Physiological development of a mixed metabolic and respiratory umbilical cord blood acidemia with advancing gestational age

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Objective: To investigate respiratory and metabolic components of gestational age-dependent umbilical cord blood gas changes.

Study design: Cord blood gases were determined in 1336 vigorous singletons with uncomplicated cephalic vaginal delivery at 37-43 weeks. Linear regression analysis and non-parametric statistics were used with a $P < 0.05$ being significant.

Results: Gestational age correlated negatively with arterial pH and HCO_3^- and positively with pCO_2 and base deficit. Venous blood showed corresponding changes except for pCO_2, which was independent of gestational age. Arterial pCO_2, but not venous, correlated positively with birthweight deviation from the mean. The fractional fetal CO_2 production per birthweight unit and the fractional placental CO_2 clearance per placental weight unit were not correlated with gestational age.

Conclusions: A mixed respiratory and metabolic cord blood acidemia develops with advancing gestational age. The respiratory component depends on an increased 'CO_2 load' from the growing fetus and not on deterioration of placental gas exchange. The etiology of the metabolic component is yet unknown.

Key words: Acidosis; Blood gases; Fetal; Gestational age; Pregnancy; Umbilical cord.

LIST OF ABBREVIATIONS

AGA: appropriate-for-gestational age; AVG: arteriovenous carbon dioxide partial pressure gradient; BD: base deficit; BE: base excess; BWD: birthweight deviation; FFP: fractional fetal carbon dioxide production; FPC: fractional placental carbon dioxide clearance; Hb: hemoglobin; HbA: adult hemoglobin; HbF: fetal hemoglobin; LGA: large-for-gestational age; SD: standard deviation; SGA: small-for-gestational age; 2,3-DPG: 2,3–diphosphoglycerate

INTRODUCTION

Umbilical cord blood gases change with advancing gestational age. It is well established that the arterial and venous pO_2 and pH decrease and the arterial and venous pCO_2 increase [1-4]. Changes of bicarbonate and base contents are less well investigated. Weiner *et al*. [2] found a non-significant rise of venous bicarbonate but unchanged base deficit (BD), whereas Arikan *et al*. [5] reported the arterial and venous base excess (BE) to decrease (i.e., BD to increase).

The etiology of these physiological changes is unknown. Since the pCO_2 increases, it is plausible that the decline of pH is a result of carbon dioxide accumulation. Accumulation of carbon dioxide in cord blood with advancing gestational age may arise from an increased carbon dioxide production by the growing fetus, parallel to a limited placental gas exchange. In addition, deterioration of placental gas exchange by aging may cause an inadequate oxygen supply and decline of fetal pO_2, which may result in anaerobic metabolism, increased lactate production, and a fall of pH.

The aim of the present study was to investigate changes of umbilical cord blood gas parameters and the acid-base balance relative to advancing gestational age in newborns exposed to uncomplicated vaginal deliveries. The contributions of the respiratory and metabolic components to the development of a relative acidemia were estimated. Hence, the fetal production and placental clearance of carbon dioxide were of particular interest.

MATERIAL AND METHODS

Umbilical cord blood gas analysis at birth is a routine procedure at the Malmö University Hospital maternity unit. Immediately after birth and before the newborn's first breath, the umbilical cord is double-clamped and arterial and venous cord blood sampled in pre-heparinized syringes. Blood gases are analyzed within 5 minutes after sampling in a Radiometer ABL 735 blood gas analyzer (Radiometer, Copenhagen, Denmark), which also stores the results. From March 2001 to July 2003, samples from 6054 newborns were analyzed. From that cohort, a consecutive series of uncomplicated spontaneous vaginal vertex deliveries at 37 – 43 completed gestational weeks (confirmed by an early second trimester fetometry), was compiled by combining data from an obstetric database and data stored in the blood gas analyzer. Only pregnancies with singleton vertex presentations, complete information about all the investigated parameters, and validated cord blood samples, were included. The quality of paired umbilical arterial and venous blood samples was validated by excluding samples obtained from the same umbilical vessel according to the criteria that pH in the artery should be $\geq$ 0.02 units lower than in the vein [6,7]. Single-vessel samples were excluded due to uncertain origin. To reduce the influence of iatrogenic interventions and fetal distress in labor, cases with induced labor and/or oxytocin augmentation of labor and/or epidural analgesia and/or operative delivery (cesarean section, ventouse or forceps delivery) and/or an Apgar score of $\leq$ 8 at 5 and 10 minutes and/or transfer to the neonatal intensive care unit, were excluded. After exclusions, 1336 cases fulfilled the inclusion criteria.

