

Maternal Haemoglobin and Short-Term Neonatal Outcome in Preterm Neonates

Elodie Savajols¹, Antoine Burguet¹, Marianne Grimaldi¹, Florence Godoy¹, Paul Sagot², Denis S. Semama^{1*}

¹ Department of Paediatrics, Centre Hospitalier Universitaire, Dijon, France, ² Department of Obstetrics, Centre Hospitalier Universitaire, Dijon, France

Abstract

Objective: To determine whether there is a significant association between maternal haemoglobin measured before delivery and short-term neonatal outcome in very preterm neonates.

Study design: We included prospectively all live births occurring from 25 to 32+6 weeks of gestation in a tertiary care centre between January 1st 2009 and December 31st 2011. Outborn infants and infants presenting with lethal malformations were excluded. Three hundred and thirty-nine mothers and 409 infants met the inclusion criteria. For each mother-infant pair a prospective record of epidemiologic data was performed and maternal haemoglobin concentration recorded within 24 hours before delivery was retrospectively researched. Maternal haemoglobin was divided into quartiles with the second and the third one regarded as reference as they were composed of normal haemoglobin values. Short-term outcome was defined as poor in case of death during hospital stay and/or grades III/IV intraventricular haemorrhage and/or periventricular leukomalacia and/or necessity of ventriculoperitoneal shunt.

Results: The global rate of poor short-term neonatal outcome was 11.4% and was significantly associated with low maternal haemoglobin values. This association remained significant after adjustment for antenatal corticosteroids therapy, gestational age, parity, mechanism of preterm birth, mode of delivery and birth weight (aOR = 2.97 CI 95% [1.36–6.47]). There was no relation between short-term neonatal outcome and high maternal haemoglobin concentration values.

Conclusion: We show that low maternal haemoglobin concentration at delivery is an independent risk factor for poor short-term neonatal outcome in very preterm neonates. This study is one of the first to show such an association within the preterm population.

Citation: Savajols E, Burguet A, Grimaldi M, Godoy F, Sagot P, et al. (2014) Maternal Haemoglobin and Short-Term Neonatal Outcome in Preterm Neonates. PLoS ONE 9(2): e89530. doi:10.1371/journal.pone.0089530

Editor: Martin Gerbert Frasc, Université de Montréal, Canada

Received: October 1, 2013; **Accepted:** January 22, 2014; **Published:** February 25, 2014

Copyright: © 2014 Savajols et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Funding: The authors have no support or funding to report.

Competing Interests: The authors have declared that no competing interests exist.

* E-mail: denis.semama@chu-dijon.fr

Introduction

Preterm delivery accounts for 75% of perinatal mortality and more than half of long-term morbidity.[1] Its overall incidence keeps increasing, especially in very preterm infants (born before 33 weeks of gestation) who present the poorest outcomes and the highest mortality rates.[1–3]

Several authors have reported a potential association between maternal haemoglobin concentration and various neonatal outcomes in the whole neonatal population. Described associations usually follow a U-shaped distribution with adverse outcomes at both ends of the haemoglobin range. The main underlying mechanisms involved are preterm birth and low birth weight.[4–12]

We decided to check if this association remained in very preterm neonates born before 33 weeks of gestation. We tested this hypothesis in a hospital based observational study with prospective data collection.

Patients and Methods

This study was approved by our institutional review board (Comité de Protection des Personnes Est I, Bourgogne, France). After deliberation, the board decided that no written consent was needed.

We included prospectively all live births from 25 to 32weeks + 6 days of gestation that occurred in the university-based tertiary care centre in Dijon (Burgundy, France) between January 1st 2009 and December 31st 2011. All infants were hospitalized in our neonatal intensive care unit after primary care in the delivery room.

Outborn infants were excluded as maternal haemoglobin concentration values were usually unavailable in those cases. Inborn infants with missing data for maternal haemoglobin and infants presenting with lethal malformations (oesophageal atresia, diaphragmatic hernia, pulmonary hypoplasia and major congenital heart diseases) were also excluded.

For each mother-infant pair, a prospective and continuous record of epidemiologic data is routinely performed within our perinatal network since 1998.

