Foetal haemoglobin concentration at postmenstrual age is unaffected by gestational age at birth

Watanabe, Yuki ; Osawa, Kayo ; Sato, Itsuko ; Iwatani, Sota ; Kono, Ruri ; Hayakawa, Ikuyo ; Hayashi, Nobuhide ; Iijima, Kazumoto ;…

(Citation)
Annals of Clinical Biochemistry,55(3):400-403

(Issue Date)
2018-05-01

(Resource Type)
journal article

(Version)
Accepted Manuscript

Short Report

Fetal hemoglobin level at postmenstrual age is unaffected by gestational age at birth

Short title: HbF level and postmenstrual age

Yuki Watanabe[1*], Kayo Osawa[2,3*], Itsuko Sato[1], Sota Iwatani[4], Ruri Kono[1], Ikuyo Hayakawa[1], Nobuhide Hayashi[1], Kazumoto Iijima[4], Jun Saegusa[1], Ichiro Morioka[2,4]

[1] Department of Clinical Laboratory and [2] Infection Control and Prevention, Kobe University Hospital, Kobe, Japan

[3] Department of Biophysics, Kobe University Graduate School of Health Sciences, Kobe, Japan

[4] Department of Pediatrics, Kobe University Graduate School of Medicine, Kobe, Japan

* These authors contributed equally.

Corresponding author: Ichiro Morioka, MD, PhD

Department of Pediatrics, Kobe University Graduate School of Medicine

7-5-1, Kusunoki-cho, Chuo-ku, Kobe 6500017, Japan

Tel: +81-78-382-6090; Fax: +81-78-382-6099; E-mail: ichim@med.kobe-u.ac.jp

Competing interests: None of the authors have any conflicts of interest to declare in this study.

Funding: This work was supported in part by grants from Arkray, Inc.

Ethical approval: This study was approved by the institutional review board of the Kobe University Graduate School of Medicine (reference number: 1652). All procedures performed in studies involving human materials were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Anonymous residual blood samples, obtained after performing routine laboratory tests, were used. We also opened this study project to the public using the notice board in our hospital and our homepage; therefore, formal consent was not required for this type of study.

Guarantor: I.M.

Contributorship: All authors contributed to the intellectual content of this manuscript. Y.W., K.O., and I.M. wrote the first draft of this manuscript. Y.W., I.S., S.I., R.K., I.H., N.H., and J.S. collected the clinical samples and data. Y.W., K.O., I.S., S.I., and I.M. performed analysis of the clinical and laboratory findings. K.O., I.S., K.I., and I.M. designed this study.

Acknowledgements: This research is partially supported by the Practical Research Project for Intractable Diseases from Japan Agency for Medical Research and Development, AMED.

Abstract word count: 243

Actual word count excluding abstract and references: 957

Abstract

Background: Our aim was to determine whether the postnatal age or postmenstrual age is a more appropriate criterion for evaluating fetal hemoglobin (HbF) levels.

Methods: Blood samples (n=1095) were obtained from 394 infants and divided into 2 groups based on gestational age (GA) at birth: <37 weeks (n=491) and ≥37 weeks (n=604). 1) HbF levels divided by one month at age after birth were compared between the groups. 2) HbF levels divided into ≤9 months from last menstruation and one month thereafter were compared between the groups.

Results: In samples from infants ≥37 weeks GA at birth, the median HbF levels were 69.5%, 21.4%, and 3.6% at 0–1 month, 2–3 months, and ≥5 months after birth, respectively. The median HbF levels in infants <37 weeks GA at birth were 75.5%, 62.7%, and 5.1% at 0–1 month, 2–3 months, and ≥5 months after birth, respectively. The median HbF levels in infants <37 weeks GA at birth were significantly higher than that in infants ≥37 weeks GA at birth at all postnatal age points. 2) There was no significant difference between the groups at all age points after 9 months of postmenstrual age: 72.5 and 75.3% at 9–10 months, 25.1 and 26.6% at 11–12 months, and 5.5 and 4.6% at >13 months after last menstruation in infants ≥37 and <37 weeks GA at birth, respectively.

Conclusions: Evaluation of HbF levels at postmenstrual age is unaffected by GA at birth.

