HbA1c at the time of testing for gestational diabetes identifies women at risk for pregnancy complications

F. Barbry, Madleen Lemaitre, Camille Ternynck, H. Wallet, M Cazaubiel, Julien Labreuche, Damien Subtil, Anne Vambergue

HbA1c at the time of testing for gestational diabetes identifies women at risk for pregnancy complications

Short running title : **HbA1c and GDM complications**

Floriane Barbry[1], Madleen Lemaitre[1,3], Camille Ternynck[2,4,] Helene Wallet[1], Marie Cazaubiel[5], Julien Labreuche[4], Damien Subtil[2,3,5], Anne Vambergue[1,3,6]

[1] CHU Lille, Department of Diabetology, Endocrinology, Metabolism and, Nutrition Lille University Hospital, F-59000, Lille, France.

[2] University of Lille, CHU Lille, ULR 2694 - METRICS : évaluation des technologies de santé et des pratiques médicales, F-59000 Lille, France

[3] University of Lille, F-59000, Lille, France

[4] CHU Lille, Department of Biostatistics, F-59000 Lille, France.

[5] CHU Lille, Department of Gynaecology and Obstetrics, Lille University Hospital, F-59000, Lille, France.

[6] European Genomic Institute for Diabetes, University School of Medicine, F-59000 Lille, France

Corresponding author: Pr Anne VAMBERGUE,

Address: Department of Diabetology, Endocrinology and Metabolism, Claude Huriez Hospital, Polonovski Street, 59037 Lille, cedex, France

Phone number: 33 3 20 44 58 43

Email: anne.vambergue@chru-lille.fr

ABSTRACT

Objective. - It is unclear whether glycated haemoglobin (HbA1c) has utility in predicting adverse outcomes in gestational diabetes mellitus (GDM). The aims of the study were to examine the predictive value of HbA1c at GDM diagnosis with adverse pregnancy outcomes.

Research design and methods. - This was a cohort study of 4,383 women with GDM between 2011 and 2018. We assessed the association of HbA1c with pregnancy outcomes using logistic regression models before and after adjustment for predefined risk factors of GDM. We examined these associations considering HbA1c as categorical variables using five pre-specified HbA1c classes: and as a continuous variable.

Results. - An HbA1c ≥ 5.6% (38 mmol/mol) identified women with at greater risk for macrosomia: odds ratio (OR) [95% confidence interval] = 2.12 [1.29 ; 3.46] for HbA1c = 5.6-5.9% and 2.06 [1.14 ; 3.70] for HbA1c > 5.9% versus HbA1c ≤ 4.5% (26 mmol/mol). Similarly, HbA1c ≥ 5.6% (38 mmol/mol) was associated with greater risk for caesarean: 1.64 [1.06 ; 2.53] for HbA1c = 5.6-5.9% and 1.58 [0.93 ; 2.7] for HbA1c > 5.9% (41 mmol/mol) versus HbA1c ≤ 4.5% (26 mmol/mol). Using HbA1c ≤ 4.5% (26 mmol/mol) as reference category, HbA1c > 5.9% (41 mmol/mol) increased the OR of preterm delivery to 3.33 [1.27 ; 8.71]. HbA1c remained significant for Adverse Pregnancy Outcome Composite after adjustment (P < 0.0001).

Discussion. - Our finding suggests that a single HbA1c reading may be a useful pragmatic tool to identify women at risk. Such identification may be a useful guide for identifying and applying preventative treatment for women at increased risk.

Keywords: Gestational diabetes; Neurodevelopmental disorders; Type 2 diabetes

Research in context :

- What is already known about this subject?
  1. The prevalence of gestational diabetes mellitus (GDM) is rising due to increased incidence of maternal risk factors.
  2. The Hyperglycaemia and Adverse Pregnancy Outcome (HAPO) study reported that Hba1c was significantly associated with adverse neonatal outcome.
  3. Therefore, it is unclear whether HbA1c at the timing of testing GDM can identify women at risk for pregnancy complications.
- What is the key question?

To define if, among women with GDM, HbA1c could serve to identify those at greater risk of adverse pregnancy outcomes.

- What are the new findings?
  4. HbA1c ≥ 5.6% (38 mmol/mol) identified women with a greater risk for several adverse pregnancy outcomes,
  5. HbA1c ≥ 5.9% (41 mmol/mol) was associated with a higher risk of preterm delivery,
  6. Above HbA1c > 4.5%, any 0.1% increase of HbA1c was associated with an increased risk of adverse pregnancy outcomes.
- How might this impact on clinical practice in the foreseeable future?

Baseline HbA1c measurement at time of diagnosis may serve as a useful guide for heightened surveillance and intensified prenatal care for women with a higher risk of adverse pregnancy outcomes.

Introduction

Gestational diabetes mellitus (GDM) is one of the most common complications of pregnancy [1]. The prevalence of GDM is rising, due to increased incidence of maternal risk factors in developed countries such as obesity and advanced maternal age [2]. Moreover, much of the increase in GDM prevalence is due to the switch to a set of diagnostic criteria that identifies a greater proportion of the population as having GDM (i.e., the IADPSG criteria) [3]. Increased workload and resource constraints present a challenge to identify GDM patients based on their complication-risk status. Glycated haemoglobin (HbA1c) reflects average blood glucose over the most recent 2-to-3-month period. Despite being of limited value as a diagnostic test for GDM, HbA1c has been reported to be a good predictor of adverse outcomes associated with GDM [4]. However, it has high specificity and low sensitivity, changes with trimesters of pregnancy [5] and gives values varying between ethnic groups [6].

