Title: The usefulness of HbA1c in postpartum reclassification of Gestational Diabetes.

Short title: HbA1c in postpartum reclassification.

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Abstract

To investigate the role of HbA1c in postpartum reclassification of gestational diabetes (GDM) we studied 364 women with GDM attending the postpartum reclassification assessment of their glucose tolerance status. A 75 g OGTT was performed and HbA1c was determined.

Diabetes was diagnosed in 12 (3.3%), 7 (1.9%) and 2 (0.6%) of women according to the fasting plasma glucose (FPG) and/or 2h OGTT, FPG alone and HbA1c levels, respectively. The sensitivity and specificity for HbA1c to diagnose diabetes was 16.7% and 100% respectively for FPG and/or OGTT criteria. The combination of a cut off value of 5.5% for HbA1c and FPG allow to identify 95.1% of women with any kind of glucose intolerance. We conclude that in the early postpartum period, the cut off of 6.5% for HbA1c alone has low sensitivity for diabetes diagnosis compared to OGTT, but the combination of FPG and HbA1c at a lower cut off value is very useful to identify women with any kind of glucose intolerance.

Key Words: Gestational diabetes, postpartum reclassification

Introduction

Gestational diabetes mellitus (GDM) affects up to 14% of all pregnancies and identifies a group of women at risk for the development of type-2 diabetes, impaired glucose tolerance (IGT) and metabolic syndrome in the future. Recommendations of the 5th work-shop conference on GDM (1) are that women with GDM should undergo postpartum glucose tolerance testing with an oral glucose tolerance test (OGTT). The rationale for this recommendation is not only to identify women with apparent diabetes but also those with IGT in whom diabetes can be delayed or prevented. Unfortunately, the rates of postpartum evaluation are low (2). The discontinuity of care after delivery due to mothers underestimating their diabetes risk, the stress of adapting to the challenge of caring for a young baby, and the time needed in the re-evaluation testing are some of the reasons implicated. Thus the adoption of easier strategies, that do not require fasting or more than a single blood draw could help to increase the rate of postpartum testing.

Recently, HbA1c has been proposed as a diagnostic tool to identify persons with undiagnosed, or at risk of diabetes (3). The HbA1c assay is in most cases universally standardized and traceable to the Diabetes Control and Complications Trial assay (DCCT). HbA1c does not require fasting, it has better pre-analytical stability and reflects long-term glycemic exposure better than current diagnostic tests based on fasting or post-load glucose measures. Nevertheless, the diagnostic rate in the general and at risk population has been shown to be lower than FPG or OGTT. In previous reports, HbA1c has been shown to be less cost effective in the long term follow-up than OGTT for the diagnosis of DM in women with GDM (4). In a recent report, the same group

assess the usefulness of HbA1c in the postpartum evaluation of a small group of women over a longer period of time(5). But as far as we are aware, there are no studies assessing the usefulness of HbA1c in the early postpartum reclassification of gestational diabetes. The aim of this study was to analyse whether the use of HbA1c may be useful in the postpartum reclassification of women with GDM in a large cohort of women.

Methods

This analysis was conducted in the setting of an ongoing observational study at the University Hospital Joan XXIII in Tarragona, Spain. Women with GDM are recruited during pregnancy and are encouraged to return for postpartum re-evaluation. The study protocol was approved by our centre's Research Ethics Board.

Women were selected from an ongoing database in which data for all women are entered prospectively. Before inclusion, all participants provide their written informed consent. At our centre, GDM is diagnosed following the National Diabetes Data Group criteria. During pregnancy, all women follow a diet with 40% carbohydrates, and if targets of fasting glucose <5.3 $mmol \cdot L^{-1}$ (< 95 $mg \cdot dL^{-1}$) and 1 h. postpandrial glucose ≥ 7.3 $mmol \cdot L^{-1}$ (≥140 $mg \cdot dL^{-1}$) are not attained, insulin therapy is added. Neither insulin therapy nor dietary counselling is continued postpartum. In this analysis, we included women that returned for the post-delivery study visit within the first year postpartum, between January 2006 and March 2011, and had HbA1c measured at the time of the postpartum 2h. 75 g. OGTT. Results of the OGTT were evaluated according to the 1999 WHO criteria.

Blood for HbA1c was collected in EDTA vials and estimated by HPLC-based ion exchange chromatography (ADAMS-A1c HA-8160**,** Menarini Diagnostics) . This method corrects the most common haemoglobin (Hb) traits. Labile HbA1c, carbamilated Hb and acetylated Hb are eluted separately from stable HbA1c peak. The HbA1c assay is standardized and traceable to the DCCT. The intra-assay coefficients for normal and diabetic patients are 1.5 and 0.5%.