Maternal or fetal complications and diagnoses known antenatally were not considered as exclusion criteria.

pH, pCO_2 and pO_2 were measured by the blood gas analyzer. In the present study, we calculated bicarbonate and BD *post hoc* from the determinations of pH and pCO_2 by using the following equations (based on the fundamental base excess equation from Siggaard-Andersen, also called the Van Slyke equation):

(1) Base deficit in the extracellular fluid compartment (BD_{ecf}) [8]:

$$BD_{ecf} = -0.9149 \bullet [0.2325 \bullet pCO_2 \bullet 10^{(pH - 6.1)} - 24.1 + 16.21 \bullet (pH - 7.4)]$$

(2) Bicarbonate (HCO_3^-) [8]: $HCO_3^- = 0.2325 \bullet pCO_2 \bullet 10^{(pH - 6.1)}$

The fetal CO_2 production and placental clearance can be estimated from the pCO_2 values, since according to Henry's law there is a direct proportional relationship between the plasma CO_2 concentration (C_{CO2}) and pCO_2: $C_{CO2} = pCO_2 \bullet Q$, where Q represents Bunsen's solubility coefficient.

Arterial blood was denoted with the prefix 'aB-' and venous blood with 'vB-'. The following CO_2 parameters were calculated:

(1) Fractional placental carbon dioxide clearance (FPC) = $(aB\text{-}pCO_2 - vB\text{-}pCO_2)/aB\text{-}pCO_2$

(2) Fractional fetal carbon dioxide production (FFP) = $(aB\text{-}pCO_2 - vB\text{-}pCO_2)/vB\text{-}pCO_2$

(3) Arteriovenous carbon dioxide partial pressure gradient (AVG) = $aB\text{-}pCO_2 - vB\text{-}pCO_2$

The blood gas parameters were compared with gestational age at delivery, time duration of the second stage of labor, birthweight, birthweight deviation (BWD) from the mean value, placental weight, and birthweight-to-placental weight ratio.

The BWD was expressed in percent of deviation from the gestational age-adjusted mean value according to reference values [9]. Hence, 11 % of BWD corresponds to 1 standard deviation

(SD), and 22 % to 2 SD. Small-for-gestational age (SGA) was defined as a birthweight below minus 2 SD from the gestational age-adjusted mean value, appropriate-for-gestational age (AGA) as a birthweight within mean $\pm$ 2 SD, and large-for-gestational age (LGA) as above mean + 2 SD.

Statistics: Simple linear regression analysis and Spearman's rank correlation test (Spearman's rho) were used to estimate relationships between continuous variables. Relationships between blood gas parameters (dependent variables), and gestational age and the time duration of the second stage of labor (independent variables), that were obtained with simple linear regression analysis at a significance level of $P < 0.2$, were analyzed together in a multiple linear regression analysis. The Kruskal-Wallis test was used to compare variables at different gestational ages. Two-group comparisons were performed with the Mann-Whitney *U* test or Wilcoxon signed-rank matched-pairs test. The Chi-square test was used to compare discrete variables between groups. *P* values were corrected for ties and a two-tailed *P* value < 0.05 was considered statistically significant. Statistics were performed with aid of StatView® (SAS Institute, Cary, NC, U.S.A.) and MedCalc® (MedCalc Software, Mariakerke, Belgium) computer software.

The study was approved by the Research Ethics Committee at the Medical Faculty, University of Lund.

RESULTS

Positive relationships were found between gestational age and birthweight (Spearman's rho, $P < 0.0001$), placental weight ($P < 0.0001$), and birthweight-to-placental weight ratio ($P < 0.0001$). The BWD was not related to gestational age (Spearman's rho, $P = 0.7$). No relationships were found between gestational age at delivery, birthweight, BWD and placental weight, respectively, and time duration of the second stage of labor (Spearman's rho, $P = 0.4$, 0.8, 0.7 and 0.9).

Independent of each other, gestational age and the second stage time duration were determinants of cord blood gas changes, except for the relationship between venous pCO_2 and gestational age (Table 1).

Table 2 summarizes umbilical cord blood gas values relative to gestational age. In gestational weeks 37, 42 and 43, there were relatively few cases and cases in week 37 (N = 75) were therefore merged with cases in week 38 (N = 200), and cases in weeks 42 (N = 30) and 43 (N = 4) merged with cases in week 41 (N = 202). The number of cases in weeks 39 and 40 were 381 and 444, respectively. The aB-pH and vB-pH both displayed a decrease with advancing gestational age, though at different paces, which resulted in an increase of the arteriovenous pH difference (Figure 1).

The aB-pCO_2 increased with gestational age, but the vB-pCO_2 did not change significantly over the weeks, resulting in an increasing AVG with advancing gestational age (Figure 2). The aB-pCO_2, but not the vB-pCO_2, showed a positive correlation with birthweight (Spearman's rho, $P < 0.0001$ and 0.4, respectively) and BWD ($P < 0.0001$ and 0.3, respectively). The birthweight-to-placental weight ratio was not significantly related to the

aB-pCO_2 (Spearman's rho, P = 0.3), the vB-pCO_2 (P = 0.6), the AVG (rho = -0.05, P = 0.055), or the arteriovenous pCO_2 ratio (rho = -0.05, P = 0.08).