The Hyperglycaemia and Adverse Pregnancy Outcome (HAPO) study reported that both HbA1c and fasting one-hour and two-hour oral glucose tolerance test (OGTT) results were significantly associated with selected adverse neonatal outcomes and cord C-peptide measures [7]. In addition, a large cohort study found that women with and without GDM whose HbA1c early in pregnancy was between 5.9% and 6.4% had significantly greater risks of pre-eclampsia, shoulder dystocia and perinatal death than those whose HbA1c was below 5.9% [4]. The purpose of this study was to determine whether, among women with GDM, HbA1c could serve to identify those at greater risk of adverse pregnancy outcomes.

RESEARCH DESIGN AND METHODS

Study population

All patients who attended antenatal care and delivered at the Obstetrics and Gynaecology Department, Jeanne de Flandres University Hospital, Lille, France, between January 2011 and December 2018 were tested for GDM in accord with the protocol of the French-speaking Society of Diabetes and the French National College of Obstetricians and Gynaecologists [8]. That protocol requires a fasting plasma glucose (FPG) at the initial prenatal visit for women with one or more risk factors: body mass index (BMI) defined as weight in kilograms divided by the square of height in meters, ≥ 25 kg/m^2, age ≥ 35 years, personal history of GDM, prior birth of a macrosomic neonate, or familial history of diabetes. GDM was identified if the FPG was ≥

5.1 mmol/L. Women whose initial FPG was less than 5.1 mmol/L were retested between 24 and 28 weeks with a 75 g 2h OGTT. GDM was defined by IADPSG criteria [3]. The data of women who had spontaneous or induced abortions, twin gestation, or HbA1c ≥ 6.5% were excluded, so as not to include pre-existing diabetes in pregnancy.

Interventions

Once the diagnosis had been confirmed, patients attended an initial consultation where explanations concerning preventive hygiene and dietary measures were provided. Women were instructed to perform self-monitoring of blood glucose 6 times per day: (fasting, before every meal, and after every meal). The results were collected on MyDiabby© software and/or with a phone call by a specialized nurse twice a week. Specific glycaemic targets were set: ≤ 5.1 mmol/l for fasting state, ≤ 6.6mmol/l 2 hours after meals. When glycaemic objectives were not achieved after 7 to 10 days of well-conducted compliance with hygienic-dietary rules, insulin therapy, either with short-acting insulin analogues before meals and/or long-acting insulin analogues at bedtime, was initiated. Obstetrician follow-up was consistent with the French guidelines [8].

Collected data and outcomes measures

Age, BMI, previous pregnancy data, and risk factors were collected from electronic and paper hospital records. For patients with GDM, we collected the date of GDM diagnosis, type of screening and plasma glucose values (fasting or OGTT), treatment start date, type of treatment (diet or insulin therapy), and initial and final insulin dose expressed as a function of weight.

HbA1c was measured by capillary electrophoresis (Capillaris Tera SEBIA, normal range: 4.0-6.0% (20-42 mmol/mol); coefficient of variation < 3%). Assay performance was certified by Bio Rad.

Pregnancy duration, initiation of labour (spontaneous or induced), route of delivery (caesarean or vaginal) and maternal and neonatal complications were recorded. Medical records were abstracted to obtain new-borns' information. Pregnancy outcomes of interest were LGA (large-for-gestational-age) defined as birthweight ≥ 90^{th} percentile according to the AUDIPOG formula, which includes the duration, sex and birth weight [9] or macrosomia defined as birth weight greater than or equal to 4000g. Small-for-gestational-age (SGA) was defined as gestational age-specific birth weight < 10^{th} percentile for gestational age according to the Gardosi formula [9]. The Gardosi curve is the scale considered the most reliable for estimating SGA in our centre. Preterm delivery was defined as delivery prior to 37 weeks of gestation.

Preeclampsia was defined as new-onset or worsening arterial hypertension after 20 weeks of gestation and the coexistence of one or more of the following new-onset conditions: proteinuria, other maternal organ dysfunction, or foetal growth restriction as defined by the International Society for the study of Hypertension in Pregnancy [10].

Neonatal complications assessed were Apgar score at 1 and 5 minutes, hospitalisation in the neonatal intensive care unit (NICU) and umbilical cord arterial pH. Abnormal Apgar scores at 1 and 5 minutes were defined as any below 7. Cord blood arterial pH lower than 7.15 was defined as abnormal. We developed a composite endpoint of pregnancy and neonatal complications defined by the presence of at least one of the following: preeclampsia, preterm delivery, LGA, SGA, NICU admission and shoulder dystocia.

