Hyperglycaemia Recognised in Early Pregnancy is Phenotypically Type 2 Diabetes Mellitus not Gestational Diabetes Mellitus: A Case Control Study

Title Page

Full Title: Hyperglycaemia Recognised in Early Pregnancy is Phenotypically Type 2 Diabetes Mellitus not Gestational Diabetes Mellitus: A Case Control Study

Authors: R Agha-Jaffar[1], NS Oliver [1], M Kostoula [2], IF Godsland [1], C Yu [3], J Terry [3], D Johnston [1], D Gable [2] & S Robinson [2].

Affiliations: 1. Diabetes, Endocrinology & Metabolism, Department of Medicine, Imperial College London. 2. Department of Metabolic Medicine, St Mary's Hospital, Imperial College NHS Trust. 3. Department of Maternal Medicine, St Mary's Hospital, Imperial College NHS Trust.

Corresponding author: Professor Stephen Robinson, Department of Metabolic Medicine, Mint Wing, St Mary's Hospital, Imperial College NHS Trust, W2 1NY, United Kingdom. Telephone: +44 203 312 1253
Email: Stephen.Robinson15@nhs.net

Abbreviated Title: Impact of Hyperglycaemia Early in Pregnancy

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Abstract

Objective: Gestational diabetes mellitus is defined as "diabetes recognised in the second or third trimester that is not clearly overt diabetes". ~~This definition reflects the risk of unrecognised Type 2 Diabetes Mellitus (T2DM).~~ Evidence relating to women with hyperglycaemia early in pregnancy is limited. ~~and were adverse outcomes are demonstrated, maternal adiposity confounds the results.~~ We aimed to evaluate women diagnosed with hyperglycaemia early in pregnancy (eGDM) and compare them to those with pre-gestational established Type 2 Diabetes Mellitus (T2DM) and gestational diabetes diagnosed routinely at 24-28 weeks gestation (rtGDM) to determine if length of exposure to hyperglycaemia adversely affected outcomes.

Methods: Forty consecutive women with eGDM who attended a multidisciplinary antenatal clinic were reviewed. Two separate BMI-matched control groups were identified: recognised pre-gestational T2DM (n=80) and rtGDM (n=80). Baseline demographics and outcomes were compared.

Results: ~~Significant variations in HbA1c at identification of hyperglycaemia existed.~~ A higher proportion of women in the eGDM and T2DM group required insulin and the incidence of hypertensive disorders was similarly increased compared with the rtGDM group (88.6%, 77.0% versus 8.1%, p<0.001 and 42.5%, 37.5% versus 12.5% p<0.001 respectively). ~~Variations existed in the~~The proportion of infants born small for gestational age varied (eGDM 11.1%, T2DM 13.0% and rtGDM 2.5%, p=0.049). Postpartum, 7.5% of eGDM women were diagnosed with T2DM versus 1.3% in the rtGDM group (, p<0.001).

Conclusions: These novel data demonstrate that length of exposure to glucose adversely affects materno-fetal outcomes independent of maternal adiposity.

Key Words: Gestational diabetes mellitus, Pregnancy, Maternal outcomes, Fetal outcomes

1.0 Introduction

Gestational diabetes was traditionally defined as "hyperglycaemia first detected in pregnancy" thereby encompassing a wide range of clinical phenotypes and aetiologies (1). Concerns relating to the increasing incidence of obesity and the potential for unrecognised Type 2 Diabetes Mellitus (Type 2 DM) amongst women of childbearing age prompted international authorities to revise the definition to "diabetes first recognised in the second or third trimester that is not clearly overt diabetes" (2). Though the evidence was recognised to be of low grade, categorising women with hyperglycaemia diagnostic of overt diabetes separately was suggested due to the theoretical heightened risk of adverse materno-fetal outcomes in this sub-group.

Narrowing the timeframe in which gestational diabetes is diagnosed relates to glycaemic threshold revisions, which are based on findings from the Hyperglycaemia and Adverse Pregnancy Outcomes (HAPO) study. This observational study demonstrated a continuum between glucose and the proportion of infants born large for gestational age in 23,316 women who underwent 75g oral glucose tolerance tests (OGTTs) at 24-28 weeks gestation (3). Pregnancy induced physiological increases in

insulin resistance can expose a partial insulin secretory deficit in predisposed individuals precipitating hyperglycaemia, the risk of which is greatest in the third trimester (4). However, defective beta cell function is often evident prior to this (5). The optimal time to test for gestational diabetes is therefore unclear: sufficient time is needed for the hyperglycaemia to develop while simultaneously allowing an adequate treatment period for effective adverse outcome risk modification. In addition, maternal glycaemia should be considered early in pregnancy to detect pre-existing unrecognised Type 2 DM.

We hypothesised that the length of exposure to glucose would adversely affect materno-fetal outcomes and that women diagnosed with hyperglycaemia early in pregnancy would phenotypically resemble those with Type 2 DM in terms of outcomes, rather than those with gestational diabetes diagnosed on routine testing. To investigate this hypothesis, we undertook a case control study to compare women with hyperglycaemia detected prior to 20 weeks gestation to early pregnancy body mass index (BMI) matched women with established, recognised pre-gestational Type 2 DM and to those with gestational diabetes on routine testing i.e. 24-28 weeks gestation.

2.0 Materials and Methods

Pregnant women with hyperglycaemia detected prior to routine testing, who attended an inner-city multidisciplinary antenatal clinic (2010-2015) were retrospectively reviewed. Forty consecutive women were identified comprising the early hyperglycaemia (eGDM) group. These women had been identified to be at risk of

developing hyperglycaemia early either by nature of having had a previous pregnancy complicated by gestational diabetes, or due to the incidental finding of glycosuria. All women meeting the former criteria had been provided with a glucometer and standard dietary advice at 16 weeks gestation, unless a random plasma glucose (RPG) and/ or HbA1c was elevated, in which case intervention and subsequent multidisciplinary follow up were expedited. The same intervention was provided for those with glycosuria once hyperglycaemia was confirmed. Where dietary measures failed to adequately achieve target capillary blood glucose (CBG) values (fasting CBG <6.0mmol/L or 1 hour postprandial <8.0mmol/L) metformin and/or insulin, were commenced as appropriate.