The aB-HCO_3^- and vB-HCO_3^- concentrations decreased with advancing gestational age, but the arteriovenous HCO_3^- difference was not significantly correlated with gestational age (Figure 3). The overall HCO_3^- concentration was higher in arterial blood (mean ± SD, 23.7 ± 2.3 mmol/L) than in venous blood (21.8 ± 2.1 mmol/L) (Wilcoxon test, $P < 0.0001$).

Both arterial and venous BD_{ecf} concentrations increased with advancing gestational age, but the arteriovenous difference was unaltered and not correlated to gestational age (Figure 4); the overall BD_{ecf} was higher in venous blood (mean ± SD, 2.98 ± 2.22 mmol/L) than in arterial blood (2.61 ± 2.63 mmol/L) (Wilcoxon test, $P < 0.0001$).

Although there were decreasing trends, neither the FFP/kg birthweight nor the FPC/kg placental weight was significantly associated with gestational age (for FFP/kg: Spearman's rho, P = 0.1, and Kruskal-Wallis test, P = 0.2; for FPC/kg: P = 0.2 and 0.3, respectively).

The mean ± SD gestational age in the series was 279.2 ± 8.0 days, and the mean ± SD BWD was 1.6 ± 11.6 %. The number of SGA neonates was 25 (1.9 %), AGA 1252 (93.7 %), and LGA 59 (4.4 %). There were no proportional distribution changes of SGA or LGA babies over the weeks (Chi-square test, 6 degrees of freedom, P = 0.2).

DISCUSSION

The fetal acid-base status is reflected by umbilical cord arterial blood gases, from which the present study suggests development of a mixed metabolic and respiratory fetal acidemia with advancing gestational age, distinctly showed by the progressive changes in pH, pCO_2, HCO_3^- and BD_{ecf}.

The influences of iatrogenic obstetric interventions and fetal distress on the fetal acid-base balance were merely eliminated by our strict selection of cases for the study, and only validated cord blood samples were included. Moreover, the gestational age and the time duration of the second stage of labor influenced, independently of each other, the cord blood changes in the same directions. Since no relationships were found between the duration of the second stage of labor and birthweight or placental weight, it was not necessary to consider the time of the second stage further in the analyses. Finally, the calculated mean ± SD birthweight deviation (1.6 % ± 11.6 %) almost perfectly fitted with the expected average in the general population (0 % ± 11 %), and there was no skewness over the weeks of small and large babies. The results therefore indicate the blood gas changes are physiological.

The arterial pCO_2 increased with gestational age whereas the venous pCO_2 showed no significant change over the weeks, indicating that the increasing arteriovenous pCO_2 difference reflected a carbon dioxide accumulation in arterial blood. This progressively increasing 'CO_2 load' and increase of arterial pCO_2 is a logical consequence of the growing fetal mass with advancing gestational age, which was also confirmed by the positive correlation found between birthweight deviation and arterial pCO_2. The fetal CO_2 production relative to unit of fetal mass remained constant, as reflected by a lack of association between gestational age and the 'fractional fetal carbon dioxide production' per fetal weight unit.

We postulated that the respiratory component of the decreasing arterial cord blood pH was a consequence of not only an increasing carbon dioxide load from the growing fetus, but also from a limited gas exchange over aging placental membranes. Two findings contradict the latter theory: the venous pCO_2 did not change by gestational age and the 'fractional placental carbon dioxide clearance' per placental weight unit remained constant, indicating that the fetomaternal CO_2 exchange across the placenta is unrelated to gestational age in normal pregnancies. The continuously increasing progesterone level in pregnancy induces a relative maternal hyperventilation and a subsequent decrease of maternal pCO_2 [10], which would further facilitate the CO_2 exchange over the placenta.

The best parameter to express the metabolic component of any type of acidemia is BD, since BD represents a linear correlate to the degree and duration of the acidemia. Since the fetus has a relatively large extravascular fluid compartment and low plasma protein concentration compared with the adult, and hypercapnia influences BD substantially more when calculated in the fetal blood compartment, the extracellular fluid compartment should be used when estimating BD in fetuses and neonates [11,12]. In this study, the metabolic component had a critical impact on the development of fetal acidemia, as illustrated by the decreasing HCO_3^- and increasing BD concentrations. It is not known whether a gestational age-dependent relationship exits between the fetal and maternal carbonic acid-bicarbonate buffering systems, but the fetal levels of both bicarbonate and BD are lower than the maternal values [13]. Both arterial and venous cord blood HCO_3^- decreased, and the arterial bicarbonate concentration was higher than the venous, but there was no correlation between gestational age and the arteriovenous bicarbonate gradient. These findings indicate that there is no net change of the fetal blood bicarbonate buffering capacity at passage by the maternal intervillous

compartment in the placenta. Theoretically, the reduction of HCO_3^- and increase of CO_2 in fetal arterial blood might be explained by an increased fetal anaerobic metabolism with increased production of H^+ ions and non-volatile acids, as the pO_2 and oxygen saturation decrease with advancing gestational age [14].