Keywords: fetal hemoglobin; gestational age at birth; postmenstrual age; postnatal age; preterm infant; term infant

Introduction

Fetal hemoglobin (HbF) is present in the blood of fetuses and neonates. The level of HbF in the blood gradually decreases after birth and is replaced with adult hemoglobin;[1] at 6 months after birth, HbF accounts for less than 1% of the total hemoglobin. HbF is reportedly elevated in chronic lung diseases and sudden infant death syndrome.[2,3] HbF levels could therefore be used as a predictive marker for these diseases. However, an established criterion for the HbF levels does not exist, because HbF levels at various postnatal ages show variations due to the gestational age (GA, a time elapsed between the first day of the last menstrual period and the day of delivery) at birth.[4] In the present study, we assessed whether the postnatal age or postmenstrual age (PMA, gestational age plus chronological age that is a time elapsed from birth) is more appropriate as a criterion for determining the HbF level.

Materials and Methods

Blood samples (n=1095) that were collected from 394 infants < 12 months of age were analyzed. No infants with sudden infant death syndrome and chronic lung disease that required home oxygen therapy were included. Infants with congenital diseases or after blood transfusion were excluded in this study, as these conditions could have influenced the HbF level. The blood samples were divided into the following 2 groups based on the GA at birth: < 37 weeks (n=491) and ≥ 37 weeks (n=604). The HbF levels

divided by one month at age after birth were compared between the groups. Additionally, the HbF levels divided into ≤ 9 months from last menstruation and one month thereafter were compared between the groups. Statistical analyses were performed using the Mann–Whitney U test. Differences were determined to be statistically significant when $p < 0.05$.

PMA and GA at birth were calculated from the last menstrual period and corrected by sonographic fetal measurement data, if needed.

HbF levels in all samples were measured by high-performance liquid chromatography using an ADAMS A1c HA-8180T (Arkray Inc., Japan) with the appropriate calibration based on the manufacture's recommendation. The results of intra-day assay (n=20) using a sample with a mean HbF value of 4.67% and inter-day assay (n=20) using a sample with a mean HbF value of 4.93% gave coefficients of variation of 0.2% and 0.4%, respectively (Supplementary table).

Results and Discussion

Patient background

The median (range) of GA at birth and the birth weight of the infants were 36 (22–41) weeks and 2541 (478–4176) g, respectively. The preterm and term groups had a GA at birth of 32 (22–36) and 38 (37–41) weeks, respectively, and birth weight of 1834 (478–3460) and 2996 (2320–4176) g, respectively. The median postnatal HbF level at

0–1 month after birth was 72.0% regardless of GA at birth.

HbF levels at postnatal age

HbF levels at postnatal age are shown in Figures 1A and C. In samples from infants ≥ 37 weeks GA at birth, the median HbF level was 69.5% at 0–1 month after birth, and gradually declined thereafter, measuring 10.9% at 4–5 months and 3.6% at ≥ 5 months after birth. Colombo et al. reported that the mean HbF level obtained using electrophoresis in 30 samples of umbilical cord blood in full-term infants was 64.8%,[1] which was close to our result in spite of the different materials and different measurement method used. The mean HbF level decreased to approximately 5% by 5 months of age.[1] Garby et al. also measured HbF levels from 0 to 140 days after birth in 19 infants ≥ 37 weeks GA at birth and found that the HbF level was 50–60% immediately after birth and decreased to approximately 5% at 100–140 days after birth.[5] These are similar to the results obtained in our study. In samples from infants < 37 weeks GA at birth, the median HbF levels were 75.5% at 0–1 month after birth, 28.2% at 4–5 months, and 5.1% at ≥ 5 months after birth. The decrease in the HbF levels was delayed compared to those of infants ≥ 37 weeks GA at birth. The HbF level of an infant with 22 weeks GA at birth was approximately 30% even at 6 months of age (the value was over the reference range, as seen in Figure 1A and within the reference range, as seen in Figure 1B). Cottom has shown that the HbF levels in umbilical cord blood are higher in infants with a lower GA.[4] Our results also show that the HbF levels in infants

< 37 weeks GA at birth were significantly higher than those in infants with a GA at birth ≥ 37 weeks. These findings suggest that the HbF levels at a certain postnatal age can have variations due to the GA at birth.

HbF levels at PMA

The HbF levels at PMA are shown in Figures 1B and C. When we compared HbF levels between in infants with GA at birth ≥ and < 37 weeks, there was no statistically significant difference between them at the age points after the PMA of 9 months. The HbF levels at PMA were not affected by the GA at birth, which confirms the report by Colombo et al.[1] Our results are compatible with those of a previous animal study, in which it was confirmed that the switching from fetal to adult hemoglobin production occurred at a time related to the postmenstrual age.[6]

Conclusion

The HbF levels at the postnatal age are higher when the GA at birth is low. However, the HbF levels at the PMA did not differ according to the GA at birth. Therefore, it is better to evaluate the HbF level using the PMA rather than using the postnatal age.