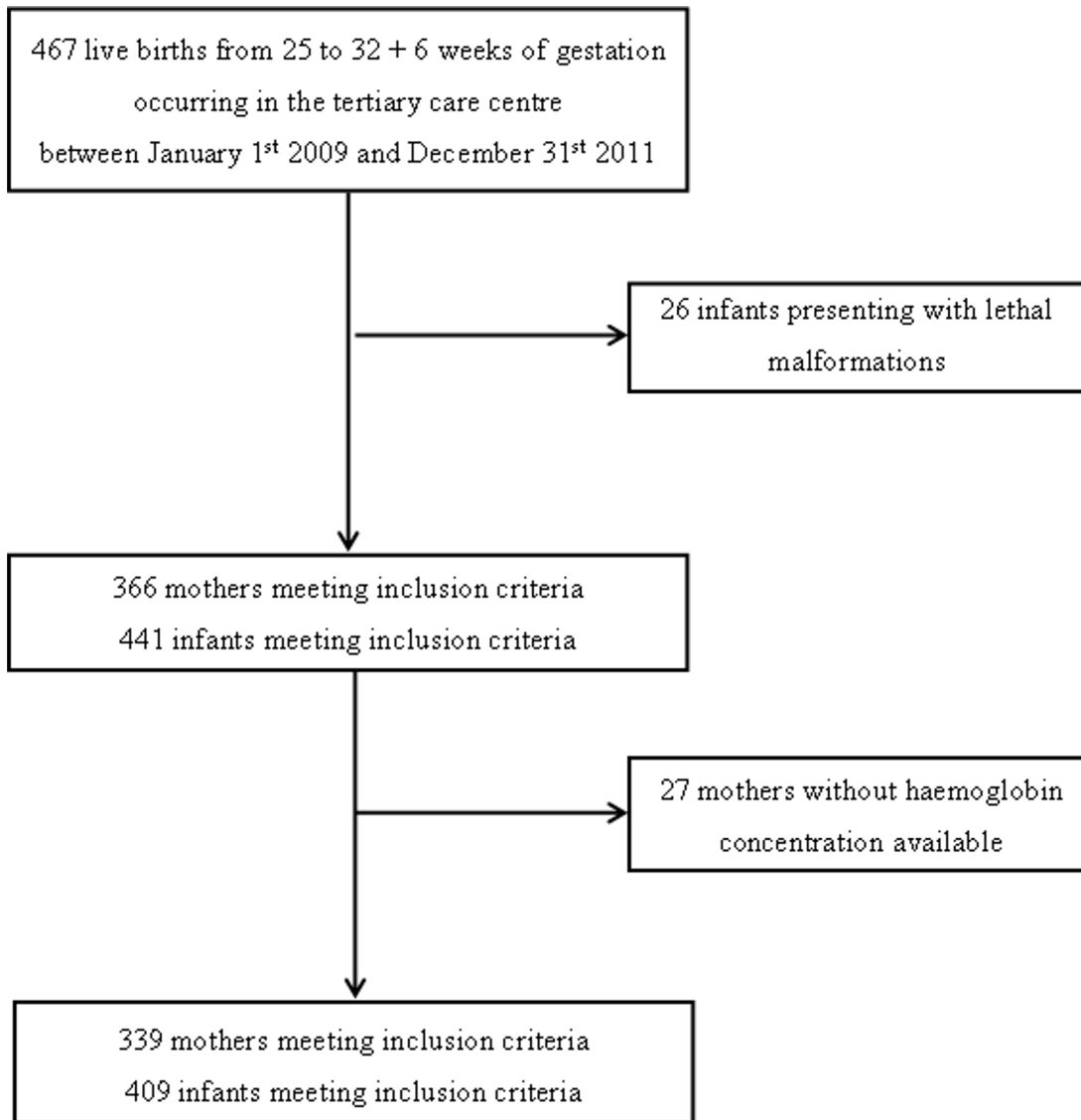


Figure 1. Flow Chart.

doi:10.1371/journal.pone.0089530.g001

In addition, for each birth, we retrospectively reported both the maternal haemoglobin concentration value and the maternal mean cell volume (MCV) recorded within the 24 hours before delivery. The recorded data were divided into quartiles (Q) with Q2 and Q3 clustered together and regarded as reference.