Two separate control groups matched for early pregnancy BMI, were retrospectively identified from the cohort attending the same multidisciplinary antenatal clinic. The first group consisted of 80 consecutive pregnant women with a clinician-assigned diagnosis of Type 2 diabetes mellitusDM established at least 3 months prior to conception (T2DM group); the second comprised 80 women with gestational diabetes diagnosed on routine testing over a one--year period (2014-2015: rtGDM group). In accordance with the National Institute for Clinical Health and Excellence (NICE) guidelines, all women at our centre are screened for gestational diabetes risk factors at their initial antenatal assessment (6). The risk factors that defined the need for a diagnostic 75g OGTT at 24-28 weeks gestation consisted of non white-European ethnicity, an early pregnancy BMI $\geq$30kg/m^2, a previous pregnancy with macrosomia ($\geq$4000g) and a first degree relative with Type 2 diabetes mellitus. Modified 1999 WHO gestational diabetes diagnostic criteria were in use at the time of this study (fasting plasma glucose threshold $\geq$6.1mmol/L, 120 minute post 75g glucose load

value ≥7.8mmol/L) (7). Women who fulfilled criteria for overt diabetes either by 75g OGTT or HbA1c, which was routinely measured on confirmation of hyperglycaemia, were excluded from this second control group.

Prospectively collected maternal antenatal and delivery records were examined to establish baseline maternal demographics including self reported ethnicity, obstetric history, anthropometry and biochemical data. Hypertension at baseline was defined as either a BP measuring ≥140/90mmHg or anti-hypertensive use. Maternal outcomes evaluated included requirement for insulin during the antenatal period, delivery modality and development of pregnancy related hypertensive disorders. The latter was recorded as a composite outcome and a score of 1 applied if either of the following developed: pregnancy induced hypertension (PIH) i.e. hypertension developing after 20 weeks gestation (≥140/90mmHg or a rise in systolic BP >30mmHg/ >15-20mmHg in diastolic BP) and/or pre-eclampsia (PET) defined as new hypertension presenting after 20 weeks gestation with one or more of the following 1. ssignificant proteinuria (urine protein: creatinine ratio >30mg/mmol), 2. evidence of systemic involvement (renal/ hepatic/ neurological/ haematological) or 3. fetal growth restriction. The final maternal outcome assessed was postpartum glycaemia: all women diagnosed with hyperglycaemia in pregnancy were invited to a 6-week postpartum FPG assessment with a 75g OGTT and HbA1c planned in those with impaired fasting glycaemia.

Delivery and neonatal records were examined to establish fetal characteristics at birth and neonatal complications. The GROW gestation network calculator was used to determine customised birth weight centiles through adjusting birth weight for maternal height, weight, ethnicity, parity, fetal gestational age and gender (8). Large for gestational age (LGA) infants were defined as infants with an adjusted birth

weight ≥>90th centile: small for gestational age (SGA) as those with a birth weight <10th centile. Preterm delivery was defined as delivery prior to 37 weeks gestation. Neonatal complications were recorded as a composite outcome with a score of 1 applied if one or more of the following adverse events developed: shoulder dystocia, neonatal hypoglycaemia requiring treatment (defined as glucose <2.8mmol/L requiring either supplemental feeding or intravenous glucose), respiratory distress syndrome requiring oxygen therapy or continuous positive airway pressure for a minimum of four hours, admission to the neonatal intensive care unit (necessitated by preterm delivery <34 weeks gestation, low birth weight or medical conditions requiring management), or hyperbilirubinaemia requiring phototherapy.

2.1 Statistical Analysis

Continuous data are expressed as mean (±SD) or median (interquartile range) depending on the distribution of the data: ANOVA or Kruskal-Wallis tests were used as appropriate to detect significant variation in continuous variables between the groups. Categorical data are expressed as proportions and variation between groups tested by Chi-squared tests, with Fisher exact tests used where the expected cell frequency was less than five. A p value <0.05 was accepted as statistically significant. Where significant variation between groups was detected, hypothesis driven post-hoc between-group comparisons were undertaken using t-test, Mann-Whitney test or proportions test as appropriate. All analyses were performed with STATA v13.1 (StataCorp, Texas, USA).

3.0 Results

Across the cohort, mean age was 33.9 (±4.5) years and BMI 31.7 (±5.3) kg/m^2: 81% were non-White with women of South Asian ethnicity forming the largest sub-group (27.5%). Maternal baseline demographics are tabulated (Table 1). In addition to the control groups being matched for age and early-pregnancy BMI, the proportion of women of non-White ethnicity were similar.

There was significant variation in HbA1c at initial identification of hyperglycaemia between the groups (Table 1), with no difference in HbA1c (p=0.1) between the eGDM group and Type 2 DM controls on post hoc testing, and a significantly higher HbA1c in the eGDM compared with the rtGDM group (p<0.001). Analysis by HbA1c category demonstrated that 80.0% in the eGDM group and 18.7% in the rtGDM group had an HbA1c ≥ 6.1% (43mmol/mol). In the eGDM group, 37.5% had an HbA1c ≥ 6.5% (48mmol/mol): by definition, no women in the rtGDM group had an HbA1c diagnostic of Type 2 DM. In the T2DM group, 56.3% of women had an initial HbA1c exceeding the national recommendation for pre-conception i.e. ≥ 6.5% (48mmol/mol) (6). On average, women with Type 2 DM had been diagnosed 3.0 (2.0-6.5) years prior to pregnancy.

There was significant variation in parity statusParity status varied in the three groups (Table 1). In post hoc analysis, primigravida status was lower in the eGDM than the rtGDM group (17.5% versus 37% respectively p=0.002) and multiparity status higher (25.0% versus 4.0% p=0.001): parity status in parity status did not differ significantly between the eGDM and T2DM groups was similar. There was also significant variation between the groups in the proportion of women with a previous pregnancy complicated by gestational diabetes. No women in the rtGDM group had a previous

pregnancy complicated by gestational diabetes, whereas in the eGDM group the proportion was 71.8% (p<0.001). This was additionally higher than the 38.5% in the Type 2 DM group (p<0.001). There was significant variation in the The proportion of women with essential hypertension at baseline varied, with a higher proportion in the eGDM compared with the rtGDM group (p=0.004) but no difference between the eGDM versus the T2DM group (p=0.6).

