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Short Communication

Brief Communication: Antenatal glucocorticoids and neonatal outcomes in type 1 diabetes pregnancy

Claire L. Meek [ORC ID 0000-0002-4176-8329] [1,2,3*], Zoe Stewart[4], Samuel Furse[1], Jennifer Yamamoto[5], Catherine E. Aiken[1,6], Denice S. Feig[7], Albert Koulman[1], Helen R. Murphy[2,8,9]

[1]The Wellcome Trust-MRC Institute of Metabolic Science, Metabolic Research Laboratories, University of Cambridge, Addenbrookes's Hospital, Box 289, Hills Road, Cambridge, CB2 0QQ, United Kingdom. [2]Wolfson Diabetes and Endocrinology Clinic, Cambridge University Hospitals, Addenbrookes's Hospital, Box 289, Hills Road, Cambridge, CB2 0QQ, United Kingdom. [3]Department of Clinical Biochemistry, Cambridge University Hospitals, Addenbrookes's Hospital, Box 281, Hills Road, Cambridge, CB2 0QQ, United Kingdom. [4]Academic Clinical Lecturer in Obstetrics and Gynaecology, Department of Cardiovascular Sciences, University of Leicester, Leicester, UK. [5]Department of Medicine, University of Manitoba, Winnipeg, Canada; Department of Medicine, Cumming School of Medicine, University of Calgary, Calgary, Canada. [6]Department of Obstetrics, Cambridge University Hospitals, Addenbrookes's Hospital, Box 281, Hills Road, Cambridge, CB2 0QQ, United Kingdom. [7]Mount Sinai Hospital, Department of Medicine, University of Toronto; Lunenfeld-Tanenbaum Research Institute, Toronto, Canada. [8]Norwich Medical School, University of East Anglia, Norwich, UK. [9]Department of Women and Children's Health, King's College London, London, UK.

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Abstract

Rationale: Antenatal glucocorticoids are associated with improved outcomes in preterm infants, but their role is unclear in term of offspring of high-risk pregnancies. For example, antenatal glucocorticoid administration in mothers with type 1 diabetes (T1D) in pregnancy has been reported to increase neonatal hypoglycemia risk, a common complication in this population. Both neonatal hypoglycemia and its cause, neonatal hyperinsulinism, may have chronic consequences on offspring neurological and cardiometabolic function. Objective: We aimed to assess the impact of antenatal glucocorticoid administration upon neonatal hypoglycemia risk and hyperinsulinism (assessed using cord blood C-peptide) in T1D pregnancy. Methods: We used data from the CONCEPTT randomized controlled trial of continuous glucose monitoring in pregnant women with T1D. Antenatal glucocorticoid administration was not randomised but given according to local protocols for perceived clinical need. C-peptide was measured in cord blood using an immunoassay. Results: Infants exposed to antenatal glucocorticoids had increased rates of neonatal complications, as expected, which were mostly explained by differences in gestational age at delivery. However, associations with elevated cord blood C-peptide, a marker of offspring hyperinsulinism, remained significant despite adjustment for gestational age and maternal hyperglycemia. Conclusions: Further assessment of risks and benefit of antenatal glucocorticoid administration in T1D pregnancy is warranted.

Keywords: Type 1 diabetes; pregnancy; antenatal glucocorticoids; neonatal hypoglycemia; Cord C-peptide; hyperinsulinism; perinatal complications.

INTRODUCTION

Offspring of pregnant women with type 1 diabetes (T1D) are at increased risk of neonatal hypoglycemia, attributable to fetal hyperinsulinism, with adverse consequences upon future cardiometabolic health (Feig *et al*., 2017; Zhang *et al*., 2018). Antenatal glucocorticoids

Corresponding author E-mail: clm70@cam.ac.uk

Table 1. Associations of antenatal glucocorticoid exposure with neonatal outcomes using unadjusted and adjusted linear/logistic regression. Model 1 includes unadjusted data. Model 2 included data which had been adjusted for gestational age at birth (based on estimated delivery date derived from ultrasound assessment at each study site). Model 3 is a fully adjusted model, and included gestational age, maternal third trimester glycemia (based on glucose time in range derived from continuous glucose monitoring at 34 weeks gestation), maternal age, ethnicity, BMI, education level (post-secondary school), parity (primiparous/multiparous), neonatal sex, and Caesarean delivery. Antenatal glucocorticoids are given to women considered at high risk of preterm delivery, and as expected, exposure is associated with increased risks of many complications. However, almost all of these complications reflect differences in gestational age at birth (i.e. antenatal glucocorticoids do not appear to increase the risk of complications such as neonatal hypoglycemia). In the fully adjusted model, only cord blood C-peptide, a marker for neonatal hyperinsulinism, is significantly increased in the offspring exposed to antenatal glucocorticoids. BMI: body mass index. CI: confidence intervals. Coeff: coefficient. NICU: neonatal intensive care unit. OR: odds ratio. NICU: neonatal intensive care unit. T1DM: type 1 diabetes mellitus.