Statistical analysis

Categorical variables were reported as number (percent). Distribution of variables were described by means ± standard deviation in case of Gaussian distribution or median (interquartile range (IQR)) otherwise. Normality of data distribution was checked graphically and tested using the Kolmogorov-Smirnov test. We assessed the association of HbA1c with pregnancy outcomes (all binary) using logistic regression models before and after adjustment in predefined risk factors of gestational diabetes (age, BMI, family history of diabetes, personal history of GDM, personal history of macrosomia). We first examined the associations considering HbA1c at the time of testing for GDM as a categorical variable using five pre-specified HbA1c classes: ≤ 4.5% (26 mmol/mol), 4.6-4.9% (27-30 mmol/mol), 5-5.5% (31-37 mmol/mol), 5.6-5.9% (38-41 mmol/mol) and > 5.9% (> 41 mmol/mol), and second by treating HbA1c as a continuous variable. The results were expressed as odds ratios (OR) and their 95% confidence intervals (CI), calculated using HbA1c ≤ 4.5% (< 26mmol/mol) as reference or calculated per 0.1% increase in HbA1c. Associations between the occurrence of at least one of the six complications (composite criterion) and glycaemic values of the OGTT were also studied using logistic regression without adjustment. Testing was done at the two-tailed α level of 0.05. Statistical analyses were conducted using SAS software (SAS Institute 9.4, Cary, USA).

RESULTS

Demographic characteristics of the population

Between January 1, 2011 and December 31, 2018, 4,772 women enrolled for prenatal care and were tested for GDM per protocol. Of the 4,772 women diagnosed with GDM, 4,383 women had a least one known risk factor and 389 without or with missing data on risk factors were excluded. Among these 4,383 women, 62 women were excluded due to missing data for HbA1c levels, yielding that the present study was conducted in 4,321 women (Figure 1).

Clinical outcomes

Maternal characteristics are presented in Table I. Of note is that 23% of women had GDM in a previous pregnancy and that their mean baseline HbA1c was 5.2%. The subjects were on average 31.9 (± 5.4) years old; their mean pregravid BMI was 28.4 (± 6.4) kg/m^2. 52.9% of them reported a family history of diabetes, 23% a personal history of GDM in a previous pregnancy and 13.5% had a personal history of macrosomia. HbA1c was measured at a mean of 25 (± 7.5) weeks' gestation. Mean baseline HbA1c was 5.2% (± 0.4) (33 ± 4 mmol/mol). GDM was diagnosed by fasting plasma glucose in 54.2% of women at a mean time of 11.1 (± 6.3) weeks. Diagnosis was established by OGTT in 45.8 % at a mean time of 26.8 (± 2.9) weeks. Insulin treatment was ultimately given for 33% of patients. Treatment (diet and/or diet and insulin) was introduced at a mean of 26.9 (± 7.2) weeks' gestation and for a mean period of 14.1 (± 7.6) weeks.

Pregnancy outcomes are reported in Table II. Mean gestational age at delivery was 39.1 (± 1.6) weeks. There was a 5.1% rate of preterm delivery. Caesarean section was performed in 22.2% of the population and 26.2% of patients had their labour induced. Instrumental extraction was required in 16.1% and shoulder dystocia was found in 2.4%. The average birth-weight was 3410g (± 532). Macrosomia (birth weight > 4000g) was recorded in 11.9% of the neonates and the rate of LGA was 17.3%. SGA was present in 19.3%. Admission to the NICU was required for 2.6% of new-borns (respiratory distress syndrome 0.7%, intra-uterine growth retardation 0.5%, and other grounds for transfer 1.3%).

HbA1c and number of risk factors

There was no consistent relationship between the HbA1c levels and the number of risk factors in each HbA1c class (data not shown). On the other hand, the mean Hba1c in women with only one risk factor did not differ regardless of the risk factor studied (data not shown).

HbA1c and pregnancy outcomes

Table III shows the overall results of maternal HbA1c association with pregnancy outcomes. We compared the occurrence of each outcome between five HbA1c groups then treated

HbA1c as a continuous variable with ORs calculated per 0.1% increase in HbA1c. Our results were provided first without and then with adjustment for predefined risk factors of GDM.

There was a clear positive association between increasing baseline HbA1c and macrosomia, caesarean delivery and preterm delivery. While comparing the five groups, higher levels of maternal HbA1c were significantly associated with increased frequency of macrosomia, preterm delivery, and caesarean ($P < 0.001$ for each). Using HbA1c ≤ 4.5% as the reference category, HbA1c from 5.6-5.9% (38-41mmol/mol) was associated with a 2.12-fold [CI 95%, 1.29 ; 3.46] and 1.64-fold [1.06 ; 2.53] increased odds of macrosomia and caesarean, respectively, and HbA1c > 5.9% (41 mmol/mol) increased the odds of preterm delivery to 3.33 [1.27 ; 8.71]. This significant association for HbA1c and macrosomia ($P < 0.001$), caesarean ($P = 0.006$) and preterm delivery ($P < 0.001$) remained even after adjustment for predefined risk factors for GDM. It was observed that a 0.1% increase in HbA1c, was associated with 1.06 [1.03 ; 1.08]-times higher odds of macrosomia, 1.03 [1.01 to 1.05]-times higher odds of caesarean and 1.07 [1.04 ; 1.11]-times higher odds of preterm delivery. Shoulder dystocia was statistically significant after adjustment when HbA1c was considering as a continuous variable (OR per 0.1% increase 1.08 [1.02 ; 1.13]). However, this association with shoulder dystocia was not found after adjustment for comparison between five the HbA1c groups. Preeclampsia was significantly associated when we compared HbA1c between the five groups ($P = 0.02$) but not when HbA1c was treated as a continuous variable ($P = 0.14$ and $P = 0.19$ after adjustment).

For neonatal outcomes (pH arterial, Apgar score at 1 and 5 min, and NICU admission), no significant differences were observed. After adjustment, results were similar.