3.1 Maternal Outcomes

There were significant differences in both theThe proportion of women requiring insulin and those developing pregnancy-related hypertensive disorders differed (Table 2): post-hoc , with, on post hoc testing demonstrated, no significant differences in the proportions between the eGDM and T2DM groups (p=0.1 and p=0.2 respectively) and significantly higher proportions in the eGDM compared to the rtGDM group (p<0.001 and p<0.001 respectively). Differences existed in delivery modalityOverall, delivery modality differed across the three groups (Table 2) though a sub-analysis demonstrated that emergency caesarean delivery rates were similar (22.5%, 27.5% and 21.3%, p=0.2) (Table 2).

3.2 Fetal outcomes

In total, eight stillbirths were recorded in this cohort: 4 in the eGDM group, 3 in the T2DM group and 1 in the rtGDM group (10.0%, 3.8%, 1.3% stillbirth rate respectively, p=0.069). Stillbirth data were excluded from the subsequent fetal outcome analyses. No congenital malformations or neonatal deaths were recorded in the remaining cohort.

Median fetal birth weight and adjusted ~~and~~ birth weight centile were similar in the three groups as were the proportion of neonates born large for gestational age (LGA) and macrosomic (birth weight $\geq$4000g) (Table 2). ~~No differences existed in the proportion of infants born either LGA or macrosomic (birth weight $\geq$4000g). Significant variations existed in the~~ The proportion ~~of infants~~ born ~~SGA~~small for gestational age (SGA) differed~~:~~ with post hoc analysis ~~demonstrated~~ demonstrating, at borderline significance, ~~no significant difference in the proportion between the eGDM and Type 2 DM group (p=0.7) but a~~ a higher proportion born SGA to ~~in~~ the eGDM compared ~~with~~ to the rtGDM group ~~at borderline significance~~ (p=0.05). ~~There was significant variation in the proportion~~Preterm delivery rates also varied ~~of neonates born preterm,~~ with women with eGDM ~~significantly~~ more likely to deliver prior to 37 weeks gestation than those with rtGDM on post hoc analysis: there was no ~~significant~~ difference in the preterm delivery rate between the eGDM and T2DM groups (p=0.2). ~~No significant difference existed in neonatal~~Neonatal complication rates were similar in the three groups (11.1%, 13.0% and 11.4%, p=0.9).

3.3 Postpartum Glucose Assessments

Postpartum glucose assessments were offered to all women diagnosed with hyperglycaemia in pregnancy: 18 women with eGDM (45.0%) and 57 women with rtGDM (71.3%) attended. Median (IQR) FPG was higher in the latter group: 5.7 (4.9-6.8) mmol/L versus 5.0 (4.6-5.3) mmol/L, p=0.02. Individuals with an impaired FPG had a subsequent 75g OGTT. Overall, a higher proportion of women in the eGDM group were diagnosed with either impaired glucose tolerance or Type 2 DM within a 3 month period: 20.0% versus 1.3% and 7.5% versus 1.3% respectively, p<0.001.

4.0 Conclusions

These data suggest that women with hyperglycaemia detected early in pregnancy resemble women with established Type 2 DM ~~in terms of maternal outcomes~~, with a similar proportion of women requiring insulin and developing hypertensive disorders compared to those diagnosed with gestational diabetes on routine testing. Furthermore, risk of glucose intolerance persisting postpartum was heightened in women with early hyperglycaemia. ~~In terms of fetal outcomes, a~~ A similar proportion of neonates were born preterm in women with early hyperglycaemia and Type 2 DM~~:~~ ~~the rate in the former group: was significantly higher than among~~ women with routinely diagnosed gestational diabetes had lower preterm delivery rates. In addition, rtGDM women had ~~Variations in stillbirth rate and proportion of infants born small for gestational age were also observed, with women with routinely diagnosed gestational diabetes having the lowest rates~~ the lowest stillbirth rate and lowest proportion of infants born small for gestational age.~~.~~

These data add to those described by a retrospective study conducted in Australia (9). In this study, data from 4873 women attending an antenatal centre over a ten-year period were examined and women were categorised into one of 4 groups: pre-existing diabetes, hyperglycaemia detected at <12 weeks gestation, hyperglycaemia detected at 12-23 weeks and hyperglycaemia diagnosed ≥24 weeks gestation. Requirement for insulin therapy, hypertensive disorders, preterm delivery, and caesarean sections were all more prevalent in women with pre-existing diabetes and early gestational diabetes. Maternal age and obesity are independent risk factors for adverse materno-fetal outcomes including macrosomia and pregnancy-related hypertensive disorders (10,

11). Significant variations existed in the mean age and pre-pregnancy BMI across the four groups in the Australian study. In contrast, maternal age and BMI were matched across the groups in our study, removing the potential for confounding and clearly suggesting that the spectrum of gestational diabetes to Type 2 DM is defined not only by the degree of glycaemia as illustrated by the HAPO study, but also by the length of exposure to hyperglycaemia (3).

In contrast to the Australian study, no significant variations existed in the proportion of infants born macrosomic (≥4000g) in our study. However, variations existed in the proportion of infants born small for gestational age. Our study was not designed to demonstrate the cause of small for gestational age neonates. This observational finding could relate to placental insufficiency associated with the increased incidence of hypertensive disorders observed in these groups. The non-significant increase in stillbirth rate observed in women with eGDM is also an important finding. Both Type 1 and Type 2 DM are associated with an increased risk of congenital malformations mediated by the teratogenic effects of hyperglycaemia together with the oxidative stress observed during the period of organogenesis (12). The higher stillbirth rate demonstrated in the eGDM group could indeed indicate developmental malformations secondary to early pregnancy hyperglycaemia and similar pathophysiological features.

Our study has further limitations. The diagnosis of Type 2 DM was clinician assigned. In addition, there were no antibody results available for women in the eGDM group. There are data demonstrating that ethnicity is an independent risk factor for adverse materno-fetal outcomes (13). Though the proportion of women of non-White ethnicity

was similar in the three groups, residual confounding on sub-ethnicity classifications may have existed. Decisions to intensify treatment were generally based on home capillary blood glucose values rendering it difficult to compare the effectiveness of glycaemic control strategies across the groups. Finally, postpartum glucose assessments were dependent on subsequent clinic attendance. This was incomplete with 37.5% of women diagnosed with hyperglycaemia in pregnancy failing to attend. Though 72.5% of the women who attended in the eGDM group had normoglycaemia postpartum, the length of follow-up may have been insufficient particularly when considering evidence suggesting the delay in progression to Type 2 DM associated with breastfeeding (14).