	Model 1 **Unadjusted**	**Model 2** **Adjusted for gestation at birth**	**Model 3** **Fully Adjusted**
	OR (95% CI)	**OR (95% CI)**	**OR (95% CI)**
Respiratory Distress	1.58 (0.45 to 5.52)	0.62 (0.14 to 2.81)	0.67 (0.10 to 4.36)
Neonatal hypoglycemia	2.20 (1.06 to 4.59)*; p=0.035	1.27 (0.54 to 2.94)	0.55 (0.18 to 1.67)
NICU admission	2.34 (1.15 to 4.74)*; p=0.019	0.81 (0.33 to 1.95)	0.50 (0.16 to 1.52)
Hyperbilirubinemia	3.72 (1.75 to 7.88)**; p=0.001	1.93 (0.82 to 4.54)	2.88 (0.83 to 10.08)
	Coefficient (95% CI)	**Coefficient (95% CI)**	**Coefficient (95% CI)**
Cord blood C-peptide	0.81 (0.46 to 1.16)***; p<0.001	0.64 (0.25 to 1.04)**; p=0.002	0.54 (0.07 to 1.00)*; p=0.025
Neonatal Length of Stay	2.72 (0.75 to 4.70)**; p=0.007	-1.33 (-1.09 to 0.43)	-1.27 (-3.36 to 0.82)

* p<0.05; **p<0.01; *** p<0.001

reduce neonatal morbidity in preterm infants (Gyamfi-Bannerman *et al*., 2016). However, previous work has demonstrated associations between antenatal glucocorticoid administration and increased neonatal hypoglycemia risk (Gyamfi-Bannerman *et al.*, 2016). This is concerning in pregnancies affected by T1D, where rates of neonatal hypoglycemia are already elevated. We examined the impact of antenatal glucocorticoid exposure in T1D pregnancy upon neonatal outcomes and hyperinsulinism, quantified using cord C-peptide, to address the hypothesis that glucocorticoid exposure increases neonatal hypoglycemia rates.

METHODS

We used data from the CONCEPTT trial (Continuous glucose monitoring in pregnant women with T1D) described elsewhere (Feig *et al.*, 2017). We included 176/225 (78.2%) women in this analysis with details of antenatal glucocorticoid administration, given according to local clinical protocols for perceived clinical need (no timing/dose details available). Cord C-peptide was measured using Dynacare turbidimetric inhibition immunoassay for C-Peptide using a Siemens Immulite 2000 platform. Regression analysis assessed associations between glucocorticoid exposure and pregnancy outcomes (table 1).

RESULTS

Women with antenatal glucocorticoid exposure (n=43/176; 24.4%) had similar characteristics and glycemia to unexposed women but they had more Caesarean sections (38/43(88%) vs 78/133(60%), p=0.001), preterm births (32/43(74%) vs 38/133(29%), p<0.001), and higher rates of neonatal hypoglycemia (17/43(40%) vs 30/133(23%), p=0.033), hyperbilirubinemia (19/43(44%) vs 23/133(18%), p<0.001), neonatal intensive care admissions >24hr (21/43(49%) vs 30/133(29%), p=0.017) and higher median

cord C-peptide (1934 vs 880 pmol/l; p<0.001; unadjusted). Associations between glucocorticoid exposure and neonatal complications were not significant after adjustment for gestational age at birth (Table 1). However, cord C-peptide concentrations remained significantly higher in exposed neonates (Coeff 0.64; 95%CI 0.25- 1.04; p=0.002), both preterm (<37 weeks; Coeff 0.59; 95%CI 0.03- 1.15; p=0.038) and term offspring (≥37 weeks; Coeff 0.67; 95%CI 0.04-1.29; p=0.037).

DISCUSSION

Associations between antenatal glucocorticoid exposure and neonatal complications were explained by differences in gestational age at birth; except increased cord C-peptide, which persisted after adjustment for materno-fetal characteristics. Increased cord C-peptide may reflect unquantified differences in materno-fetal characteristics, glucocorticoid-induced maternal hyperglycemia, or the direct influence of glucocorticoids on fetal metabolism.

CONCLUSIONS

Given known associations between elevated cord blood C-peptide and future cardiometabolic health, (Brunner *et al.*, 2013, Zhang *et al*., 2018), further assessment of risks and benefits of glucocorticoid administration in T1D pregnancy may be warranted.

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Conflict of interest/ Disclosures

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CLM is the guarantor of this work and, as such, has had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Contribution Statement

CLM identified the study question, designed the study, analysed and interpreted the data, wrote and revised the manuscript. ZS arranged metabolomics analysis, and reviewed and revised the manuscript. SF, JY, CEA, and AK contributed to the discussion providing perspectives on metabolomics, lipidomics, neonatal care and obstetric medicine, and reviewed and revised the final manuscript. DSF and HRM designed the CONCEPTT study, contributed to study design for this analysis, contributed to the discussion and reviewed and revised the final manuscript. All authors reviewed the final version of the manuscript prior to publication.
CLM is the guarantor for this analysis.

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