Although the differences were small, the venous cord blood concentration of HCO_3^- was lower, and that of BD_{ecf} higher, than in arterial blood. Two circumstances may explain the findings: firstly, at placental passage the umbilical artery CO_2 will escape and result in lower CO_2 and HCO_3^- concentrations in venous blood; Secondly, neither the HCO_3^- concentration nor BD_{ecf} are actually measured by the blood gas analyzer – they are estimated by calculations based on the pH and pCO_2 measurements. That introduces an unavoidable methodological approximation that might not perfectly adjust to the biologic reality.

In an organism the pH homeostasis is maintained by various buffering systems. The fetal buffering capacity may be affected by the hemoglobin (Hb) types. Fetal hemoglobin (HbF) is dominating during fetal life but decreases towards term, when 20 % of the circulating hemoglobin is of the adult type (HbA) [15]. Moreover, deoxygenated hemoglobin is a better buffer than oxygenated. The enzyme 2,3–diphosphoglycerate (2,3-DPG) in erythrocytes stabilizes the deoxygenated form of Hb, and as HbF binds 2,3-DPG less avidly than HbA, the concentration of this enzyme together with the shift of hemoglobin types may play a critical role in the regulation of fetal acid-base balance. However, Soothill and co-workers [16] found an unchanged concentration of 2,3-DPG by gestation in normal fetuses. Finally, differences in the erythrocyte content of carbonic anhydrase, enhancing the reaction $H_2CO_3 \leftrightarrow CO_2 + H_2O$ with a quicker placental elimination of CO_2, relative to fetal and adult hemoglobin types may also affect the buffering capacity.

In summary, this study showed that the fetal acid-base balance, as reflected by umbilical cord blood gases, changes with advancing gestational age. A mixed respiratory and metabolic relative 'acidemia' develops in umbilical arterial blood. The respiratory component, represented by an increasing arterial CO_2 partial pressure, is caused by an increased 'carbon dioxide load' from the growing fetus, whereas an effective placenta clearance of CO_2, with no sign of deterioration by age, prevents accumulation of CO_2 in venous cord blood. The etiology of the metabolic component, as revealed by an increasing BD_{ecf}, is yet unknown. The CO_2 load is important by charging the carbonic acid-bicarbonate buffering system, but shifts of hemoglobin types and enzyme activity with advancing gestational age may be of importance as well.

ACKNOWLEDGEMENTS

The study was supported by grants from the Medical Faculty at the Lund University and Region Skåne. Ms. Emma Nilsson is gratefully acknowledged for technical compilation of blood gas data.

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LEGENDS TO FIGURES

Figure 1

Umbilical cord blood pH changes with advancing gestational age. Mean values, as indicated, were calculated on 275 validated blood samples in weeks 37-38, 381 in week 39, 444 in week 40 and 236 samples in weeks 41-43. Both the arterial and venous pH increased (Spearman's rho, $P < 0.0001$ and $= 0.004$, respectively; Kruskal-Wallis test, $P = 0.0002$ and 0.03, respectively). The arteriovenous gradient showed an increment as well ($P = 0.08$ and 0.04, respectively), but significant only for 37-38 versus 39 weeks (Mann-Whitney *U* test, $P = 0.009$).

Figure 2

Umbilical cord blood pCO_2 changes with advancing gestational age. Both the arterial pCO_2 and the arteriovenous gradient (Spearman's rho, $P = 0.03$ and 0.03, respectively; Kruskal-Wallis test, $P = 0.03$ and 0.02, respectively) increased with advancing gestational age, whereas the venous pCO_2 remained unchanged ($P = 0.6$ and 0.7, respectively).

Figure 3

Umbilical cord blood bicarbonate changes with advancing gestational age. Both the arterial and venous bicarbonate concentrations decreased (Spearman's rho, $P = 0.02$ and 0.0002, respectively; Kruskal-Wallis test, $P = 0.1$ and 0.002, respectively). The arteriovenous gradient remained unchanged (Spearman's rho, $P = 0.2$; Kruskal-Wallis test, $P = 0.2$).

Figure 4

Umbilical cord blood base deficit changes with advancing gestational age. Base deficit was calculated in the extracellular fluid compartment. Both the arterial and venous concentrations

increased (Spearman's rho, $P = 0.0002$ and < 0.0001, respectively; Kruskal-Wallis test, $P = 0.002$ and < 0.0001, respectively). The arteriovenous gradient remained unchanged (Spearman's rho, $P = 0.4$; Kruskal-Wallis test, $P = 0.6$).

Table 1.

Influence of gestational age (days) and length of second stage of labor (minutes) on umbilical cord blood acid-base status. Figures obtained at multiple linear regression analyses. Relationships with a $P > 0.2$ at simple linear regression analysis were not included in the multiple regression analyses.