Ours was an exploratory, observational study examining whether there might be an issue relating to the length of exposure to hyperglycaemia independent of variation in adiposity. Future work should focus on viable screening strategies for high-risk women. In our study, the majority of women were screened for hyperglycaemia early in pregnancy due to a history of previous gestational diabetes (71.8%). Differences in parity status were also found with women with early hyperglycaemia being less likely to be in their first pregnancy and more likely to be multiparous. Data from the Australian study indicate that a higher incidence of a family history of Type 2 DM is found in women with early hyperglycaemia compared to those with GDM diagnosed ≥24 weeks gestation.

The most appropriate diagnostic criteria to diagnose hyperglycaemia in early pregnancy are the subject of considerable debate. In our study significant variations existed in HbA1c at initial diagnosis. However, twenty per cent of individuals in the

eGDM group had an HbA1c that would be considered normal in a non-pregnant population implicating its limitations as a diagnostic tool. The increased red cell turn over observed in pregnancy together with ethnicity based variations renders it difficult to clearly define an appropriate HbA1c threshold (15, 16). One prospective study conducted in New Zealand demonstrated that women with an HbA1c above 41mmol/mol (5.9%) had a positive predictive value of developing gestational diabetes prior to 20 weeks gestation of 52.9%. In women with an HbA1c that exceeded this threshold, relative risk of major congenital anomalies, preeclampsia, shoulder dystocia and perinatal death were all increased (17). Ethnicity-based variations in HbA1c were addressed in a subsequent prospective cohort study conducted in Barcelona, which demonstrated that an HbA1c exceeding 41mmol/mol (5.9%) was associated with a significantly increased risk of macrosomia and development of pre-eclampsia in a multi-ethnic cohort following adjustment for confounding factors (18). In relation to the most appropriate diagnostic glucose threshold, international authorities including IADPSG and ADA recommend an FPG $\geq$5.1mmol/L for diagnosis even in the early stages of pregnancy (1, 19). Prospective cohort studies conducted in China and Italy suggest that this value is poorly predictive, instead demonstrating a substantial fall in glucose in early pregnancy, even in those that later develop glucose intolerance (20, 21). Given that reductions in insulin sensitivity are observed in high-risk groups prior to the onset of hyperglycaemia, suitable methods and thresholds to diagnose this could also be explored (5).

Despite early intervention and management, women with early hyperglycaemia had an increased risk of adverse outcomes compared to those diagnosed routinely at 24-28 weeks gestation. Addressing factors other than glycaemia could mitigate this. The

benefit of aspirin as a means of preventing or delaying pre-eclampsia or of folic acid in reducing congenital malformation risk could be explored. The need for early delivery in the same way that delivery of neonates prior to 39 weeks gestation is recommended for women with pre-gestational diabetes to avoid the risk of still birth could also be considered (6).

This study has shown that women with hyperglycaemia detected early in pregnancy represent a separate clinical entity to those diagnosed with hyperglycaemia on routine diagnostic testing, implicating the importance of length of exposure to hyperglycaemia independent of maternal adiposity. Indeed, an overlap has been demonstrated between women with early hyperglycaemia and those with established and recognised Type 2 DM in terms of materno-fetal outcomes signifying the importance of screening in high-risk population groups. Practical considerations in this group include effective screening strategies, early identification and prevention of risk.

5.1 Disclosure Summary: The authors have no conflicts of interest to disclose.

5.2 Author Contributions:

R.A.J. analysed the data and wrote the manuscript. N.O. contributed to the analysis and reviewed/ edited the manuscript. M.K. collected the data. I.F.G. analysed the data and reviewed/ edited the manuscript. C.Y., J.T. and D.G. contributed to the discussion of the analysis and reviewed the manuscript. D.J. contributed to the analysis and reviewed the manuscript. S.R. contributed to analysis and wrote/ revised the manuscript. S.R. is the guarantor of this work and, as such, takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Individual to who reprint requests should be sent to:

Professor Stephen Robinson, Department of Metabolic Medicine, Min Wing, St Mary's Hospital, Imperial College NHS Trust, W2 1NY, United Kingdom. Telephone: +44 203 312 1253   Email: Stephen.Robinson@imperial.nhs.uk

Table 1: Maternal baseline demographics and biochemical data in women with hyperglycaemia diagnosed prior to 20 weeks gestation, women with recognised pre-gestational type 2 diabetes and women with gestational diabetes diagnosed on routine testing

	eGDM (n=40)	T2DM (n=80)	rtGDM (n=80)	Significance
Mean (SD) Age (years)	33.9 (±4.5)	34.2 (±5.1)	33.7 (±5.5)	0.35
Mean (SD) Height (cm)	161.7 (±7.3)	161.5 (±7.2)	160.8 (±6.0)	0.79
Mean (SD) Weight (kg)	83.6 (±15.8)	84.1 (±19.2)	78.8 (±12.5)	0.14
Median (IQR) BMI (kg/m^2)	32.0 (27.0-35.0)	31.0 (28.0-35.9)	30.4 (27.9-33.9)	0.50
Non-White ethnicity % (n)	80.0 (32)	86.2 (69)	76.3 (61)	0.27
Black African-Caribbean	25.0 (10)	26.2 (21)	22.5 (18)	
Arab/ North African	20.0 (8)	15.0 (12)	7.5 (6)	
South Asian	25.0 (10)	37.5 (30)	18.8 (15)	
Other	10.0 (4)	7.5 (6)	27.5 (22)	
Parity				
Primigravida % (n)	17.5 (7)	18 (22.5)	37 (46.3)	<0.001
Multiparous %(n) [a]	25.0 (10)	11 (13.8)	4 (5.0)	
History previous pregnancy complicated by GDM % (n)	71.8 (28)	38.5 (30)	0.0 (0)	<0.001
Diagnosis Hypertension %(n) [b]	20.0 (8)	23.4 (18)	3.8 (3)	0.001
Median (IQR) HbA1c (%)	6.4 (6.1-7.3)	6.8 (6.1-7.8)	5.6 (5.3-5.8)	<0.001
Median (IQR) HbA1c (mmol/mol)	46 (43-56)	51 (43-62)	38 (34-40)	<0.001

Footnotes:

eGDM Hyperglycaemia identified prior to 20 weeks gestation; *T2DM* Type 2 diabetes; *rtGDM* Gestational diabetes diagnosed on routine testing (24-28 weeks gestation); *IQR* Interquartile range; *BMI* Body mass index (measured at initial antenatal visit); *GDM* Gestational diabetes.

a. Defined as four or more deliveries after 24 weeks gestation

b. On anti-hypertensive medications and/ or blood pressure measured ≥140/90mmHg at initial antenatal visit.

