

## ORIGINAL ARTICLE

# Glycated haemoglobin is a good predictor of neonatal hypoglycaemia in pregnancies complicated by diabetes

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### Abstract

We investigated the usefulness of a single value of maternal HbA1c in late pregnancy as a predictor for neonatal hypoglycaemia and secondly, to find the appropriate threshold value. A prospective analysis of the HbA1c concentration between 36 to 38 weeks of gestation in 150 pregnant mothers with either pre-existing or gestational diabetes was performed. At delivery, glucose levels in the cord blood were analysed. Neonatal hypoglycaemia was defined as a blood sugar level of < 2.6 mmol/l. Receiver operator characteristic curve was constructed to evaluate the value of HbA1c concentration in predicting hypoglycaemia. There were 16 foetuses who were hypoglycaemic at delivery. The area under the ROC curve for predicting neonatal hypoglycaemia was 0.997 with a 95% confidence interval of 0.992 to 1, a very good prediction rate. The optimal threshold value for HbA1c in predicting hypoglycaemia in the foetus was 6.8% (51 mmol/mol). HbA1c level in late pregnancy is a good predictor for hypoglycaemia in the newborn.

**Keywords:** neonatal hypoglycaemia, prediction, glycated haemoglobin, HbA1c

### INTRODUCTION

Poor glycaemic control in the diabetic mother gives rise to fetal hyperglycaemia which in turn results in hyperplasia of the islets of Langerhans, increased peripheral insulin receptors, a decreased glucagon response to hypoglycaemia and a delayed evocation of hepatic gluconeogenic pathway.<sup>1</sup> At delivery, the transplacental supply of glucose is stopped and hypoglycaemia in the neonate occurs. Poor maternal glycaemic control during the third trimester has been shown to be strongly and independently correlated with neonatal hypoglycaemia requiring intervention.<sup>2</sup>

Glucose is an essential primary substrate for the brain and its consumption by the brain cells is high. Because of this, neurons and glial cells are susceptible to hypoglycaemia. The vulnerable areas are the parieto-occipital regions of the cerebral cortex. Less commonly involved are neurons of the hippocampus, caudate nucleus and putamen. Glial injury may give rise to subsequent disturbances in myelination.<sup>1</sup> It has

been suggested that unrecognised postnatal hypoglycaemia may lead to neonatal seizures, coma, and brain damage.<sup>2</sup>

Fortunately, in most of these neonates, hypoglycaemia is transient and asymptomatic. However, if the diagnosis is missed, and the neonate fails to achieve normoglycaemia, it may become symptomatic and suffer long term complications of cerebral injury.<sup>3</sup> It would be useful, therefore, if we could predict foetal hypoglycaemia from the state of maternal glycaemic control.

Red blood cells are freely permeable to glucose and glycated haemoglobin (HbA1c) is formed at a rate dependent on the prevailing blood glucose levels. Consequently, the level of HbA1c at a certain point reflects the glycaemic history of the previous 120 days, i.e., the average red cell lifespan.<sup>4</sup> Glycated haemoglobin levels are now extensively used as a measure of glycaemic control.<sup>4</sup> Indirectly, therefore, it may serve as a good surrogate marker for predicting hypoglycaemia in the foetus.

There were two purposes for our study. The first was to investigate if HbA1c was a good predictor for neonatal hypoglycaemia and, secondly, if it was established to be so, to find the appropriate threshold value.

## PATIENTS AND METHODS

A prospective analysis of 150 pregnant mothers with either pre-existing or gestational diabetes attending the antenatal clinic at Hospital Tengku Ampuan Rahimah, Klang, from December 2008 to May 2009 was performed. They were managed according to the standard and established protocol and no special intervention was given. The patients were either on diet control or insulin. Those mothers who had insulin treatment were induced at 38 weeks while those with good glycaemic control with diet alone, were induced at term. Mothers with pregnancy-induced hypertension, multiple pregnancy, or foetal anomalies were excluded.

Blood samples for HbA1c were taken between 36 and 38 weeks of gestation. They were collected in tubes containing EDTA. HbA1c levels were measured by the BioRad D-10 fully automated Hemoglobin Testing System which uses reversed phase cation exchange high performance liquid chromatography (HPLC). HbA1c was expressed as a percentage of total haemoglobin. Briefly, HbA1c of 6% (42 mmol/mol) was shown to correspond to a mean blood glucose of 7.49 mmol/L and each 1% increase in HbA1c to a 1.94mmol/L- increase in blood glucose.<sup>4,5</sup> In our study, HbA1c of 5.6% (38 mmol/mol) was taken as the upper limit of normal as suggested by Nielsen *et al.*<sup>6</sup>

Neonatal hypoglycaemia was defined as a blood sugar level of < 2.6 mmol/l at 3 hours of life.<sup>7</sup>

### Statistical analysis

Receiver operator characteristic curve (ROC) was constructed to evaluate the value of HbA1c concentration in predicting hypoglycaemia. The test is assessed by the area under the curve; the

greater the area under the curve the better the global performance of the prediction, i.e., the higher the true positive rate is relative to the false negative rate, the greater the area under the curve. If the area is around 0.5, the model is performing no better than a 'toss of coin'. A satisfactory area should exceed 0.70.<sup>8,9</sup> A perfect test will have an area of 1.

Based on the detailed output for the curve three important cut-points for HbA1c levels were determined. Firstly, for 5.6% (38 mmol/mol) being the accepted upper limit of normal, secondly, for the best threshold value associated with hypoglycaemia from the ROC curve and, thirdly, the levels above which some hypoglycaemic fetuses may be missed.

The Stata Version 10 Statistical Software (StataCorp LP) was used.