SGA was significantly associated with HbA1c ($P = 0.02$). Interestingly the lowest prevalence of SGA was seen in those with the highest baseline HbA1c possibly suggesting a protective effect of elevated HbA1c for SGA (OR = 0.98 [0.96 ; 1.00]). The lack of significance, after adjustment ($P = 0.07$), demonstrated that risk factors for GDM might influence SGA.

Finally, Table III demonstrates a statistically significantly increased risk for the composite endpoint ($P < 0.001$). A baseline HbA1c between 5.6% (38 mmol/mol) and 5.9% (41 mmol/mol) was related to a 1.62 [1.13 ; 2.33]-fold increased risk of at least one complication: LGA, SGA, preeclampsia, preterm delivery, neonatal intensive care unit admission and shoulder dystocia. HbA1c remained statistically significant even after adjustment ($P < 0.0001$).

DISCUSSION

In this large cohort of women with GDM we found that a baseline of HbA1c ≥ 5.6% (38 mmol/mol) predicted an increased risk of several adverse pregnancy outcomes including LGA, SGA, preeclampsia, preterm delivery, NICU admission and shoulder dystocia. More precisely, a HbA1c threshold ≥ 5.6% (38 mmol/mol) was significantly associated with an increased risk of macrosomia and caesarean delivery compared to the group whose HbA1c was ≤ 4.5% (26 mmol/mol). A HbA1c > 5.9% (41 mmol/mol) was associated with an increased risk of preterm delivery. It was observed that a 0.1% increase in HbA1c, was associated with 1.06 times higher odds of LGA, 1.03 times higher odds of caesarean, 1.07 times higher odds of preterm delivery and, 1.08 times higher odds of shoulder dystocia. Overall, our data support the use of a baseline HbA1c measurement taken at the time of diagnosis of GDM to alert clinicians to a higher risk of GDM-associated pregnancy complications and, where possible, to initiate and/or intensify prenatal care in an effort to avert these problems.

Our findings are in agreement with those of Sweeting et al. [11], who found that a baseline HbA1c > 5.9% (41 mmol/mol) was associated with increased risk of LGA (OR = 2.7 [1.5 ; 4.9]), macrosomia (3.5 [1.4 ; 8.6]), caesarean section (3.6 [2.1 ; 6.2]), and hypertensive disorders (2.6 [1.1 ; 5.8]) in GDM diagnosed ≥ 24 weeks' gestation. However, these authors did not find an association between HbA1c and preterm delivery. In contrast with our results, these authors reported that an early GDM HbA1c > 5.9% (41 mmol/mol) did not adequately identify all the adverse pregnancy outcomes. On the other hand, Capula et al. [12] showed that in women diagnosed with GDM in the second trimester, HbA1c levels were strong negative predictors of adverse outcomes regardless of the type of treatment. In particular, a cut-off HbA1c value less than 5.3% (34 mmol/mol) was associated with a 2-fold likelihood of the absence of adverse outcomes. Recently, it has also been demonstrated that if HbA1c is above the 5.7% (39 mmol/mol) threshold, the relative risk of developing a complication is double. At a sensitivity of > 70%, a receiver operating characteristic curve demonstrated that the optimal threshold of HbA1c associated with the risk of occurrence of at least one complication was 5.2% (33 mmol/mol) [12]. Similarly, Mane et al. found a higher risk of macrosomia among participants with a higher HbA1c in a multi-ethnic cohort using the National Diabetes Data group (NDDG) OGTT criteria following a 50 g glucose challenge test [13]. Our results are in contrast with other studies that found no association between HbA1c values and outcome variables such as preeclampsia, birthweight, macrosomia, SGA and hypertensives disorders [14]. More recently, Immanuel et al. have shown that a HbA1c threshold of 5.7% (39 mmol/mol) was a specific but insensitive biomarker for GDM and was not associated with adverse pregnancy outcomes in obese European women [15]. In agreement with previous studies, we did not find any associations with Apgar scores and cord arterial pH. These findings could be attributed to the fact that HbA1c reflects the metabolic control of the preceding weeks and has less of an

association with neonatal complications. A direct comparison between previous studies is difficult as their population characteristics and samples sizes differed substantially. Also, there is variability in the criteria adopted for GDM diagnosis (those adopted included IADPSG criteria, National Diabetes Data Group (NDDG) criteria.

The Hyperglycaemia and Adverse Pregnancy Outcome study found strong positive associations of maternal glucose levels with birth-weight and other outcomes such as preterm delivery, preeclampsia, birth injury and intensive neonatal care. However, the occurrence of any complication was compared with maternal glucose levels below those required for the diagnosis of diabetes [16]. In our study, we found no significant associations between OGTT values and neonatal or maternal complications in the present population. These findings contrast with results of Lowe et al. who showed that such associations were significantly stronger with glucose measures than with HbA1c. Indeed, after adjustment for glucose values, HbA1c was associated with caesarean delivery, preeclampsia, and preterm delivery but not with birth-weight [7]. One of the explanations could be that the mean HbA1c level was lower than in our study (4.79 vs 5.2% (29 vs 33mmol/mol)). Knowing that HbA1c reflects mean glucose levels over an interval of several preceding weeks, higher HbA1c at GDM screening could indicate a lower likelihood of achieving optimal glycaemic control and a higher likelihood of developing adverse pregnancy outcomes. The discordance in association between HbA1c and GDM associated adverse outcomes could be due to the impact of GDM treatment (diet and insulin-therapy). In our study, all the women were treated by the same team in accordance with French guidelines.