Our main outcome was poor short term neonatal outcome defined as: death during hospital stay and/or grades III–IV intraventricular haemorrhage (defined as per the Papile classification)[13], and/or cystic periventricular leukomalacia and/or necessity of ventriculoperitoneal shunt for post hemorrhagic hydrocephaly.[14] Intraventricular haemorrhage and cystic periventricular leukomalacia were diagnosed using cerebral ultrasound scanning performed by senior paediatricians and/or senior radiologists (Philips Type IE33).

In order to examine poor short-term neonatal outcome in relation to maternal haemoglobin concentration, we defined potential confounding variables classified as follows. Maternal characteristics: maternal age at delivery (divided into ≤ 24 years, 25–34 years and ≥ 35 years), parity (nulliparous or multiparous),

maternal pre-pregnancy body mass index (BMI, kg/m^2) and maternal smoking (defined as one cigarette or more per day during pregnancy). Pregnancy characteristics: gestational age, foetal gender, number of foetus and mode of delivery. Pregnancy characteristics also included mechanism of preterm birth (divided into spontaneous labour with no premature rupture of membranes, maternal bleeding (usually occurring after blood sample collection), premature rupture of membranes (PROM), gestational hypertension and others) and antenatal corticosteroids therapy (defined as at least one dose of betamethasone before delivery). Neonatal characteristics: intubation in the delivery room, surfactant use, blood cells transfusion, patent ductus arteriosus, hemodynamic instability, necrotizing enterocolitis (as defined per the Bell classification)[15] and chronic lung disease (defined as ventilator and/or oxygen dependence at 36 weeks of post-conceptional age).

Table 1. Short term neonatal outcome according to maternal and pregnancy characteristics.

	N infants (n = 409)	Poor short-term neonatal outcome		P value
		Yes (n = 48)	No (n = 361)	
		%	%	
Maternal age		(46)	(357)	
15–24 years	(80)	12.5	87.5	
25–34 years	(248)	10.5	89.5	0.75
35–45 years	(75)	13.3	86.7	
Parity		(48)	(361)	
0	(219)	11.4	88.6	0.83
1 and more	(190)	12.1	87.9	
Pre-pregnancy body mass index		(30)	(307)	
<18.5	(23)	4.4	95.7	
18.5–24.9	(191)	7.9	92.2	0.41
25.0–45.0	(123)	11.4	88.6	
Smoking		(44)	(331)	
No	(269)	11.5	88.5	0.84
1 cigarette/day and more	(106)	12.3	87.7	
Gestational age		(48)	(361)	
25–27	(75)	29.3	70.7	
28–30	(163)	11.0	89.0	0.001
31–32 weeks	(171)	4.7	95.3	
Foetal Gender		(48)	(361)	
Boy	(213)	13.6	86.4	0.23
Girl	(194)	9.7	90.3	
Multiple pregnancy		(48)	(361)	
Yes	(140)	8.6	91.4	0.15
No	(269)	13.4	86.6	
Mechanism of preterm birth		(48)	(361)	
Spontaneous labour with no PROM	(126)	11.9	88.1	
Maternal bleeding	(29)	17.2	82.8	
PROM	(133)	11.3	88.7	0.77
Gestational hypertension	(79)	12.7	87.3	
Others	(42)	7.1	92.9	
Mode of delivery		(48)	(361)	
Vaginal	(119)	10.1	89.9	0.51
Caesarean	(290)	12.4	87.6	
Antenatal corticosteroids therapy		(47)	(361)	
No	(18)	33.3	66.7	0.01
Yes	(390)	10.5	89.5	

doi:10.1371/journal.pone.0089530.t001

Statistical analysis

Qualitative variables were expressed as percentage and quantitative variable were expressed as mean \pm SD.

The analysis followed 4 steps. We first sought to determine the potential relations between the confounding variables and short-term neonatal outcome in bivariate analysis. We performed the same analysis studying this time the potential relations between the confounding variables and maternal haemoglobin concentration quartiles.

We then studied in bivariate analysis the association between maternal haemoglobin concentration and short-term neonatal outcome.

We finally studied in multivariate analysis the association between maternal haemoglobin concentration and short term poor outcome while adjusting on the potential confounding variables previously defined.

