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PhD title:

'THE IMPACT OF DIABETES MELLITUS IN PREGNANCY ON MATERNAL HEALTH OUTCOMES'

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Abstract

Background

Hyperglycaemia in pregnancy, encompassing all types of diabetes, is on the rise with an alarming global prevalence of 17%, of which 84% of these being accounted for by hyperglycaemia first detected in pregnancy (HFDP). Alongside the well-established adverse short-term outcomes of poorly managed or untreated disease, HFDP has a significant impact on the future health of both mother and offspring, playing a crucial role in the global diabetes epidemic. Until recently, HFDP, for which the highest prevalence occurs in low to middle income countries (LMIC), played a minor role in the shadow of more obvious determinants of maternal and fetal morbidity in these low-resource settings. More recently it has been recognised as an important public health issue given its immediate burden on maternal health services and the transgenerational and population level impact of the far-reaching ramifications for mother and child alike. Though our knowledge surrounding the burden, determinants, and immediate consequences of HFDP in South Africa (SA) is growing, the appreciation of its long-term consequences is poorly explored. Understanding and appreciating the adverse health consequences of HFDP creates an informed platform for developing health interventions for a condition which is aggressively fuelling the non-communicable diseases (NCD) burden.

Objective:

Our study seeks to investigate the cardiometabolic outcomes in an urban cohort of black SA women with a history of HFDP, 3-6 years following their delivery, compared to a group of women non-exposed to HFDP on the backdrop of a high human immunodeficiency virus (HIV) burden. Additionally, we explore the safety and efficacy of exposure to oral hypoglycaemic agents (OHAs) on maternal and neonatal outcomes.

Design and Methods:

An initial retrospective review of all women identified with diabetes in pregnancy, including type 1 diabetes mellitus (T1DM), type 2 diabetes mellitus (T2DM) and HFDP at the Gestational Endocrine Clinic at Chris Hani Baragwanath Academic Hospital (CHBAH) for the period 2012 through to 2018 was performed in order to investigate the immediate maternal and neonatal outcomes as well as to explore the impact of HIV infection and exposure to OHAs on these outcomes. Twin pregnancies and more than one pregnancy for the same individual during the time frame were excluded. Secondly, a prospective follow up study of women identified with prior HFDP between 2014 and 2017 were recruited for a cross-sectional analysis between March and November 2019 (3-6 years following their index pregnancy) and compared with women time-matched post-partum, who tested negative for HFDP (non-HFDP group) using the same diagnostic test and criteria. Two hundred and four participants were enrolled of which 103 were exposed and 101 non-exposed to HFDP. All participants were subject to a detailed questionnaire as well as various measurements including anthropometric parameters, blood pressure, the performance of an oral glucose tolerance test (OGTT), fasting serum creatinine, insulin, lipids, and glycated haemoglobin (HbA1C), urine analysis, body composition analysis via dual-energy x-ray (DXA) and ultrasonography of the carotid arteries to determine intima media thickness (cIMT) and the presence of plaque. For the retrospective review, descriptive statistics were used for comparing various maternal and neonatal outcomes by diabetes groups and for statistically significant outcomes, logistic regression analysis was performed using backwards selection following univariate analysis. For the prospective evaluation of HFDP exposed vs. non-exposed HFDP participants, unadjusted and multivariate adjusted odds ratio were estimated for the outcomes T2DM, metabolic syndrome (MetS) and 10-year cardiovascular risk calculated using Framingham risk score (FRS) from logistic regression models. Further multivariate models were designed to explore the potential association of historical maternal factors with the outcomes including fat mass index (FMI), T2DM, and cIMT using logistic or linear regressions.

Results:

Of the initial 1071 diabetic pregnancies retrospectively identified, majority of the women had pregestational diabetes (57%), with the remainder having HFDP (43%). Within the HFDP group, 51% had “overt” GDM (DIP) vs. 49% “true” gestational diabetes (GDM). Despite good glycaemic control across all the groups (as measured by HbA1C at term), adverse maternal and

neonatal outcomes were higher than in the background population with initial maternal HbA1C and body mass index (BMI) being predictors of poorer neonatal outcomes. Overall HIV prevalence within the group was 24%, lowest in those with HFDP (17.4%) and accounted for significantly higher perinatal mortality (PNM) in HIV-infected 9.4% than non-HIV-infected pregnancies 1.8%, $p<0.001$. The exposure to either oral hypoglycaemic agents (metformin and glibenclamide) versus insulin on immediate maternal and neonatal outcomes in two cohorts of women diagnosed with HFDP, was found to be safe and effective and was only significant for an association between glibenclamide and macrosomia. In the prospective, cross-sectional analysis of 103 women exposed to HFDP (identified using 75g OGTT, adopting IADPSG criteria) versus 101 women not exposed to HFDP, higher rates of progression to all three outcomes were noted with 44.6% of those exposed progressing to T2DM (adjusted risk of 10.5(95%CI 3.7-29.5)), 40.8% having MetS (adjusted risk 6.3(2.2-18.1)) and higher cardiovascular risk as identified by FRS (adjusted risk 4.3(1.6-11.5)), however cIMT did not remain significant after adjusting for confounders. Though HFDP exposure was a significant predictor for T2DM, MetS and cardiovascular risk, certain maternal factors present either pre-pregnancy, during the index pregnancy and/or post-partum were significantly associated with the outcomes. HIV, however, was not found to play a role in progression to any of these outcomes. Body composition was significantly altered in women exposed to HFDP versus those non-exposed with significantly higher FMI (13.9 vs. 12.3, $p=0.008$) and visceral fat indices between the groups and this remained significant after adjusting for confounders.

Conclusion:

The growing epidemic of obesity, T2DM, and cardiovascular diseases (CVD), particularly amongst LMIC, poses a significant public health burden in addition to the persistent infectious disease scourge. Our study confirmed the significant immediate adverse maternal and neonatal outcomes in women with diabetes in pregnancy and provided reassuring data on the safety and efficacy of OHAs in pregnancy when compared with the gold standard of insulin. Additionally, we identified a group of young black women at high risk of cardiometabolic diseases in the short-term following HFDP exposure. Appreciating these risks on the background of the growing prevalence of HFDP assists in providing evidence to incorporate universal screening programmes for detecting HFDP, expansion of specialized antenatal services for these women in addition to the post-partum interventions including targeted screening, counselling, and lifestyle and/or therapeutic interventions in order to preserve future maternal health and

interrupt the intergenerational cycle of chronic diseases. Future prospective studies are needed to explore the best timing and impact of these interventions in curtailing these adverse outcomes and improving cardiometabolic health in this vulnerable group of women.