The strengths of our study include the large number of subjects, the standardised treatment and the HbA1c analysis in the same centre, which provide a robust investigational data set. Some potential limitations require discussion. First, we did not know the haemoglobin and mean corpuscular volume (MCV) levels in our patients, so we were unable to account for the presence of haemoglobinopathy or iron deficiency and anaemia, which can impact the accuracy of HbA1c assessment during pregnancy [17]. Full blood count data were not available for the identification of possible shorter or longer red blood cell longevity, so results were not adjusted for the presence of anaemia. In our study, we did not identify women with B-thalassaemia minor and this may lead to a mistaken assumption of low blood glucose levels. Zhang et al. have demonstrated that HbA1c may not be a suitable indicator for monitoring blood glucose in pregnant GDM women with B-thalassaemia minor [18].

Furthermore, we were unable to compare these results with a control group of nondiabetic women or untreated women with GDM. It should also be noted that the assessment scales for LGA and SGA are not consensual, making it difficult to compare studies of these parameters.

Last, this study was in a predominantly Caucasian population, and it would be of interest to investigate the diagnosis performance of HbA1c threshold in other populations.

In summary, HbA1c ≥ 5.6% (38 mmol/mol) appears to identify women with a greater need of surveillance for macrosomia, and HbA1c >5.9% (41 mmol/mol) seems to be associated with a higher risk of preterm delivery. A single HbA1c test at the time of diagnosis of GDM may serve as a useful guide for heightened surveillance and applying preventative treatment to women at risk for such adverse outcomes as macrosomia, SGA, preeclampsia, preterm delivery, NICU admission and shoulder dystocia.

REFERENCES:

1. WHO | Diagnostic criteria and classification of hyperglycaemia first detected in pregnancy. WHO. World Health Organization; [cited 2020 Apr 10]. Available from: https://www.who.int/diabetes/publications/Hyperglycaemia_In_Pregnancy/en/.

2. Lean SC, Derricott H, Jones RL,Heazell AEP. Maternal age and the risk of gestational diabetes mellitus: A systematic review and meta-analysis. Plos One 2027;12: e0186287.

3. International Association of Diabetes and Pregnancy Study Groups Consensus Panel. International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. Diabetes Care 2010;33:676–82.

4. Hughes RCE, Moore MP, Gullam JE, Mohamed K, Rowan J. An early pregnancy HbA1c ≥ 5.9% (41 mmol/mol) is optimal for detecting diabetes and identifies women at increased risk of adverse pregnancy outcomes. Diabetes Care 2014; 37: 2953–9.

5. O'Connor C, O'Shea PM, Owens LA, Carmody L, Avalos G, Nestor L, et al. Trimester-specific reference intervals for haemoglobin A1c (HbA1c) in pregnancy. Clin Chem Lab Medi 2012; 50: 905-9.

6. Renz PB, Chume FC, Timm JRT, Pimentel AL, Camargo JL. Clin Chem Lab Med 2019; 57: 1435–49.

7. Lowe LP, Metzger BE, Dyer AR, Lowe J, McCance DR, Lappin TRJ, et al. Hyperglycemia and adverse pregnancy outcome (HAPO) Study: Associations of maternal A1C and glucose with pregnancy outcomes. Diabetes Care 2012; 35: 574–80.

8. Vambergue A. Expert consensus on gestational diabetes mellitus. Diabetes Metab 2010 ;36 :511. doi: 10.1016/j.diabet.2010.11.003. PMID: 21163415.

9. Mamelle N, Munoz F, Grandjean H. [Fetal growth from the AUDIPOG study I. Establishment of references curves]. J Gynecol Obstetrique Biol Reprod 1996; 25: 61-70.

10. Brown MA, Magee LA, Kenny LC, Karumanchi SA, McCarthy FP, Saito S, et al, International Society for the Study of hypertension in Pregnancy (ISSHP). Pregnancy Hypertens 2018; 13: 291-310.

11. Sweeting AN, Ross GP, Hyett J, Molyneaux L, Tan K, Constantino M, et al. Baseline HbA1c to identify high risk Gestational diabetes: utility in early versus standard gestational diabetes. J Clin Endocrinol Metab 2017; 1: 150-6.

12. Capula C, Mazza T, Vero R, Costante G. HbA1c levels in patients with gestational diabetes mellitus: Relationship with pre-pregnancy BMI and pregnancy outcome. J Endocrinol Invest 2013; 36: 1038–45.

13. Mane L, Flores-Le Roux JA, Benaiges D, Rodriguez M, Marcelo I, Chillaron JJ, et al A. Role of first Trimester HbA1c as a predictor of adverse obstetric outcomes in a multiethnic cohort. J Clin Endocrinol Metab 2017; 102: 390-7.

14. Amylidi S, Mosimann B, Stettler C, Fiedler GM, Surbek D, Raio L. First trimester glycosylated hemoglobin in women at high risk for gestational Diabtes. Acta Obstet Gynéco Scand 2016; 95: 93-7.

15. Delantado JM, Devlieger R, Lapolla A, Dalfra MG, Bertolotto A, Harreiter J, et al. Performance of early pregnancy HbA1c for predicting gestational diabetes mellitus and adverse pregnancy outcomes in obese European women. Diabetes Res Clin Pract 2020; 168: 108378.