Table 2: Maternofetal outcomes in women with hyperglycaemia diagnosed prior to 20 weeks gestation, women with recognised pre-gestational type 2 diabetes and women with gestational diabetes diagnosed on routine testing

	eGDM (n=40)	T2DM (n=80)	rtGDM (n=80)	Significance
Proportion requiring insulin treatment % (n)	88.6 (31)	77.0 (57)	8.1 (6)	<0.001
Hypertensive disorders of pregnancy % (n) [a]	42.5 (17)	37.5 (26)	12.5 (5)	<0.001
Delivery modality % (n)				
SVD	27.5 (11)	31.3 (25)	46.3 (37)	
AVD	12.5 (5)	5.0 (4)	16.3 (13)	0.01
Elective Caesarean Section	37.5 (15)	36.3 (28)	16.3 (13)	
Emergency Caesarean Section	22.5 (9)	27.5 (22)	21.3 (17)	
Postpartum Haemorrhage				
Moderate (500-1000ml) % (n)	35.9 (14)	32.5 (26)	31.3 (25)	0.98
Severe (≥1000ml) % (n)	10.3 (4)	8.8 (7)	8.8 (7)	
Stillbirth % (n)	10.0 (4)	3.8 (3)	1.3 (1)	0.07
Median (IQR) fetal birthweight (g)	3350 (2820-3840)	3225 (2855-3735)	3370 (3090-3670)	0.34
Median (IQR) birthweight centile [b]	63.6 (26.0-98.1)	61 (26.0-91.4)	50 (29.0-76.7)	0.50
Infants born LGA % (n)	30.6 (11)	27.3 (21)	17.7 (14)	0.22
Infants born macrosomic (≥4000g) % (n)	19.4 (7)	15.6 (12)	11.4 (9)	0.50
Infants born SGA % (n)	11.1 (4)	13.0 (10)	2.5 (2)	0.05
Preterm delivery (<37 weeks gestation) % (n)	30.0 (12)	20.0 (16)	3.8 (2)	<0.001
Neonatal complications % (n) [c]	11.1 (4)	13.0 (10)	11.4 (9)	0.94
Median (IQR) postpartum fasting glucose (mmol/L)	5.7 (4.9-6.8)	NA	5.0 (4.6-5.3)	0.03

Footnotes:

eGDM Hyperglycaemia detected prior to 20 weeks gestation, *T2DM* Type 2 diabetes mellitus, *rtGDM* Gestational diabetes diagnosed on routine diagnostic testing (24-28 weeks gestation), *SVD* Spontaneous vertex delivery, *AVD* Assisted vaginal delivery, *LGA* Large for gestational age (adjusted birth weight ≥90th centile), *SGA* Small for gestational age (adjusted birth weight <10th centile).

a. Hypertensive disorders of pregnancy recorded as a composite outcome if one of more of the following developed: a. Pregnancy induced hypertension (PIH: development of blood pressure ≥140/80 or increase in systolic blood pressure by 20mmHg from 20 weeks gestation) b. Pre-eclampsia (PET: defined as development proteinuria and hypertension).

b. Fetal birth weight centile is equal to fetal birth weight adjusted for maternal height, weight, ethnicity, fetal gender and gestational age at delivery.

c. Composite outcome with score of 1 applied if one of the following occurred: shoulder dystocia, neonatal hypoglycaemia requiring treatment, neonatal hyperbilirubinaemia requiring phototherapy, respiratory distress requiring either oxygen or continuous positive airway pressure and requirement for neonatal intensive care.

Title Page

Full Title: Hyperglycaemia Recognised in Early Pregnancy is Phenotypically Type 2 Diabetes Mellitus not Gestational Diabetes Mellitus: A Case Control Study

Authors: R Agha-Jaffar[1], NS Oliver [1], M Kostoula [2], IF Godsland [1], C Yu [3], J Terry [3], D Johnston [1], D Gable [2] & S Robinson [2].

Affiliations: 1. Diabetes, Endocrinology & Metabolism, Department of Medicine, Imperial College London. 2. Department of Metabolic Medicine, St Mary's Hospital, Imperial College NHS Trust. 3. Department of Maternal Medicine, St Mary's Hospital, Imperial College NHS Trust.

Corresponding author: Professor Stephen Robinson, Department of Metabolic Medicine, Mint Wing, St Mary's Hospital, Imperial College NHS Trust, W2 1NY, United Kingdom. Telephone: +44 203 312 1253
Email: Stephen.Robinson15@nhs.net

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Abstract

Objective: Gestational diabetes mellitus is defined as "diabetes recognised in the second or third trimester that is not clearly overt diabetes". Evidence relating to women with hyperglycaemia early in pregnancy is limited. We aimed to evaluate women diagnosed with hyperglycaemia early in pregnancy (eGDM) and compare them to those with pre-gestational established Type 2 Diabetes Mellitus (T2DM) and gestational diabetes diagnosed routinely at 24-28 weeks gestation (rtGDM) to determine if length of exposure to hyperglycaemia adversely affected outcomes.

Methods: Forty consecutive women with eGDM who attended a multidisciplinary antenatal clinic were reviewed. Two separate BMI-matched control groups were identified: recognised pre-gestational T2DM (n=80) and rtGDM (n=80). Baseline demographics and outcomes were compared.

Results: A higher proportion of women in the eGDM and T2DM group required insulin and the incidence of hypertensive disorders was similarly increased compared with the rtGDM group (88.6%, 77.0% versus 8.1%, p<0.001 and 42.5%, 37.5% versus 12.5% p<0.001 respectively). The proportion of infants born small for gestational age varied (eGDM 11.1%, T2DM 13.0% and rtGDM 2.5%, p=0.049). Postpartum, 7.5% of eGDM women were diagnosed with T2DM versus 1.3% in the rtGDM group (p<0.001).