Data are presented as numbers and proportions for categorical variables or as median and interquartile range [IQR] for continuous variables. Accordingly, a Pearson χ^2 test or non parametric tests were used to test for differences between groups Spearman's correlation was used to analyse the relationship between glucose and HbA1c values. The receiver operating characteristic curve (ROC) was used to analyse the performance of the HbA1c test to diagnose diabetes or any kind of glucose intolerance by OGTT. A significance level of <0.05 was adopted.

Results.

Three hundred and sixty-four women had postpartum OGTT and HbA1c performed simultaneously. They were Caucasian (91.5%), Arabic (5.5%), Hispanic (1.6%) and others (1.4%). Among them, according to the OGTT results, 263 women (72.3%) had normal glucose tolerance, 89 (24.5%) pre-diabetes (impaired fasting glucose, IGT or both) and 12 (3.3%) diabetes. Seven of the diabetic women fulfilled the FPG criteria (2.7%) and 2 had an HbA1c of 6.5% or more (0.6%). No difference in the time of postpartum evaluation (3 [2-5] vs. 3 [3-5] months), age (33 [30-36] vs. 36 [30.5-39.75] years) or breastfeeding (65.8 vs 77.8%) was observed between non-diabetic and diabetic women,

respectively. Diabetic compared to non-diabetic women had higher HbA1c levels (5.6 [5.4-6.3]% vs 5.1[4.8-5.3]%; p<0.001), pre-gravid and postpartum BMI values (30.1 [26.8-32.7] vs 24.8 [22.2-25.6] $kg \cdot m^{-2}$; p<0.01 and 29.2 [26.4-33.5] vs 25.7 [22.7-30.2] $kg \cdot m^{-2}$; p<0.05, respectively). All women diagnosed with diabetes had been treated with insulin during pregnancy compared to 47% in the non-diabetic group (p<0.001).

Correlations were r:0.296 (p<0.001) for HbA1c vs. FPG and r:0.196 (p<0.001) for HbA1c vs. 2 h glucose. We also performed the same analysis separating the women into three groups according to the time of postpartum evaluation: Group 1 (from 6 weeks to 3 months after delivery, n=260), Group 2 (from 4 to 6 months, n=69), and Group 3 (from 7 months to 1 year, n=35). The correlation coefficients for HbA1c versus FPG and HbA1c versus 2 h OGTT were r:0.281 (p<0.001) and r: 0.162 (p<0.05), respectively, for group 1; r:0.399 (p=0.004) and r:0.160 (p=0.263), respectively, for group 2; and r: 0.243 (p=0.232) and r: 0.054 (p=0.795), respectively, for group 3.

To determine differences in HbA1c levels across the first year postpartum, we compared mean HbA1c levels observed in each of the three groups considered, and a significantly lower HbA1c value was observed in group 2 compared to group 1 (HbA1c in group 1: 5.19 [4.94-5.39]%, in group 2: 4.89 [4.79-5.30]% and in group 3: 5.18 [4.79-5.39];p=0.025). We also evaluated whether there were any differences between HbA1c in the third trimester of pregnancy and in the postpartum period, and we found that both measures were correlated (r:0.604; p<0.001) and a significant increase in HbA1c was observed in the postpartum period (4.89 [4.60-5.19] vs. 5.09 [4.80-5.3]; p<0.001).

Sensitivity and specificity of HbA1c for diabetes diagnosis for a cut off of 6.5% or more were 16.7% and 100% respectively. When to diagnose diabetes we used the FPG criteria alone, sensitivity increased to 28.6% and specificity remained unchanged. To analyse whether the information of a single blood draw could improve sensitivity against FPG alone, we tested the combination of FPG and HbA1c. No increase in sensitivity was observed. All the women with HbA1c over 5.9% had diabetes. Table 1 shows sensitivity and specificity of HbA1c at various cut off levels attending to the OGTT or FPG criteria. The area under the ROC curve for diagnosis of diabetes was 0.870. See figure 1 A.

The sensitivity and specificity of HbA1c ≥ 5.7% to diagnose any kind of glucose intolerance was 13.5% and 97.3%, respectiviely. The area under the ROC curve for HbA1c for any kind of glucose intolerance was 0.674 (figure 1 B) with a sensitivity of 44.6% and a specificity of 78.8% for a cut off value of 5.3%. The use of this threshold to select women for the OGTT might reduce the number of women for testing to about a 30%, but 15.4% of women with some kind of glucose intolerance will be overlooked. In order to reduce the number of women with some kind of glucose intolerance lost without increasing the number of women for testing, we combined FPG and HbA1c with a cut off value of 5.5% . To select women for the OGTT the method had a sensitivity of 82.2% and a specificity of 92.0% to identify women with pre-diabetes reducing the number of women to for testing to 28.5%.