16. HAPO Study Cooperative Research Group, Metzger BE, Lowe LP, Dyer AR, Trimble ER, Chaovarindr U, et al. Hyperglycemia and adverse pregnancy outcomes. N Engl J Med 2008; 358: 1991-2002.

17. Ahmad J, Rafat D. HbA1c and iron deficiency: A review. Diabetes Metab Syndr 2013;7: 118–22.

18. Zhang X, Xiao Y, Fan Y. investigating the reliability of HbA1c monitoring for blood glucose control during late pregnancy in patients with gestational diabetes (GDM) with and without B-thalassemia Minor. Diabetes Ther 2018 9: 2305-13.

Acknowledgments

Funding None

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Author Contributions. F.B collected data and wrote the manuscript. C.T and J.L. directed and conducted the statistical analyses. M.L, H.W, C.T, M.C, J.L D.S and A.V reviewed the manuscript. A.V. initiated and directed the study and reviewed the manuscript. A.V. is the guarantor of this work and, as such, 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.

Figure 1: Flow chart of women included in our study

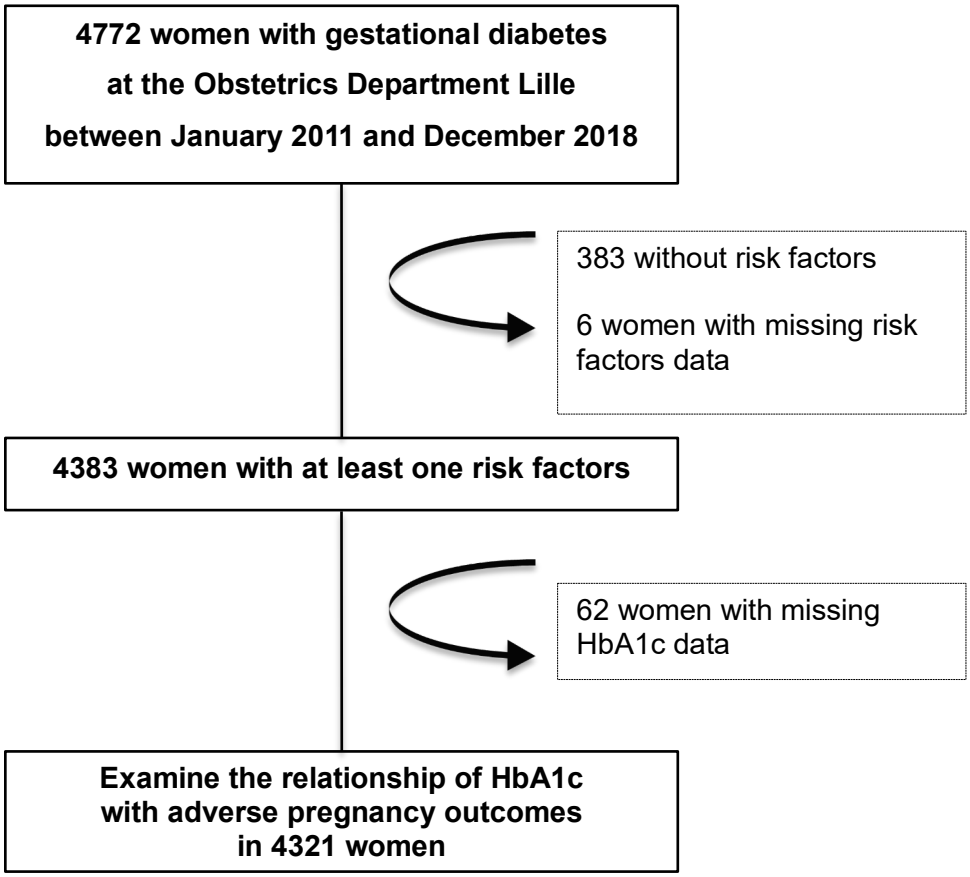

Table I: Maternal Characteristics

Maternal Characteristics (N=4383)		
Maternal Characteristics	Values	n=
Age, years	31.9 ± 5.4	4383
Pregravid BMI, kg/m^2	28.4 ± 6.4	4381
Parity >1 (%,n)	67.4%	2951 / 4380
Family history of diabetes (%, n)	52.9%	2314 / 4374
Personal history of GDM (%, n)	23%	1007 / 4381
Personal history of macrosomia (%, n)	13.5%	591 / 4382
Baseline HbA1c, % (mmol/mol)	5.2 ± 0.4 (33 +/- 4)	4321
GDM diagnosed by first trimester fasting plasma glucose (%, n)	54.2%	2370 / 4376
Gestation at fasting plasma glucose, (weeks, n)	11.1 ± 6.3	2251 / 2370
Blood glucose value, (g/l, n)	1.0 (0.9 to 1.0)	2370 / 2370
GDM diagnosed by OGTT (%, n)	45.8%	2006 / 4376
Gestation at OGTT, weeks	26.8 ± 2.9	1933 / 2006
OGTT values, g/l		
0 min	0.9 (0.9 to 1.0)	2004 / 2006
60 min	1.7 (1.4 to 1.9)	1984 / 2006
120 min	1.5 (1.2 to 1.6)	1983 / 2006
Insulin treatment (%, n)	33%	1474 / 4339

Values are %, mean ± SD or median (IQR)

SD : standard deviation , IQR : interquartile range

BMI: Body Mass Index; GDM: Gestational Diabetes Mellitus; OGTT: Oral Glucose Tolerance Test.