All analyses were performed using chi2 test, Fisher test, variance analysis and logistic regression when needed. When variance analysis could not be used (i.e. Bartlett's test for equal variance was

Table 2. Quartiles (Q) of maternal haemoglobin concentration according to maternal and pregnancy characteristics.

	Quartiles of maternal haemoglobin concentration				p
	Women	Q1	Q2-Q3	Q4	
	(n = 339)	≤10.7 g/dl (n = 85)	10.8–12.4 g/dl (n = 165)	≥12.5/dl (n = 89)	
	%	%	%		
Maternal mean corpuscular volume					
Mean (SD)		89.4 (7.9)	91.8 (5.6)	92.8 (5.1)	0.01
Maternal age					
15–24 years	(70)	30.0	41.4	28.6	
25–34 years	(199)	22.6	55.3	22.1	0.07
35–45 years	(65)	26.1	38.5	35.4	
Parity					
0	(177)	17.5	53.1	29.4	0.01
1 and more	(162)	33.3	43.8	22.8	
Pre-pregnancy body mass index					
<18.5	(18)	27.8	61.1	11.1	
18.5–24.9	(160)	23.7	53.7	22.5	0.07
25.0–45.0	(101)	23.8	43.6	35.6	
Smoking					
No	(218)	24.8	49.1	26.1	0.86
1 cigarette/day and more	(91)	27.5	46.1	26.4	
Gestational age					
25–27	(63)	28.6	47.6	23.8	
28–30	(143)	23.8	47.5	28.7	0.89
31–32 weeks	(133)	24.8	50.4	24.8	
Multiple pregnancy					
Yes	(70)	31.4	47.1	21.4	0.32
No	(269)	23.4	49.1	27.5	
Mechanism of preterm birth					
Spontaneous labour with no PROM	(98)	20.4	59.2	20.4	
Maternal bleeding	(26)	19.2	53.8	26.9	
PROM	(103)	43.7	44.7	11.6	0.001
Gestational hypertension	(77)	6.5	42.9	50.6	
Others	(35)	28.6	40.0	31.4	
Mode of delivery					
Vaginal	(97)	21.6	60.8	17.5	0.01
Caesarean	(242)	26.4	43.8	29.7	
Antenatal corticosteroids therapy					
No	(15)	20.0	53.3	26.7	0.89
Yes	(323)	25.1	48.6	26.3	

doi:10.1371/journal.pone.0089530.t002

statistically significant with $p < 0.05$), Kruskal-Wallis test had to be used. P values < 0.05 were considered statistically significant. All analyses were performed with STATA 9[®] software (StataCorp. 2005. *Stata Statistical Software: Release 9*. College Station, TX: StataCorp LP).

Results

Four hundred and nine infants and 339 mothers met the inclusion criteria as represented in the flow chart (figure 1).

Maternal haemoglobin concentration values ranged from 7.6 g/dl to 10.7 g/dl within Q1 (n = 103), from 10.8 g/dl to 12.4 g/dl within Q2 and Q3 (n = 199) and from 12.5 g/dl to 15.7 g/dl within Q4 (n = 107).

Associations between short-term neonatal outcome, maternal characteristics and pregnancy characteristics are shown in table 1. There were significantly more preterm neonates presenting with poor short-term outcome when they did not receive antenatal corticosteroids therapy and when their gestational age decreased.

Table 3. Relation between short term neonatal outcome and maternal hemoglobin concentration.

	n (409)	Poor short term outcome		OR [CI 95%]	aOR ¹ [CI 95%]	aOR ² [CI 95%]	aOR ³ [CI 95%]	aOR ⁴ [CI 95%]
		Yes (n = 48)	No (n = 361)					
		%	%					
Q1 ≤10.7 g/dl	(103)	(20) 19.4	(83) 80.6	2.42 [1.22–4.82]	2.55 [1.24–5.25]	2.99 [1.37–6.53]	2.97 [1.36–6.47]	2.97 [1.36–6.47]
Q2-3 10.8–12.4 g/dl	(199)	(18) 9.0	(181) 91.0	1.0	1.0	1.0	1.0	1.0
Q4 ≥12.5/dl	(107)	(10) 9.3	(97) 90.7	1.04 [0.44–2.43]	0.82 [0.35–1.93]	0.80 [0.33–1.94]	0.78 [0.31–1.98]	0.78 [0.31–1.98]

aOR¹: adjustment for gestational age, birth weight.