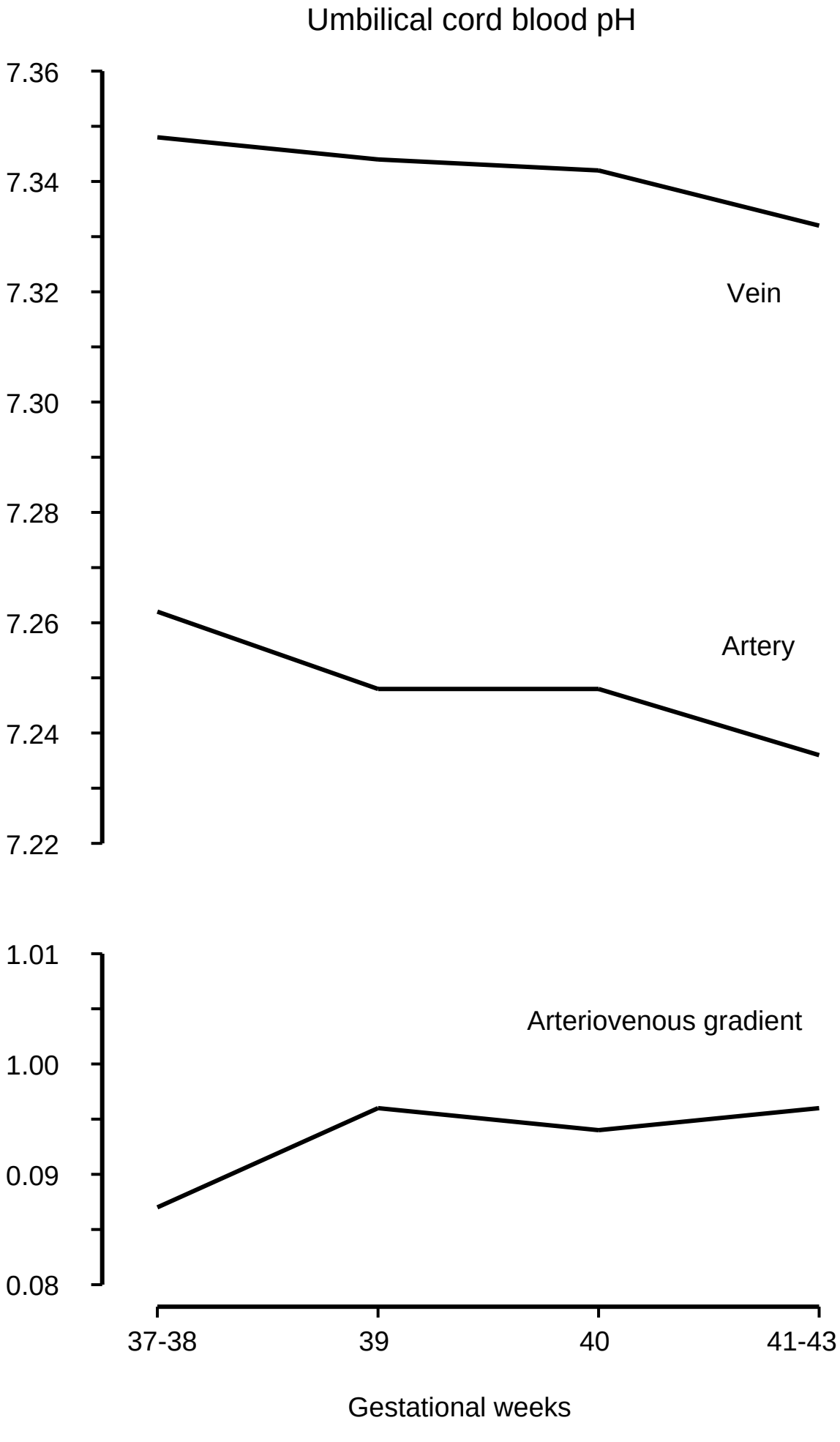
	Gestational age			Time duration of 2nd stage of labor		
	Coefficient	95 % confidence interval	*P*	Coefficient	95 % confidence interval	*P*
Artery						
pH	-0.001	-0.00056, -0.0014	0.0007	-0.001	-0.00087, -0.0011	< 0.0001
pCO_2	0.008	0.00016, 0.016	0.049	0.003	0.005, 0.001	0.004
BD_{ecf}	0.026	0.0084, 0.044	0.002	0.032	0.026, 0.038	< 0.0001
HCO_3^-	-0.016	-0.00032, -0.032	0.03	-0.024	-0.020, -0.028	< 0.0001
Vein						
pH	-0.00047	-0.000066, -0.00088	0.02	-0.001	-0.00088, -0.0011	< 0.0001
pCO_2	-	-	-	0.003	0.001, 0.005	0.0002[a]
BD_{ecf}	0.026	0.012, 0.04	0.0003	0.030	0.026, 0.034	< 0.0001
HCO_3^-	-0.021	-0.073, -0.035	0.003	-0.021	-0.017, -0.025	< 0.0001