References

1. Colombo B, Kim B, Atencio P, et al. The pattern of fetal haemoglobin disappearance after birth. *Br J Haematol* 1976; 32: 79–87.
2. Bard H, Prosmanne J. Elevated levels of fetal hemoglobin synthesis in infants with bronchopulmonary dysplasia. *Pediatrics* 1990; 86: 193–6.
3. Giulian GG, Gilbert EF, Moss RL. Elevated fetal hemoglobin levels in sudden infant death syndrome. *N Engl J Med* 1987; 316: 1122–6.
4. Cottom DG. Foetal haemoglobin and postmaturity. *J Obstet Gynaecol Br Emp* 1955; 62: 945–8.
5. Garby L, Sjolin S, Vuille JC. Studies on erythro-kinetics in infancy. II. The relative rate of synthesis of haemoglobin F and haemoglobin A during the first months of life. *Acta Paediatrica* 1962; 51: 245–54.
6. Wood WG, Bunch C, Kelly S, et al. Control of haemoglobin switching by a developmental clock? *Nature* 1985; 313: 320–3.

Figure Legends

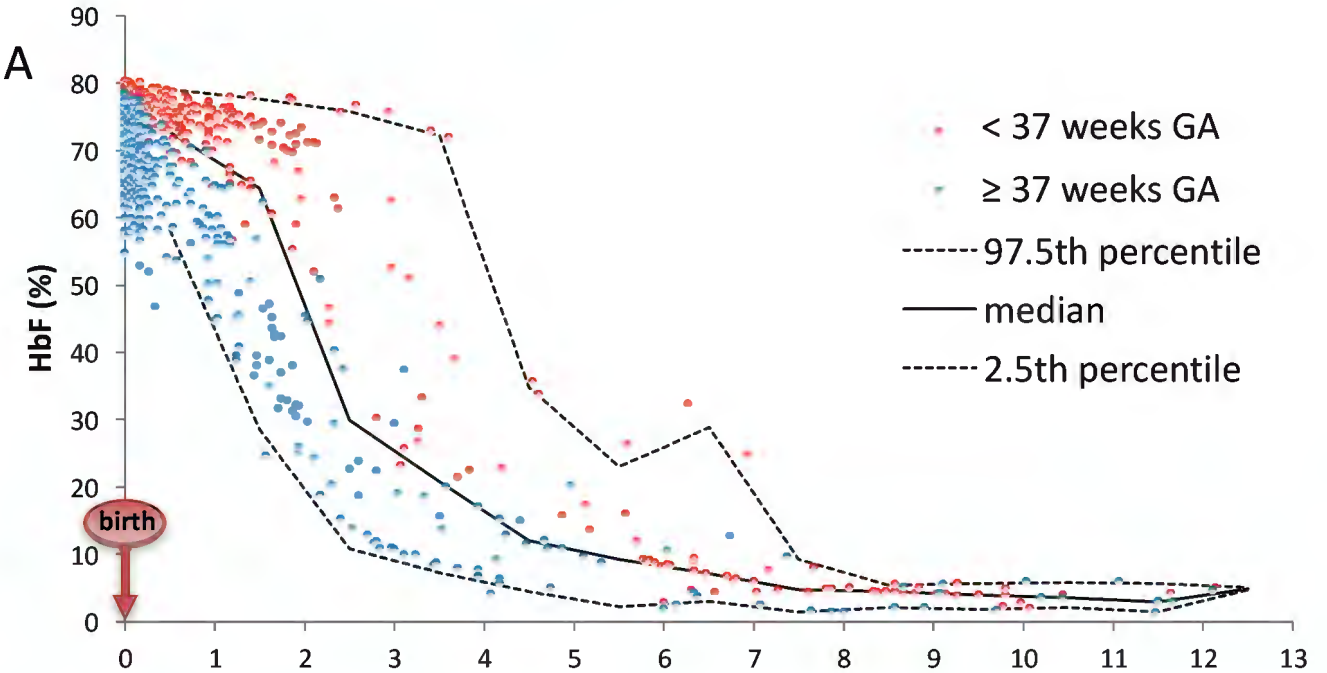
Figure 1

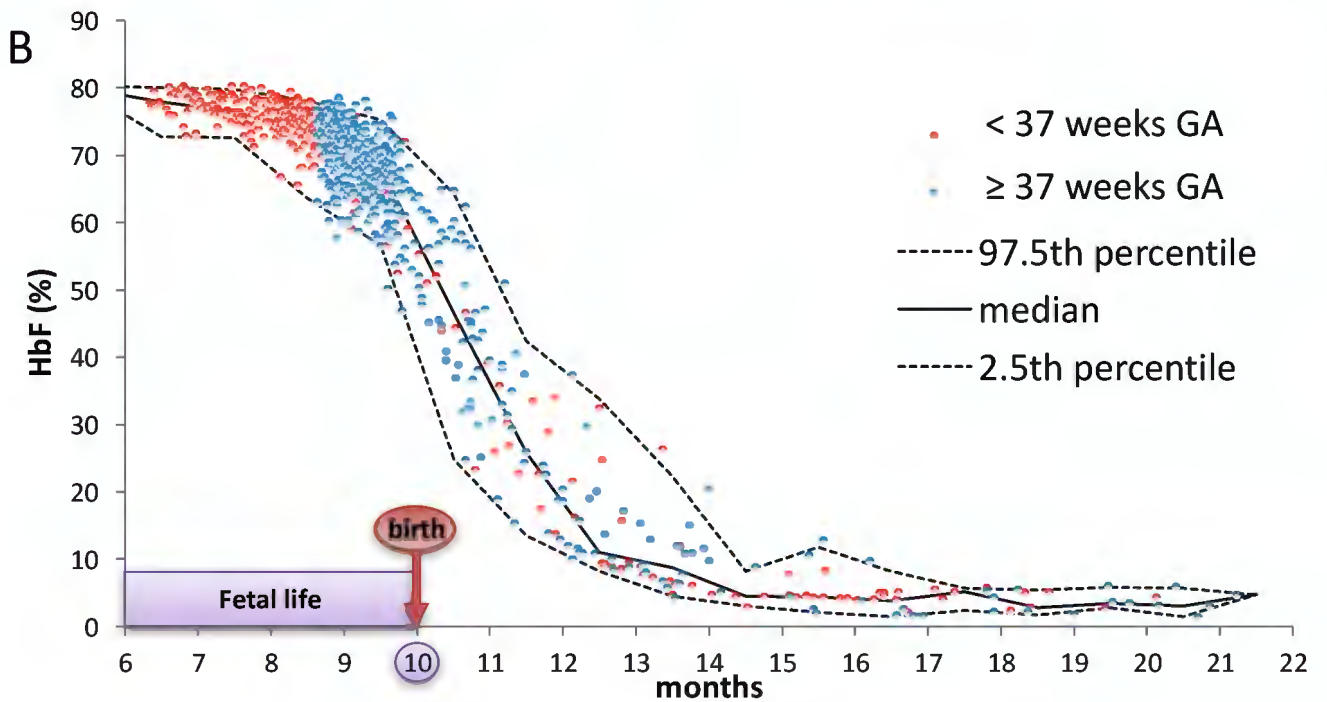
A: Plots and reference ranges of HbF level at postnatal age.