aOR²: adjustment for gestational age, birth weight, mechanism of preterm birth.

aOR³: adjustment for gestational age, birth weight, mechanism of preterm birth, antenatal corticosteroids therapy.

aOR⁴: adjustment for gestational age, birth weight, mechanism of preterm birth, antenatal corticosteroids therapy, maternal age, parity, mode of delivery.

doi:10.1371/journal.pone.0089530.t003

Associations between quartiles of maternal haemoglobin concentration values, maternal MCV, maternal characteristics and pregnancy characteristics are shown in table 2. A significant shift of haemoglobin concentrations towards lower values was observed in multiparous women when compared to nulliparous women. A similar shift was observed in women presenting with PROM, while women presenting with gestational hypertension had significantly higher haemoglobin concentration values when compared with other mechanisms of preterm birth.

Infants whose mothers had high haemoglobin concentration values (Q4) had a significantly lower mean birth weight than the ones whose mothers had haemoglobin concentration values within Q1 or Q2–Q3 (1184±383 g, 1378±389 g, 1353±379 g respectively; $p = 0.001$).

There was no statistically significant association between maternal haemoglobin concentration values and rates of intubation in the delivery room, surfactant use, need for blood transfusion, patent ductus arteriosus, hemodynamic instability, necrotizing enterocolitis and chronic lung disease.

The global rate of poor short-term neonatal outcome was 11.4%. There was a statistically significant association between maternal haemoglobin concentration values and short-term neonatal outcome with an increased rate of poor outcome in infants whose mothers had low haemoglobin concentration values (Q1). This association remained significant after adjustment for antenatal corticosteroids therapy, gestational age, parity, mechanism of preterm birth, mode of delivery and birth weight (table 3). There was no statistically significant relation between short-term

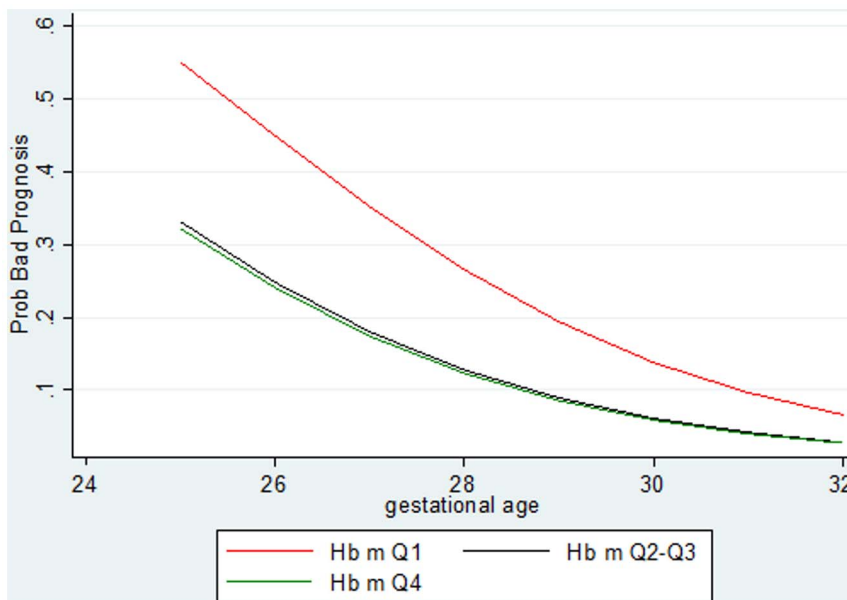


Figure 2. Probability of poor short-term neonatal outcome in relation to gestational age and maternal haemoglobin quartile (Hb m Q). The results are adjusted for birth weight, mechanism of preterm birth, antenatal corticosteroid therapy, maternal age, parity and mode of delivery.

doi:10.1371/journal.pone.0089530.g002

neonatal outcome and high maternal haemoglobin concentration values, before or after adjustment for the confounding variables.