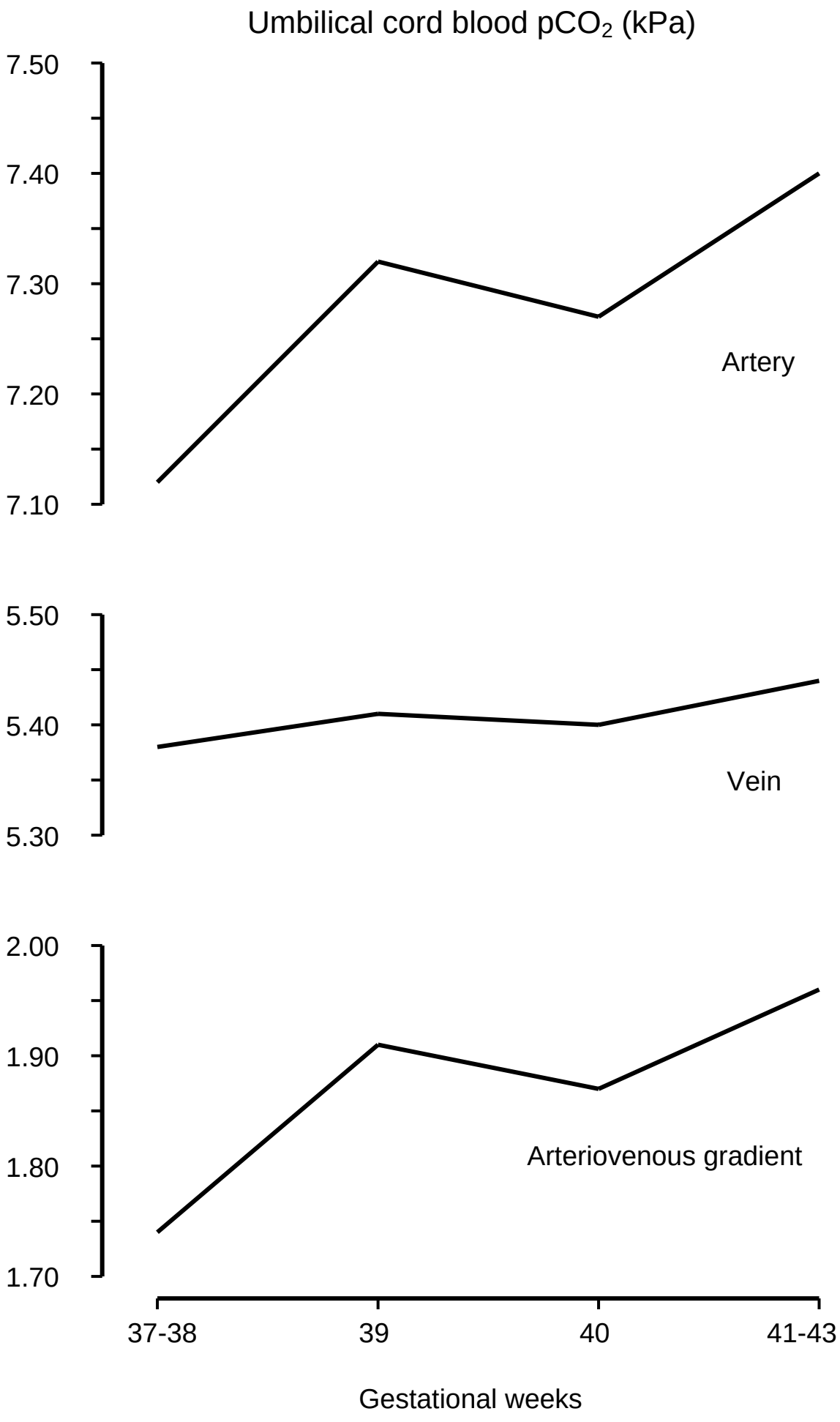
pH = Power of H^+; pCO_2 = CO_2 partial pressure; BD_{ecf} = Base deficit in extracellular fluid; HCO_3^- = Bicarbonate.