Table II: Pregnancy outcomes

Small for gestational age (SGA); Large for Gestational Age (LGA).

Pregnancy outcomes			
Pregnancy outcomes	%	N = 4383	95% CI
Macrosomia (birth weight > 4000g) (%, n)	11.9%	501 / 4212	10.9 to 12.9
Large for Gestational Age (LGA) (%, n)	17.3%	730 / 4211	16.2 to 18.5
Small for gestational Age (SGA) (%, n)	19.3%	814 / 4214	18.1 to 20.5
Preeclampsia (%, n)	3.5%	154 / 4382	3.0 to 4.1
Preterm delivery(%, n)	5.1%	224 / 4379	4.5 to 5.8
Intensive care unit admission (%, n)	2.6%	114 / 4355	2.2 to 3.1
Abnormal Apgar score at 1 min (%, n)	3.7%	160 / 4281	3.2 to 4.3
Abnormal Apgar score at 5 min (%, n)	0.9%	40 / 4312	0.7 to 1.3
Cord arterial pH < 7.15 (%, n)	15.9%	612 / 3854	14.7 to 17.1

Values are % and their 95% confidence intervals (CI)

Table III: Association of HbA1c with pregnancy outcomes

	HbA1c, % (mmol/mol) N = 4321							
	≤ 4.5 (≤ 26) N = 158	4.6 - 4.9 (27-30) N = 1 025	5 – 5.5 (31-37) N = 2 436	5.6 – 5.9 (38-41) N = 556	> 5.9 (> 41) N = 146	P^1	OR (95% CI)[2]	P^2
LGA								
no. / Total no. (%)	22 / 152 (14.5)	148 / 969 (15.3)	373 / 2 339 (15.9)	145 / 549 (26.4)	37 / 143 (25.9)			
Unadjusted OR (95% CI)	1.00 (ref)	1.06 (0.65 to 1.72)	1.12 (0.70 to 1.78)	2.12 (1.29 to 3.46)	2.06 (1.14 to 3.70)	<0.001	1.07 (1.04 to 1.09)	<0.001
Adjusted OR (95% CI)[3]	1.00 (ref)	1.04 (0.63 to 1.71)	1.03 (0.64 to 1.67)	1.87 (1.13 to 3.12)	1.84 (1.00 to 3.40)	<0.001	1.06 (1.03 to 1.08)	<0.001
SGA								
no. / Total no. (%)	31 / 152 (20.4)	199 / 969 (20.5)	461 / 2 341 (19.7)	94 / 550 (17.1)	19 / 143 (13.3)			
Unadjusted OR (95% CI)	1.00 (ref)	1.00 (0.66 to 1.54)	0.95 (0.63 to 1.43)	0.80 (0.51 to 1.26)	0.59 (0.32 to 1.11)	0.18	0.98 (0.96 to 1.00)	0.020
Adjusted OR (95% CI)[3]	1.00 (ref)	1.03 (0.67 to 1.58)	0.98 (0.65 to 1.49)	0.87 (0.55 to 1.39)	0.63 (0.34 to 1.19)	0.36	0.98 (0.96 to 1.00)	0.071
Preeclampsia								
no. / Total no. (%)	8 / 158 (5.1)	25 / 1 025 (2.4)	82 / 2 435 (3.4)	31 / 556 (5.6)	6 / 146 (4.1)			
Unadjusted OR (95% CI)	1.00 (ref)	0.46 (0.20 to 1.05)	0.65 (0.31 to 1.37)	1.10 (0.49 to 2.45)	0.80 (0.27 to 2.37)	0.021	1.03 (0.99 to 1.08)	0.14
Adjusted OR (95% CI)[3]	1.00 (ref)	0.46 (0.20 to 1.05)	0.63 (0.30 to 1.34)	1.10 (0.49 to 2.46)	0.78 (0.26 to 2.33)	0.020	1.03 (0.99 to 1.07)	0.19
Preterm delivery								
no. / Total no. (%)	6 / 158 (3.8)	41 / 1 024 (4.0)	113 / 2 434 (4.6)	43 / 555 (7.7)	17 / 146 (11.6)			
Unadjusted OR (95% CI)	1.00 (ref)	1.05 (0.44 to 2.53)	1.23 (0.53 to 2.84)	2.12 (0.88 to 5.09)	3.33 (1.27 to 8.71)	<0.001	1.08 (1.04 to 1.11)	<0.001
Adjusted OR (95% CI)[3]	1.00 (ref)	1.00 (0.42 to 2.41)	1.16 (0.50 to 2.70)	2.00 (0.83 to 4.83)	3.09 (1.18 to 8.11)	<0.001	1.07 (1.04 to 1.11)	<0.001
Caesarean								
no. / Total no. (%)	31 / 157 (19.7)	188 / 1 022 (18.4)	534 / 2 425 (22.0)	160 / 556 (28.8)	41 / 146 (28.1)			
Unadjusted OR (95% CI)	1.00 (ref)	0.92 (0.60 to 1.40)	1.14 (0.76 to 1.71)	1.64 (1.06 to 2.53)	1.58 (0.93 to 2.7)	<0.001	1.04 (1.02 to 1.06)	<0.001