Conclusions

In this prospective study, we show that in early postpartum evaluation the cut off values of 6.5% and 5.7% for HbA1c have low sensitivity to diagnose diabetes

and pre-diabetes, respectively, despite their high specificity, but FPG and HbA1c with a lower cut off value can be useful to select women for OGTT. The low agreement between HbA1c and 2 h OGTT has also been observed in other high risk populations(6). In a recent work, Kim et al. compare HbA1c with the results of FPG and/or OGTT in 54 women in a period of time that goes from 6 weeks after delivery to more than two years(5). In contrast to our results, they report a higher sensitivity and specificity for HbA1c ≥ 5.7% to detect glucose intolerance in the postpartum evaluation. There are some differences between both studies that must be pointed out. In the study by Kim et al., the postpartum evaluation was performed over a longer period of time, the sample studied is smaller, women were heavier and sedentary, and a higher percentage of women belonging to high risk ethnic groups was included. These differences could be responsible for the higher rate of diabetes, IGT and IFG found in their study compared to ours.

In our population we observe significant correlation coefficients between FPG and HbA1c among the women evaluated up to 6 months postpartum, and this association is lost among women evaluated from 7 to 12 months after delivery. But in accordance with our data, Kim et al. also found that the relationship between fasting plasma glucose and HbA1c period differ in the different periods studied.

More interesting is the finding that HbA1c can be useful to detect women with any degree of glucose intolerance alone or in combination with FPG, and it might be used to select women candidates for the OGTT. When HbA1c ≥5.5% with plasma glucose ≥ 100 mg/dl, information that could be obtained in a single blood draw are used to select women for OGTT, the number of women for

testing would decrease by more than 70%, overlooking less than 4.9% of women with any kind of glucose intolerance.

Little is known about the change of HbA1c levels during the first year postpartum. We observed higher HbA1c in the postpartum period than in the third trimester of pregnancy, which could be due to the lower glucose levels and the increased turnover of red blood cells at the end of pregnancy. The blood loss due to delivery, a factor that could contribute to falsely decreased HbA1c values in the early postpartum period, seems not to be a (3) relevant factor, at least in our series. In fact, we found lower mean HbA1c concentrations in the group of women evaluated between the fourth and the sixth month postpartum compared to those evaluated earlier.

Taking these results into account and considering that early detection and treatment of diabetes are of utmost importance in preventing diabetic complications and improving short- and long-term outcomes in this subset of women, we believe that the recently introduced HbA1c criterion cannot be considered a good reclassification test for GDM in the early postpartum evaluation, but lowering the cut off for HbA1c to 5.5% with the combination of FPG to select women for the OGTT is a useful tool to select women candidates for OGTT that allows us to decrease the number of candidate patients for OGTT. However, longitudinal studies are needed to determine whether postpartum HbA1c could be considered a good predictor of DM, cardiovascular disease or metabolic syndrome in women with previous GDM.

Disclosure of interests

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

Author's contributions

AM conducted the study, data collection, analysis and wrote the manuscript. SN contributed to the data collection and reviewed the manuscript. LH designed the study.

REY contributed with data collection. NS contributed with data analysis. IS and JV contributed to writing the manuscript.

Details of ethics approval

The study protocol was approved by the Joan XXIII Hospital Research Ethics Board (p01/06/2009; 22p/2009). Informed consent was obtained from all the participants at inclusion.

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Table 1. Sensitivity and specificity of HbA1C at various cutoff levels in the postartum reclassification assessment attending to the OGTT or FPG criteria.

HbA1C cutoff level (%)	OGTT criteria		FPG criteria	
	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)
5.3	91.67	72.44	100	77.03
5.4	75.00	82.67	85.71	82.07
5.5	66.67	88.07	85.71	82,07
5.6	41.67	92.05	57.14	91.88
5.7	41.67	96.31	57.14	96.08
5.8	41.67	98.86	57.14	97.76
5.9	33.33	100	57.14	98.60
6.0	25.00	100	42.86	99.72
6.5	16.67	100	28.57	100

OGTT: oral glucose tolerance test. FPG: Fasting plasma glucose.

Figure 1. ROC curves for HbA1c used for detection of diabetes (A) and any kind of glucose intolerance from an OGTT (B).