Conclusions: These novel data demonstrate that length of exposure to glucose adversely affects materno-fetal outcomes independent of maternal adiposity.

Key Words: Gestational diabetes mellitus, Pregnancy, Maternal outcomes, Fetal outcomes

1.0 Introduction

Gestational diabetes was traditionally defined as "hyperglycaemia first detected in pregnancy" thereby encompassing a wide range of clinical phenotypes and aetiologies (1). Concerns relating to the increasing incidence of obesity and the potential for unrecognised Type 2 Diabetes Mellitus (Type 2 DM) amongst women of childbearing age prompted international authorities to revise the definition to "diabetes first recognised in the second or third trimester that is not clearly overt diabetes" (2). Though the evidence was recognised to be of low grade, categorising women with hyperglycaemia diagnostic of overt diabetes separately was suggested due to the theoretical heightened risk of adverse materno-fetal outcomes in this sub-group.

Narrowing the timeframe in which gestational diabetes is diagnosed relates to glycaemic threshold revisions, which are based on findings from the Hyperglycaemia and Adverse Pregnancy Outcomes (HAPO) study. This observational study demonstrated a continuum between glucose and the proportion of infants born large for gestational age in 23,316 women who underwent 75g oral glucose tolerance tests (OGTTs) at 24-28 weeks gestation (3). Pregnancy induced physiological increases in insulin resistance can expose a partial insulin secretory deficit in predisposed individuals precipitating hyperglycaemia, the risk of which is greatest in the third trimester (4). However, defective beta cell function is often evident prior to this (5).

The optimal time to test for gestational diabetes is therefore unclear: sufficient time is needed for the hyperglycaemia to develop while simultaneously allowing an adequate treatment period for effective adverse outcome risk modification. In addition, maternal glycaemia should be considered early in pregnancy to detect pre-existing unrecognised Type 2 DM.

We hypothesised that the length of exposure to glucose would adversely affect materno-fetal outcomes and that women diagnosed with hyperglycaemia early in pregnancy would phenotypically resemble those with Type 2 DM in terms of outcomes, rather than those with gestational diabetes diagnosed on routine testing. To investigate this hypothesis, we undertook a case control study to compare women with hyperglycaemia detected prior to 20 weeks gestation to early pregnancy body mass index (BMI) matched women with established, recognised pre-gestational Type 2 DM and to those with gestational diabetes on routine testing i.e. 24-28 weeks gestation.

2.0 Materials and Methods

Pregnant women with hyperglycaemia detected prior to routine testing, who attended an inner-city multidisciplinary antenatal clinic (2010-2015) were retrospectively reviewed. Forty consecutive women were identified comprising the early hyperglycaemia (eGDM) group. These women had been identified to be at risk of developing hyperglycaemia early either by nature of having had a previous pregnancy complicated by gestational diabetes, or due to the incidental finding of glycosuria. All women meeting the former criteria had been provided with a glucometer and standard

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dietary advice at 16 weeks gestation, unless a random plasma glucose (RPG) and/ or HbA1c was elevated, in which case intervention and subsequent multidisciplinary follow up were expedited. The same intervention was provided for those with glycosuria once hyperglycaemia was confirmed. Where dietary measures failed to adequately achieve target capillary blood glucose (CBG) values (fasting CBG <6.0mmol/L or 1 hour postprandial <8.0mmol/L) metformin and/or insulin, were commenced as appropriate.

Two separate control groups matched for early pregnancy BMI, were retrospectively identified from the cohort attending the same multidisciplinary antenatal clinic. The first group consisted of 80 consecutive pregnant women with a clinician-assigned diagnosis of Type 2 diabetes mellitus established at least 3 months prior to conception (T2DM group); the second comprised 80 women with gestational diabetes diagnosed on routine testing over a one-year period (2014-2015: rtGDM group). In accordance with the National Institute for Clinical Health and Excellence (NICE) guidelines, all women at our centre are screened for gestational diabetes risk factors at their initial antenatal assessment (6). The risk factors that defined the need for a diagnostic 75g OGTT at 24-28 weeks gestation consisted of non white-European ethnicity, an early pregnancy BMI $\geq$30kg/m^2, a previous pregnancy with macrosomia ($\geq$4000g) and a first degree relative with Type 2 diabetes mellitus. Modified 1999 WHO gestational diabetes diagnostic criteria were in use at the time of this study (fasting plasma glucose threshold $\geq$6.1mmol/L, 120 minute post 75g glucose load value $\geq$7.8mmol/L) (7). Women who fulfilled criteria for overt diabetes either by 75g OGTT or HbA1c, which was routinely measured on confirmation of hyperglycaemia, were excluded from this second control group.

Prospectively collected maternal antenatal and delivery records were examined to establish baseline maternal demographics including self reported ethnicity, obstetric history, anthropometry and biochemical data. Hypertension at baseline was defined as either a BP measuring ≥140/90mmHg or anti-hypertensive use. Maternal outcomes evaluated included requirement for insulin during the antenatal period, delivery modality and development of pregnancy related hypertensive disorders. The latter was recorded as a composite outcome and a score of 1 applied if either of the following developed: pregnancy induced hypertension (PIH) i.e. hypertension developing after 20 weeks gestation (≥140/90mmHg or a rise in systolic BP >30mmHg/ >15-20mmHg in diastolic BP) and/or pre-eclampsia (PET) defined as new hypertension presenting after 20 weeks gestation with one or more of the following 1. significant proteinuria (urine protein: creatinine ratio >30mg/mmol), 2. evidence of systemic involvement (renal/ hepatic/ neurological/ haematological) or 3. fetal growth restriction. The final maternal outcome assessed was postpartum glycaemia: all women diagnosed with hyperglycaemia in pregnancy were invited to a 6-week postpartum FPG assessment with a 75g OGTT and HbA1c planned in those with impaired fasting glycaemia.