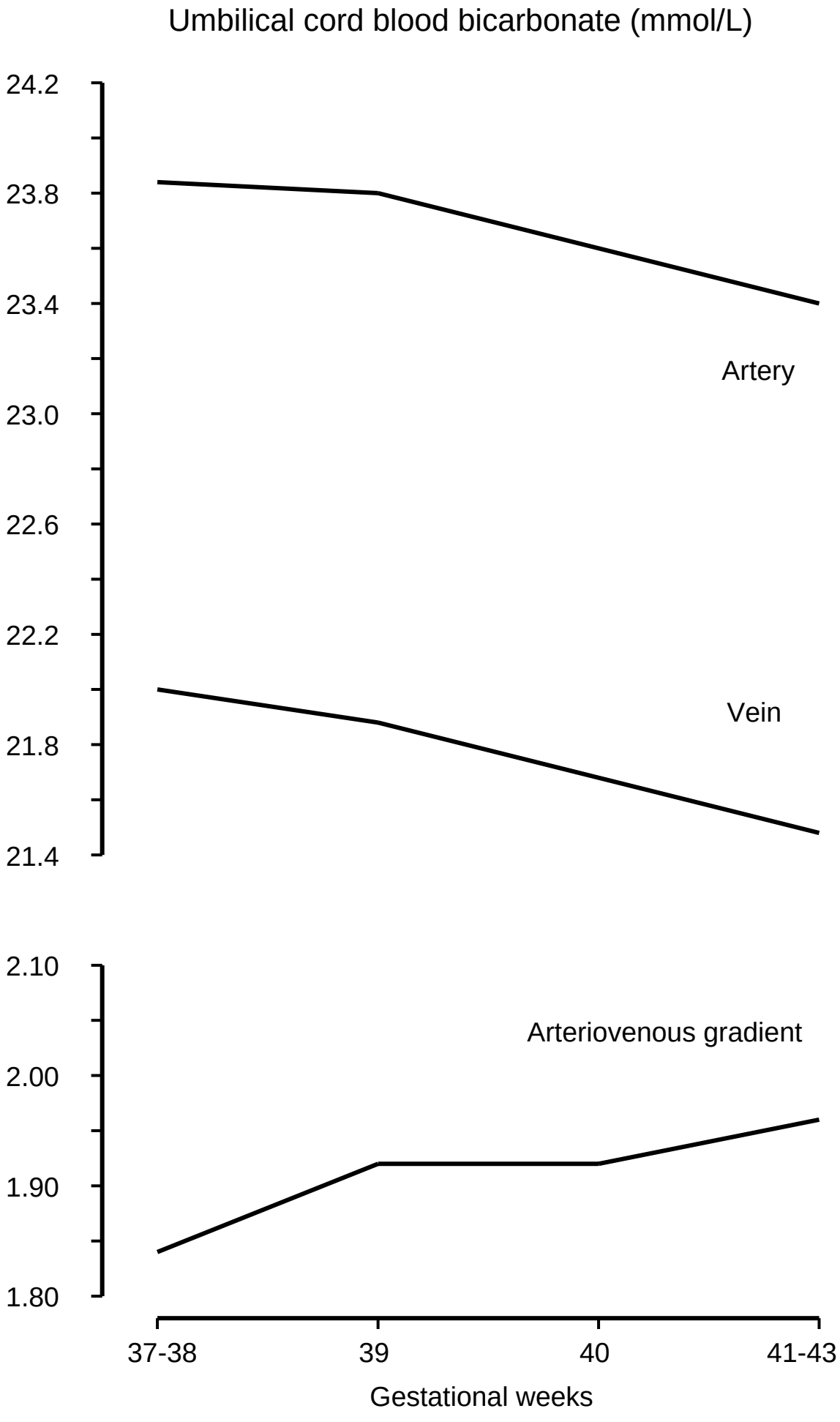
a) Figure obtained at simple linear regression analysis

Table 2. Umbilical cord blood gases relative to gestational age. Values are mean ± standard deviation (median). ’vB’ -denotes venous blood and ’aB’-arterial blood

Gestational age (weeks)	N	vB-pH	aB-pH	vB-pCO_2	aB-pCO_2	vB-HCO_3^-	aB-HCO_3^-	vB-BD_{ecf}	aB-BD_{ecf}
37-38	275	7.348 ± .057 (7.349)	7.262 ± .069 (7.265)	5.38 ± .82 (5.33)	7.12 ± 1.08 (7.05)	22. 00 ± 2.31 (22.08)	23.84 ± 2.23 (24.19)	2.68 ± 2.38 (2.45)	2.29 ± 2.58 (1.97)
39	381	7.345 ± .064 (7.347)	7.249 ± .069 (7.254)	5.41 ± .92 (5.33)	7.32 ± 1.17 (7.26)	21.89 ± 1.81 (21.99)	23.81 ± 2.19 (23.92)	2.84 ± 1.95 (2.77)	2.50 ± 2.49 (2.31)
40	444	7.342 ± .065 (7.351)	7.249 ± .068 (7.258)	5.40 ± .94 (5.33)	7.27 ± 1.16 (7.18)	21.70 ± 2.20 (21.72)	23.62 ± 2.51 (23.73)	3.06 ± 2.33 (2.83)	2.69 ± 2.78 (2.37)
41-43	236	7.333 ± .063 (7.336)	7.237 ± .066 (7.237)	5.44 ± .88 (5.39)	7.40 ± 1.16 (7.38)	21.47 ± 2.01 (21.51)	23.43 ± 2.30 (23.56)	3.40 ± 2.16 (3.11)	3.03 ± 2.55 (2.86)
Kruskal-Wallis test (*P*)		0.03	0.0002	0.7	0.03	0.002	0.1	0.0001	0.004
Spearman’s rho (*P*)		0.005	< 0.0001	0.5	0.03	0.002	0.02	< 0.0001	0.0002