The association between poor short-term neonatal outcome, gestational age and maternal haemoglobin concentration value is shown in figure 2. After adjusting for birth weight, mechanism of preterm birth, antenatal corticosteroid therapy, maternal age, parity and mode of delivery, infants whose mothers had a haemoglobin concentration value within Q1 had a poorer short-term neonatal outcome, whatever their gestational age. No difference was found between other quartiles.

Discussion

This observational study showed that neonates born before 33 weeks of gestation had a poorer short-term neonatal outcome when prenatal maternal haemoglobin concentration was low. This association remained strong and significant after adjustment for gestational age, birth weight, mechanism of preterm birth, antenatal corticosteroids therapy, maternal age, parity and mode of delivery. To our knowledge, our study is the first to focus on the potential impact of maternal haemoglobin concentration on very preterm neonates. It is also to be noted that the upper limit of Q1 concurs with the definition of anaemia in pregnancy by World Health Organization.[16]

The association between maternal haemoglobin and neonatal outcomes has already been studied in the general population of neonates and seems to follow a U-shaped distribution with adverse outcomes at both ends of the haemoglobin range largely mediated through preterm birth and low birth weight.[7,8,17] However, as our study was dealing only with preterm neonates, the effect of preterm birth could not be taken into account. In our very preterm population, we did not find a U-shaped distribution: preterm neonates whose mothers had low haemoglobin concentration value (Q1) had a poorer short-term outcome but no difference was found in terms of outcome in infants whose mothers had the highest haemoglobin concentration value (Q4). This absence of difference persisted after adjusting for gestational age and birth weight. The effect of low maternal haemoglobin concentration was then neither mediated through associations with gestational age nor with birth weight in our study. Other factors were probably involved.

References

1. Goldenberg RL, Culhane JF, Iams JD, Romero R (2008) Epidemiology and causes of preterm birth. *Lancet* 371: 75–84.
2. Larroque B, Bréart G, Kaminski M, Dehan M, André M, et al. (2004) Survival of very preterm infants: Epipage, a population based cohort study. *Arch Dis Child Fetal Neonatal Ed* 89: 139–144.
3. Charkaluk ML, Truffert P, Fily A, Ancel PY, Pierrat V (2010) Neurodevelopment of children born very preterm and free of severe disabilities: the Nord-Pas de Calais Epipage cohort study. *Acta Paediatr* 99: 684–689.
4. Ren A, Wang J, Ye RW, Li S, Liu JM, et al. (2007) Low first-trimester hemoglobin and low birth weight, preterm birth and small for gestational age newborns. *Int J Gynaecol Obstet* 98: 124–128.
5. Levy A, Fraser D, Katz M, Mazor M, Sheiner E (2005) Maternal anemia during pregnancy is an independent risk factor for low birthweight and preterm delivery. *Eur J Obstet Gynecol Reprod Biol* 122:182–186.
6. Bondevik GT, Lie RT, Ulstein M, Kvåle G (2001) Maternal hematological status and risk of low birth weight and preterm delivery in Nepal. *Acta Obstet Gynecol Scand* 80:402–408.
7. Zhou L, Yang WW, Hua JZ, Deng CQ, Tao X, et al. (1998) Relation of hemoglobin measured at different times in pregnancy to preterm birth and low birth weight in Shanghai, China. *Am J Epidemiol* 148: 998–1006.
8. Little M, Brocard P, Eliott P, Steer PJ (2005) Hemoglobin concentration in pregnancy and perinatal mortality: a London-based cohort study. *Am J Obstet Gynecol* 193: 220–226.
9. Zhang Q, Ananth CV, Rhoads GG, Li Z (2009) The impact of maternal anemia on perinatal mortality: a population-based, prospective cohort study in China. *Ann Epidemiol* 19: 793–799.
10. Murphy JF, O’Riordan J, Newcombe RG, Coles EC, Pearson JF (1986) Relations of hemoglobin levels in first and second trimesters to outcomes of pregnancy. *Lancet* 1: 992–995.
11. Xiong X, Buekens P, Alexander S, Demianczuk N, Wollast E (2000) Anemia during pregnancy and birth outcome: a meta analysis. *Am J Perinatol* 17: 137–146.
12. Malhotra M, Sharma JB, Batra S, Sharma S, Murthy NS (2002) Maternal and perinatal outcomes in varying degrees of anemia. *Int J Gynaecol Obstet* 79: 93–100.
13. Papile LA, Burstein J, Burstein R, Koffler H (1978) Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants with birthweight less than 1500 g. *J Pediatr* 92: 529–534.
14. Ancel PY, Livinec F, Larroque B, Marret S, Arnaud C, et al. (2006) Cerebral palsy among very preterm children in relation to gestational age and neonatal ultrasound abnormalities: the EPIPAGE cohort study. *Pediatrics* 117: 828–835.
15. Bell MJ, Ternberg JL, Feigin RD, Keating JP, Marshall R, et al. (1978) Neonatal necrotizing enterocolitis: Therapeutic decisions based upon clinical staging. *Ann Surg* 187: 1–7.
16. United Nations Children’s Fund, United Nations University, World Health Organization (2001) Iron deficiency anaemia, assessment, prevention and control. A guide for program managers. WHO/NHD/01.3. Available: http://www.who.int/nutrition/publications/en/ida_assessment_prevention_control.pdf.
17. Steer P, Alam MA, Wadsworth J, Welch A (1995) Relation between maternal hemoglobin concentration and birth weight in different ethnic groups. *BMJ* 310: 489–491.