B: Plots and reference ranges of HbF level at postmenstrual age.

C: HbF levels at postnatal age and postmenstrual age in infants < and ≥ 37 weeks GA at birth. Data are shown as median (range).

GA, gestational age; HbF, fetal hemoglobin.





C

		<37 weeks GA at birth		≥37 weeks GA at birth		
	months	n	HbF (%)	n	HbF (%)	*p*
postnatal age	0-1	344	75.5 (64.5-80.3)	481	69.5 (44.6-78.5)	<0.0001
	1-2	58	73.2 (55.2-78.1)	47	43.6 (24.6-64.7)	<0.0001
	2-3	14	62.7 (30.2-76.7)	22	21.4 (10.7-50.9)	<0.0001
	3-4	12	40.0 (21.5-72.8)	14	11.8 (6.7-37.3)	<0.0001
	4-5	4	28.2 (15.7-35.6)	13	10.9 (4.1-20.1)	0.0017
	>5	59	5.1 (2.0-32.3)	27	3.6 (1.3-12.7)	0.0021
postmenstrual age	≤9	384	75.3 (62.6-80.3)	167	72.5 (57.5-78.5)	<0.0001
	9-10	29	68.2 (52.4-75.7)	304	68.1 (46.8-78.0)	0.7459
	10-11	8	43.4 (23.2-55.2)	52	46.8 (24.6-64.8)	0.3844
	11-12	11	26.6 (13.6-35.6)	22	25.1 (12.9-50.9)	0.8937
	12-13	13	9.3 (8.2-32.3)	16	11.8 (8.4-37.3)	0.2318
	>13	46	4.6 (2.0-26.2)	43	5.5 (1.3-20.1)	0.6078
all		491	64.9 (2.0-80.3)	604	59.7 (1.3-78.5)	