Adjusted OR (95% CI)[3]	1.00 (ref)	0.89 (0.58 to 1.37)	1.03 (0.69 to 1.55)	1.34 (0.86 to 2.08)	1.32 (0.76 to 2.27)	0.020	1.03 (1.01 to 1.05)	0.006
pH arterial								
no. / Total no. (%)	17 / 137 (12.4)	140 / 898 (15.6)	349 / 2 138 (16.3)	79 / 499 (15.8)	17 / 128 (13.3)			
Unadjusted OR (95% CI)	1.00 (ref)	1.30 (0.76 to 2.23)	1.37 (0.81 to 2.31)	1.32 (0.75 to 2.32)	1.08 (0.52 to 2.22)	0.69	1.00 (0.98 to 1.03)	0.78
Adjusted OR (95% CI)[3]	1.00 (ref)	1.39 (0.80 to 2.42)	1.45 (0.85 to 2.48)	1.39 (0.78 to 2.48)	1.14 (0.55 to 2.38)	0.64	1.00 (0.98 to 1.03)	0.87
Apgar score at 1 min								
no. / Total no. (%)	4 / 154 (2.6)	33 / 1 004 (3.3)	89 / 2 395 (3.7)	29 / 553 (5.2)	4 / 145 (2.8)			
Unadjusted OR (95% CI)	1.00 (ref)	1.27 (0.44 to 3.64)	1.44 (0.52 to 3.99)	2.07 (0.71 to 5.99)	1.06 (0.26 to 4.33)	0.30	1.03 (0.99 to 1.07)	0.22
Adjusted OR (95% CI)[3]	1.00 (ref)	1.27 (0.44 to 3.64)	1.40 (0.50 to 3.87)	1.93 (0.66 to 5.62)	1.03 (0.25 to 4.20)	0.45	1.02 (0.98 to 1.06)	0.37
Apgar score at 5 min								
no. / Total no. (%)	3 / 154 (1.9)	7 / 1 004 (0.7)	20 / 2 394 (0.8)	5 / 553 (0.9)	3 / 145 (2.1)			
Unadjusted OR (95% CI)	1.00 (ref)	0.35 (0.09 to 1.38)	0.42 (0.12 to 1.44)	0.45 (0.10 to 1.94)	1.06 (0.21 to 5.35)	0.35	1.02 (0.94 to 1.11)	0.67
Adjusted OR (95% CI)[3]	1.00 (ref)	0.34 (0.09 to 1.35)	0.39 (0.11 to 1.35)	0.41 (0.09 to 1.75)	0.94 (0.18 to 4.82)	0.36	1.01 (0.93 to 1.10)	0.83
Intensive care unit admission								
no. / Total no. (%)	3 / 155 (1.9)	26 / 1 018 (2.6)	56 / 2 420 (2.3)	19 / 555 (3.4)	5 / 145 (3.4)			
Unadjusted OR (95% CI)	1.00 (ref)	1.32 (0.39 to 4.44)	1.20 (0.37 to 3.87)	1.79 (0.52 to 6.15)	1.78 (0.42 to 7.71)	0.57	1.03 (0.98 to 1.08)	0.22
Adjusted OR (95% CI)[3]	1.00 (ref)	1.28 (0.38 to 4.30)	1.11 (0.34 to 3.61)	1.66 (0.48 to 5.73)	1.64 (0.38 to 7.05)	0.61	1.02 (0.97 to 1.08)	0.36
Shoulder dystocia								
no. / Total no. (%)	4 / 156 (2.6)	16 / 1 016 (1.6)	59 / 2 420 (2.4)	17 / 556 (3.1)	7 / 146 (4.8)			
Unadjusted OR (95% CI)	1.00 (ref)	0.61 (0.20 to 1.84)	0.95 (0.34 to 2.64)	1.19 (0.39 to 3.61)	1.91 (0.54 to 6.68)	0.12	1.08 (1.02 to 1.13)	0.004
Adjusted OR (95% CI)[3]	1.00 (ref)	0.83 (0.24 to 2.88)	1.28 (0.40 to 4.16)	1.50 (0.43 to 5.25)	2.57 (0.65 to 10.21)	0.16	1.08 (1.02 to 1.13)	0.004
Composite criterion								
no. / Total no. (%)	61 / 158 (38.6)	404 / 1 025 (39.4)	982 / 2 436 (40.3)	281 / 556 (50.5)	75 / 146 (51.4)			
Unadjusted OR (95% CI)	1.00 (ref)	1.03 (0.73 to 1.45)	1.07 (0.77 to 1.49)	1.62 (1.13 to 2.33)	1.68 (1.06 to 2.65)	<0.001	1.04 (1.02 to 1.05)	<0.001
Adjusted OR (95% CI)[3]	1.00 (ref)	1.05 (0.74 to 1.49)	1.07 (0.76 to 1.49)	1.58 (1.10 to 2.28)	1.63 (1.03 to 2.59)	<0.001	1.03 (1.02 to 1.05)	<0.001

[1] *P*-values for comparison between five HbA1c groups [2] p-values calculated treating HbA1c as a continuous variable, with odds-ratios calculated per 0.1% increase in HbA1c
[3] adjusted for predefined risk factors of gestational diabetes (age, BMI, family history of diabetes, personal history of GDM, personal history of macrosomia)

Small for gestational age (SGA); Large for Gestational Age (LGA).