A deeper analysis of our results could lead to question a potential association between maternal haemoglobin concentration and mechanisms of preterm birth. At the higher end of haemoglobin values range (Q4), we find both a significantly higher proportion of women presenting with preeclampsia and a significantly higher proportion of neonates presenting with a lower birth weight. It is known that the ability to produce a large increase in plasma volume between the first and the second pregnancy trimester is one of the hallmarks of successful pregnancy as it is probably linked with correct uterine perfusion. Failure to produce this expansion may lead to insufficient uterine perfusion and thus to preeclampsia and intra uterine growth restriction.[18] Moreover, women not undergoing this expansion are bound to present a higher haemoglobin concentration due to hemoconcentration. At the other end of haemoglobin values range, we find a potential association between a lower haemoglobin value and a higher rate of preterm rupture of the membranes. This association has already been described in the literature while the physiopathological mechanisms underlying it still remain unclear. However, in spite of those potential associations between maternal haemoglobin concentration and mechanism of preterm birth at both ends of the haemoglobin values range, the association between maternal haemoglobin concentration and short-term neonatal outcome remains significant after adjusting on those very mechanisms of preterm birth. Consequently, this association cannot be explained only through the mechanisms of preterm birth. Other possible physiopathological mechanisms could be functional impairments at tissue level created by low haemoglobin concentration [19,20] or increased oxidative stress due to iron deficiency [21,22], which is one of the major mechanisms underlying low maternal haemoglobin concentration during pregnancy.[16] Those tissue functional impairments and/or oxidative damages, should they take place within the foeto-placental unit, could result in a poorer neonatal outcome. Further research will be needed to confirm those hypotheses.

Author Contributions

Conceived and designed the experiments: ES DSS AB. Performed the experiments: AB. Analyzed the data: ES DSS AB. Wrote the paper: ES DSS MG FG PS AB.

18. Amburgey OA, Ing E, Badger GJ, Bernstein IM (2009) Maternal hemoglobin concentration and its association with birth weight in newborns of mothers with preeclampsia. *J Maternal Fetal Neonatal Med* 22: 740–744.
19. Auger N, Le TU, Park AL, Luo ZC (2011) Association between maternal comorbidity and preterm birth severity and clinical subtype: retrospective cohort study. *BMC Pregnancy Childbirth* 11: 67.
20. Zhang Q, Ananth CV, Li Z, Smulian JC (2009) Maternal anemia and preterm birth: a prospective cohort study. *Int J Epidemiol* 38: 1380–1389.
21. Allen LH (2001) Biological mechanisms that might underlie iron's effects on fetal growth and preterm birth. *J Nutr* 131: 581–589.
22. Ducsay CA (1998) Fetal and maternal adaptations to chronic hypoxia: prevention of premature labor in response to chronic stress. *Comp Biochem Physiol A Mol Integr Physiol* 119: 675–681.