Umbilical cord blood pH
7.36
7.34
7.32
7.30
7.28
7.26
7.24
7.22
Vein
Artery
1.01
1.00
0.09
0.08
Arteriovenous gradient
37-38
39
40
41-43
Gestational weeks


Umbilical cord blood pCO_2 (kPa)
7.50
7.40
7.30
7.20
7.10
Artery
5.50
5.40
5.30
Vein
2.00
1.90
1.80
1.70
Arteriovenous gradient
37-38
39
40
41-43
Gestational weeks


Umbilical cord blood bicarbonate (mmol/L)
24.2
23.8
23.4
23.0
22.6
22.2
21.8
21.4
Artery
Vein
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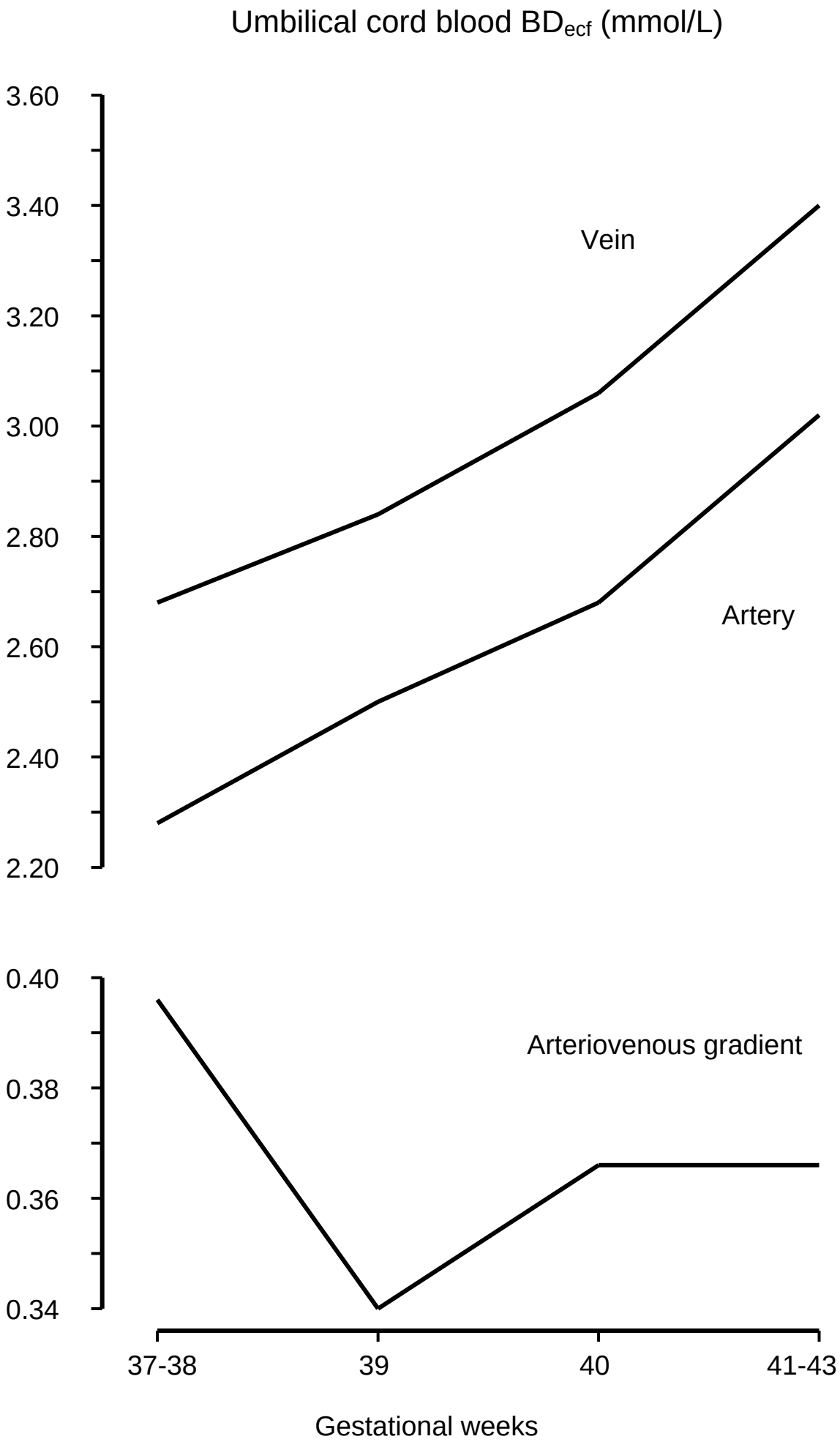
2.00
1.90
1.80
Arteriovenous gradient
37-38
39
40
41-43
Gestational weeks


Umbilical cord blood BD_{ecf} (mmol/L)
3.60
3.40
3.20
3.00
2.80
2.60
2.40
2.20
Vein
Artery
0.40
0.38
0.36
0.34
Arteriovenous gradient
37-38
39
40
41-43
Gestational weeks