## RESULTS

Of the 150 patients, 102 (68%) were Malay, 26 (17.3%) were Indian, 15 (10%) patients were Chinese and 7 (4.7%) patients were other races. One hundred and thirty-nine patients (92.7%) had gestational diabetes while the remaining 11 (7.3%) had pre-existing diabetes. The majority (76.7%) were treated with diet control while 35 (23.3%) required insulin.

There were 16 foetuses who were hypoglycaemic at delivery. Table I summarises the glycaemic status of the foetuses delivered and according to whether they were hypoglycaemic or not. The ROC curve is presented in Figure 1. The area under the curve was 0.997 with a 95% confidence interval of 0.992 to 1, a very good prediction rate. The best threshold associated with hypoglycaemia in the foetus was an HbA1c of 6.8% (51 mmol/mol). Table II summarises the sensitivity and specificity in detecting hypoglycaemia for various cut-points of HbA1c levels.

## DISCUSSION

We have shown that HbA1c levels in late

**TABLE 1. Glycaemic status of fetuses at delivery**

Glycemic status of fetus	Number	Mean ± SD	Range
Overall	150	3.64 ± 0.81	1.6 to 5.2
Hypoglycemia (= <2.6 mmol/l)	16	2.2 ± 0.29	1.6 to 2.6
Non-hypoglycemia ( =>2.7 mmol/l)	134	3.8 ± 0.66	2.7 to 5.2

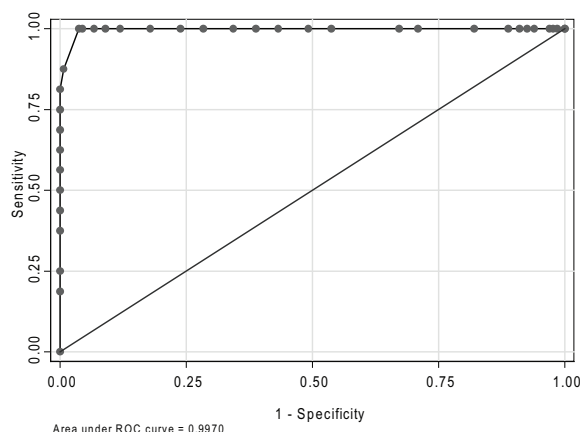


FIG. 1. Receiver operator characteristics curve for HbA1c levels in predicting neonatal hypoglycaemia

pregnancy are good predictors of hypoglycaemia in the newborn, giving an area under the curve of 0.99. In simple terms, what this means is that if there were two babies who were randomly selected, one with hypoglycaemia and the other without, the probability that the hypoglycaemic neonate would have shown an abnormally high maternal HbA1c would be around 99%.<sup>9</sup>

The most likely reason for this good prediction rate is because there was a narrow range of HbA1c levels from which the curve was constructed from a minimum of 4.3% (23 mmol/mol) to a maximum of 8.9% (74 mmol/mol)) and with a high sensitivity and specificity for a large number of values in the mid-range.

We used the ROC curve because it not only allows us to assess HbA1c as a global test for predicting neonatal hypoglycaemia but it also allows us to choose the most appropriate cut-point level for HbA1c – an important factor in our decision making process on how to manage the mother and the neonate. Secondly, it utilises sensitivity and specificity both of which are not affected by the prevalence of the disease (in this case, hypoglycaemia) in

the study population.<sup>9</sup> Others have shown similar results albeit with different methods of analysis. Kline and Edwards<sup>2</sup> using multiple logistic regression methods found that a third trimester HbA1c of > 6.5% (47.54mmol/mol) had a stronger association with neonatal hypoglycaemia requiring intervention when compared to maternal delivery blood glucose levels (odds ratio 3.89, 95% confidence interval 1.42-10.68). Ylinen *et al.*<sup>10</sup> found that neonatal hypoglycaemia was seen in those mothers with higher mean HbA1c levels in the second and third trimester.

On the other hand, using mean HbA1c levels throughout pregnancy as a marker for neonatal hypoglycaemia, Taylor *et al.*<sup>11</sup> showed that there was no correlation between neonatal hypoglycaemia and HbA1c levels at any point in pregnancy or with the mean pregnancy HbA1c levels. However, they found a significant negative correlation between neonatal blood glucose levels and maternal blood sugars during labour. Stenniger *et al.*<sup>12</sup> monitoring maternal glycaemic levels in 59 mothers with insulin-treated diabetes, showed that neonatal

**TABLE 2. Sensitivity and specificity in detecting hypoglycemia in fetus for various cutpoints of HbA1c**

Cutpoint for HbA1c (%)	Sensitivity	Specificity
>= 5.6 (38 momol/mol)*	100%	32%
>= 6.8 (51 mmol/mol)†	100%	94%
>= 7.0 (53 mmol/mol)‡	87%	99%

\* accepted normal levels,

† optimal cut-off from ROC curve

‡ level for not missing any hypoglycemic fetus

hypoglycaemia could still occur despite well controlled diabetes.

The limitations of our study are recognised. The number of hypoglycaemic infants seen in the study was only sixteen. A greater number would have added validity to the results notwithstanding the fact that the ROC curve is independent of the prevalence of the disease under study. Only one level of HbA1c in late pregnancy was used as the basis for analysis. There are obvious deficiencies in doing so but it was decided upon *a priori* because of its relevance to developing countries where facilities and costs for frequent glucose monitoring pose problems.

In conclusion, the use of ROC curve as the analytical tool in predicting hypoglycaemia in the neonate has advantages in the context of finding the appropriate cut-points for maternal HbA1c levels. The results were convincing but we look forward to larger prospective studies to either confirm or refute our findings.

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