternal BMI, and glycaemic control during the third trimester were important predictors for neonatal outcomes. Moreover, PNM was significantly higher in pregnancies additionally complicated by maternal HIV infection (9.4% vs 1.8%).

At 3-6 years old, the prevalence of childhood overweight/obesity was 10.8% in HFDP-exposed children, and 3.9% in the HFDP-unexposed group. The prevalence of stunting was 13.7% in the HFDP exposed group and 9.8% in the HFDP-unexposed group. The association between HFDP and log-transformed FMI, significant in the DIP-exposed group (unstandardized B=0.12 [95% confidence interval (CI) =0.01-0.22], standardized β=0.17, p=0.026), was attenuated and no longer significant when adjusting for maternal pregnancy BMI (B maternal BMI=0.01 [95%CI=0.003-0.015], β=0.23, p=0.004). No significant association was found for childhood BMI. GSEM indicated a direct effect of maternal pregnancy BMI and birth weight z-score on both childhood BMI and FMI.

HFDP exposure was inversely associated with higher cognitive score categorisation, independent of maternal factors such as household socioeconomic status (OR 0.33 [95%CI 0.15-0.74], p=0.007). Differences in fine motor skills were attenuated when adjusting for maternal factors, particularly household socioeconomic score (OR 0.62 [95%CI 0.28-1.37], p=0.239), and no differences were found in gross motor skills between the groups.

Conclusions

Severity of hyperglycaemia, maternal BMI, and maternal HIV infection were associated with obstetric and neonatal outcomes. Maternal BMI was found to be associated with childhood obesity and adiposity at preschool age, while stunting was present at a significant rate in the cohort. The identified association between HFDP and early cognitive development is concerning and requires further exploration and prevention efforts in our urban South African setting. These findings, relevant to other transitioning low-and middle-income countries, indicate the need for improved preconception care for maternal and child health, and highlight the need for additional research into early childhood risk factors as well as the intergenerational effects of maternal metabolic conditions.