Delivery and neonatal records were examined to establish fetal characteristics at birth and neonatal complications. The GROW gestation network calculator was used to determine customised birth weight centiles through adjusting birth weight for maternal height, weight, ethnicity, parity, fetal gestational age and gender (8). Large for gestational age (LGA) infants were defined as infants with an adjusted birth weight >90th centile: small for gestational age (SGA) as those with a birth weight <10th centile. Preterm delivery was defined as delivery prior to 37 weeks gestation. Neonatal complications were recorded as a composite outcome with a score of 1

applied if one or more of the following adverse events developed: shoulder dystocia, neonatal hypoglycaemia requiring treatment (defined as glucose <2.8mmol/L requiring either supplemental feeding or intravenous glucose), respiratory distress syndrome requiring oxygen therapy or continuous positive airway pressure for a minimum of four hours, admission to the neonatal intensive care unit (necessitated by preterm delivery <34 weeks gestation, low birth weight or medical conditions requiring management), or hyperbilirubinaemia requiring phototherapy.

2.1 Statistical Analysis

Continuous data are expressed as mean (±SD) or median (interquartile range) depending on the distribution of the data: ANOVA or Kruskal-Wallis tests were used as appropriate to detect significant variation in continuous variables between the groups. Categorical data are expressed as proportions and variation between groups tested by Chi-squared tests, with Fisher exact tests used where the expected cell frequency was less than five. A p value <0.05 was accepted as statistically significant. Where significant variation between groups was detected, hypothesis driven post-hoc between-group comparisons were undertaken using t-test, Mann-Whitney test or proportions test as appropriate. All analyses were performed with STATA v13.1 (StataCorp, Texas, USA).

3.0 Results

Across the cohort, mean age was 33.9 (±4.5) years and BMI 31.7 (±5.3) kg/m^2: 81% were non-White with women of South Asian ethnicity forming the largest sub-group (27.5%). Maternal baseline demographics are tabulated (Table 1). In addition to the

control groups being matched for age and early-pregnancy BMI, the proportion of women of non-White ethnicity were similar.

Analysis by HbA1c category demonstrated that 80.0% in the eGDM group and 18.7% in the rtGDM group had an HbA1c $\geq$ 6.1% (43mmol/mol). In the eGDM group, 37.5% had an HbA1c $\geq$ 6.5% (48mmol/mol): by definition, no women in the rtGDM group had an HbA1c diagnostic of Type 2 DM. In the T2DM group, 56.3% of women had an initial HbA1c exceeding the national recommendation for pre-conception i.e. $\geq$ 6.5% (48mmol/mol) (6). On average, women with Type 2 DM had been diagnosed 3.0 (2.0-6.5) years prior to pregnancy.

Parity status varied in the three groups (Table 1). In post hoc analysis, primigravida status was lower in the eGDM than the rtGDM group (17.5% versus 37% respectively p=0.002) and multiparity status higher (25.0% versus 4.0% p=0.001): parity status in the eGDM and T2DM groups was similar. The proportion of women with essential hypertension at baseline varied, with a higher proportion in the eGDM compared with the rtGDM group (p=0.004) but no difference between the eGDM versus the T2DM group (p=0.6).

3.1 Maternal Outcomes

The proportion of women requiring insulin and those developing pregnancy-related hypertensive disorders differed (Table 2): post-hoc testing demonstrated no differences in the proportions between the eGDM and T2DM groups (p=0.1 and p=0.2 respectively) and higher proportions in the eGDM compared to the rtGDM group (p<0.001 and p<0.001 respectively). Overall, delivery modality differed across

the three groups though a sub-analysis demonstrated that emergency caesarean delivery rates were similar (22.5%, 27.5% and 21.3%, p=0.2) (Table 2).

3.2 Fetal outcomes

In total, eight stillbirths were recorded in this cohort: 4 in the eGDM group, 3 in the T2DM group and 1 in the rtGDM group (10.0%, 3.8%, 1.3% stillbirth rate respectively, p=0.069). Stillbirth data were excluded from the subsequent fetal outcome analyses. No congenital malformations or neonatal deaths were recorded in the remaining cohort.

Median fetal birth weight and adjusted birth weight centile were similar in the three groups as were the proportion of neonates born large for gestational age (LGA) and macrosomic (birth weight ≥4000g) (Table 2). The proportion born small for gestational age (SGA) differed with post hoc analysis demonstrating, at borderline significance, a higher proportion born SGA to the eGDM compared to the rtGDM group (p=0.05). Preterm delivery rates also varied with women with eGDM more likely to deliver prior to 37 weeks gestation than those with rtGDM on post hoc analysis: there was no difference in the preterm delivery rate between the eGDM and T2DM groups (p=0.2). Neonatal complication rates were similar in the three groups (11.1%, 13.0% and 11.4%, p=0.9).

3.3 Postpartum Glucose Assessments

Postpartum glucose assessments were offered to all women diagnosed with hyperglycaemia in pregnancy: 18 women with eGDM (45.0%) and 57 women with rtGDM (71.3%) attended. Median (IQR) FPG was higher in the latter group: 5.7 (4.9-

6.8) mmol/L versus 5.0 (4.6-5.3) mmol/L, p=0.02. Individuals with an impaired FPG had a subsequent 75g OGTT. Overall, a higher proportion of women in the eGDM group were diagnosed with either impaired glucose tolerance or Type 2 DM within a 3 month period: 20.0% versus 1.3% and 7.5% versus 1.3% respectively, p<0.001.

4.0 Conclusions

These data suggest that women with hyperglycaemia detected early in pregnancy resemble women with established Type 2 DM, with a similar proportion of women requiring insulin and developing hypertensive disorders compared to those diagnosed with gestational diabetes on routine testing. Furthermore, risk of glucose intolerance persisting postpartum was heightened in women with early hyperglycaemia. A similar proportion of neonates were born preterm in women with early hyperglycaemia and Type 2 DM: women with routinely diagnosed gestational diabetes had lower preterm delivery rates. In addition, rtGDM women had the lowest stillbirth rate and lowest proportion of infants born small for gestational age.

