Journal of Perinatology (2011) 31, 807

www.nature.com/jp

LETTER TO THE EDITOR

Evaluation of the glycemic control in neonates: a novel technical approach for measuring fetal-glycated hemoglobin

Journal of Perinatology (2011) **31,** 807; doi:10.1038/jp.2011.70

In a recent article reported by Koga *et al*.,[1] the authors explored the usefulness and potential of measuring glycated hemoglobins (GHbs) and glycated albumin in cord blood, evaluated by various techniques including high-performance liquid chromatography, latex-immunoturbidimetry, enzymatic and affinity methods. They found that by using two high-performance liquid chromatography methods, the latex-immunoturbidimetry method and the enzymatic method, the determination of GHb levels were low when compared with adult normal reference values. They also mentioned that, although these techniques could specifically determine glycated β-chains, they were not capable of determining glycated γ-chains derived from fetal hemoglobin (HbF), and they concluded that serum-glycated albumin, but not GHb, could be used as a glycemic control indicator in neonates.

Clearly, the coexistence of hemoglobin F [HbF($\alpha_2\gamma_2$)], and hemoglobin A [HbA($\alpha_2\beta_2$)] in neonatal blood makes the determination of GHb a daunting challenge. There are different possible reasons for this: (1) from a molecular point of view, cord blood hemoglobin is a mixture of α-, β- and γ-subunits and glycation may occur in all of them; (2) adding to the complexity, HbF is itself a mixture of two molecular species ($\alpha_2^G\gamma_2$ and $\alpha_2^A\gamma_2$), differing only at position 136, if either a Gly or an Ala is present; (3) moreover, HbF is acetylated[2] significantly (at 11.6 ± 2.8%)[3] at the N-terminus of the γ-chain, which needs to be taken into account for acute measurements of GHb; and (4) measurement of GHb in cord blood must be selective in order to determine glycation as ratios relative to the corresponding hemoglobin chain, consequently GHb levels will not be affected by the variation in γ- and β-chains levels (fetal to adult hemoglobin 'switch' by the end of pregnancy).

Considering the above and in response to this article, we would like to emphasize that issues regarding GHb measurements in cord blood can be overcome using a novel high-resolution technical approach we reported using electrospray ionization time-of-flight mass spectrometry (EI-TOF-MS).[4] Alpha-, beta- and gamma-chains were specifically identified by molecular weight. This method also allows the measurement of glycation of α- and γ-chains. Our preliminary results showed in women−neonate pairs recruited prospectively (20 gestational diabetes mellitus women and 19 controls): (1) correlations between maternal A_{1c} and GHb, measured on α- and γ-chains ($r = 0.68$, $P < 0.0001$ and $r = 0.54$, $P < 0.001$, respectively); and (2) nearly significant differences between gestational diabetes mellitus offspring and controls (α-chain: 2.35 ± 0.21 vs 2.20 ± 0.18%, $P = 0.049$; γ-chain: 2.43 ± 0.30 vs 2.34 ± 0.26%, $P = 0.35$), whereas in mothers, A_{1c} was slightly different (5.8 ± 0.4 vs 5.5 ± 0.3%, $P = 0.004$). Measurement of glycation of the α-chain only might be a suggestion, as α-chain is produced throughout pregnancy. However, despite the fact that the chemical structure of the α-chain is identical in HbA and HbF, the rate of glycation of the α-chain in HbF and HbA may be different, considering that the activity of the glycation site is influenced by its three-dimensional structure rather than by the amino-acid sequences of the polypeptide.[5]

Therefore, notwithstanding the views expressed by Koga *et al*.,[1] we have shown that the determination of GHb in cord blood is feasible using EI-TOF-MS technology, and could be used as a potential glycemic control marker in neonatal diabetes mellitus.

Conflict of interest

The authors declare no conflict of interest.

FO Dupont[1], R Gagnon[2], J Ménard[1], C Auray-Blais[2] and JL Ardilouze[1]

[1]Department of Physiology and Biophysics, Université de Sherbrooke, CHUS, Hospital Fleurimont, Sherbrooke, Quebec, Canada and [2]Department of Pediatrics, Université de Sherbrooke, CHUS, Hospital Fleurimont, Sherbrooke, Quebec, Canada.

E-mail: christiane.auray-blais@usherbrooke.ca

References

1 Koga M, Murai J, Saito H, Yamada Y, Mori T, Suno S *et al.* Measurement of glycated hemoglobin and glycated albumin in umbilical cord: evaluation of the glycemic control indicators in neonates. *J Perinatol* 2010; 1–4.

2 Steginк LD, Meyer PD, Brummel MC. Human fetal hemoglobin F 1. Acetylation status. *J Biol Chem* 1971; **246**: 3001–3007.

3 Shiao SY, Ou CN. Accurate measurements of fetal hemoglobin for neonates with different gestational ages. *Hemoglobin* 2006; **30**: 419–435.

4 Dupont FO, Gagnon R, Auray-Blais C, Ardilouze JL. Toward a new marker assessing fetal metabolic programming: the fetal glycated hemoglobin. *Diabetes* 2010; **59**: Lb33.

5 Nacharaju P, Acharya AS. Amadori rearrangement potential of hemoglobin at its glycation sites is dependent on the three-dimensional structure of protein. *Biochemistry* 1992; **31**: 12673–12679.