These data add to those described by a retrospective study conducted in Australia (9). In this study, data from 4873 women attending an antenatal centre over a ten-year period were examined and women were categorised into one of 4 groups: pre-existing diabetes, hyperglycaemia detected at <12 weeks gestation, hyperglycaemia detected at 12-23 weeks and hyperglycaemia diagnosed ≥24 weeks gestation. Requirement for insulin therapy, hypertensive disorders, preterm delivery, and caesarean sections were all more prevalent in women with pre-existing diabetes and early gestational diabetes. Maternal age and obesity are independent risk factors for adverse materno-fetal

outcomes including macrosomia and pregnancy-related hypertensive disorders (10, 11). Significant variations existed in the mean age and pre-pregnancy BMI across the four groups in the Australian study. In contrast, maternal age and BMI were matched across the groups in our study, removing the potential for confounding and clearly suggesting that the spectrum of gestational diabetes to Type 2 DM is defined not only by the degree of glycaemia as illustrated by the HAPO study, but also by the length of exposure to hyperglycaemia (3).

In contrast to the Australian study, no significant variations existed in the proportion of infants born macrosomic (≥4000g) in our study. However, variations existed in the proportion of infants born small for gestational age. Our study was not designed to demonstrate the cause of small for gestational age neonates. This observational finding could relate to placental insufficiency associated with the increased incidence of hypertensive disorders observed in these groups. The non-significant increase in stillbirth rate observed in women with eGDM is also an important finding. Both Type 1 and Type 2 DM are associated with an increased risk of congenital malformations mediated by the teratogenic effects of hyperglycaemia together with the oxidative stress observed during the period of organogenesis (12). The higher stillbirth rate demonstrated in the eGDM group could indeed indicate developmental malformations secondary to early pregnancy hyperglycaemia and similar pathophysiological features.

Our study has further limitations. The diagnosis of Type 2 DM was clinician assigned. In addition, there were no antibody results available for women in the eGDM group. There are data demonstrating that ethnicity is an independent risk factor for adverse

materno-fetal outcomes (13). Though the proportion of women of non-White ethnicity was similar in the three groups, residual confounding on sub-ethnicity classifications may have existed. Decisions to intensify treatment were generally based on home capillary blood glucose values rendering it difficult to compare the effectiveness of glycaemic control strategies across the groups. Finally, postpartum glucose assessments were dependent on subsequent clinic attendance. This was incomplete with 37.5% of women diagnosed with hyperglycaemia in pregnancy failing to attend. Though 72.5% of the women who attended in the eGDM group had normoglycaemia postpartum, the length of follow-up may have been insufficient particularly when considering evidence suggesting the delay in progression to Type 2 DM associated with breastfeeding (14).

Ours was an exploratory, observational study examining whether there might be an issue relating to the length of exposure to hyperglycaemia independent of variation in adiposity. Future work should focus on viable screening strategies for high-risk women. In our study, the majority of women were screened for hyperglycaemia early in pregnancy due to a history of previous gestational diabetes (71.8%). Differences in parity status were also found with women with early hyperglycaemia being less likely to be in their first pregnancy and more likely to be multiparous. Data from the Australian study indicate that a higher incidence of a family history of Type 2 DM is found in women with early hyperglycaemia compared to those with GDM diagnosed ≥24 weeks gestation.

The most appropriate diagnostic criteria to diagnose hyperglycaemia in early pregnancy are the subject of considerable debate. In our study significant variations

existed in HbA1c at initial diagnosis. However, twenty per cent of individuals in the eGDM group had an HbA1c that would be considered normal in a non-pregnant population implicating its limitations as a diagnostic tool. The increased red cell turn over observed in pregnancy together with ethnicity based variations renders it difficult to clearly define an appropriate HbA1c threshold (15, 16). One prospective study conducted in New Zealand demonstrated that women with an HbA1c above 41mmol/mol (5.9%) had a positive predictive value of developing gestational diabetes prior to 20 weeks gestation of 52.9%. In women with an HbA1c that exceeded this threshold, relative risk of major congenital anomalies, preeclampsia, shoulder dystocia and perinatal death were all increased (17). Ethnicity-based variations in HbA1c were addressed in a subsequent prospective cohort study conducted in Barcelona, which demonstrated that an HbA1c exceeding 41mmol/mol (5.9%) was associated with a significantly increased risk of macrosomia and development of pre-eclampsia in a multi-ethnic cohort following adjustment for confounding factors (18). In relation to the most appropriate diagnostic glucose threshold, international authorities including IADPSG and ADA recommend an FPG $\geq$5.1mmol/L for diagnosis even in the early stages of pregnancy (1, 19). Prospective cohort studies conducted in China and Italy suggest that this value is poorly predictive, instead demonstrating a substantial fall in glucose in early pregnancy, even in those that later develop glucose intolerance (20, 21). Given that reductions in insulin sensitivity are observed in high-risk groups prior to the onset of hyperglycaemia, suitable methods and thresholds to diagnose this could also be explored (5).

Despite early intervention and management, women with early hyperglycaemia had an increased risk of adverse outcomes compared to those diagnosed routinely at 24-28

weeks gestation. Addressing factors other than glycaemia could mitigate this. The benefit of aspirin as a means of preventing or delaying pre-eclampsia or of folic acid in reducing congenital malformation risk could be explored. The need for early delivery in the same way that delivery of neonates prior to 39 weeks gestation is recommended for women with pre-gestational diabetes to avoid the risk of still birth could also be considered (6).

This study has shown that women with hyperglycaemia detected early in pregnancy represent a separate clinical entity to those diagnosed with hyperglycaemia on routine diagnostic testing, implicating the importance of length of exposure to hyperglycaemia independent of maternal adiposity. Indeed, an overlap has been demonstrated between women with early hyperglycaemia and those with established and recognised Type 2 DM in terms of materno-fetal outcomes signifying the importance of screening in high-risk population groups. Practical considerations in this group include effective screening strategies, early identification and prevention of risk.

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5.2 Author Contributions:

R.A.J. analysed the data and wrote the manuscript. N.O. contributed to the analysis and reviewed/ edited the manuscript. M.K. collected the data. I.F.G. analysed the data and reviewed/ edited the manuscript. C.Y., J.T. and D.G. contributed to the discussion of the analysis and reviewed the manuscript. D.J. contributed to the analysis and reviewed the manuscript. S.R. contributed to analysis and wrote/ revised the manuscript. S.R. is the guarantor of this work and, as such, takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Individual to who reprint requests should be sent to:

Professor Stephen Robinson, Department of Metabolic Medicine, Min Wing, St Mary's Hospital, Imperial College NHS Trust, W2 1NY, United Kingdom. Telephone: +44 203 312 1253   Email: Stephen.Robinson@imperial.nhs.uk