ORIGINAL RESEARCH ARTICLE

Gestational age-related reference values for Apgar score and umbilical cord arterial and venous pH in preterm and term newborns

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Abstract

Introduction: Despite much literature on reference values of acid-base status in umbilical cord blood at birth, there are as yet no studies performed to determine gestational age-dependent references in cord venous blood and no studies on preterm acid-base standards. Similarly, the normal reference range of Apgar scores for term and preterm infants has not yet been determined.

Material and methods: Data were obtained from the maternity units of Skåne University Hospital, Malmö and Lund, Sweden, from 2001 to 2010. Validated paired arterial and venous cord pH values were obtained from 27 175 newborns, of whom 18 584 had spontaneous, non-instrumental vaginal deliveries and a 5-minute Apgar score equal to or greater than the median value for the individual gestational week. Simple linear and polynomial regression analyses were performed. Values were reported as mean ± standard deviation and median with 2.5th and 97.5th percentiles.

Results: Median 5-minute Apgar score was 7 for gestations shorter than 28 weeks, 8 for 28 weeks, 9 for 29-30 weeks, and 10 from 31 weeks onwards. A linear decline in pH for both cord arterial and venous blood was seen with advancing gestational age (P < 0.001).

Conclusions: Median 5-minute Apgar scores were <10 before 31 weeks of gestation. Both umbilical cord arterial and venous pH decreased linearly with increasing gestational age. Further studies are needed to show whether gestational age-related pH reference ranges might be preferred to fixed cut-offs in the estimation of umbilical cord acidemia at birth.

KEYWORDS
acidemia, acidosis, Apgar score, cord blood gases, fetal, newborn, pregnancy, umbilical cord

Abbreviations: ANCOVA, analysis of covariance; ApH, umbilical cord blood arterial pH; pCO2, partial pressure of carbon dioxide; pH, negative logarithm of the hydrogen ion concentration; pO2, partial pressure of oxygen; r2, coefficient of determination; SD, standard deviation; VpH, umbilical cord blood venous pH.

[Correction added on 20 February 2020, after first online publication: The copyright line for this article was changed.]
1 | INTRODUCTION

Introduced in 1953, the Apgar score was meant to be a quick assessment of the vitality of the newborn. Preterm newborns generally have lower scores than term newborns, though the normal distribution Apgar scores at different gestational ages has not yet been determined.

The most objective assessment of the baby’s metabolic condition at birth is through determination of umbilical cord blood acid-base status. Cord blood gases reflect the fetus’s exposure and ability to resist hypoxia and the obstetric intrapartum management, and form the basis for solving medicolegal issues in the identification of severe intrapartum hypoxia. Furthermore, cord blood gases are important in clinical research and in assessing the quality of care provided by the maternity unit.

The diagnosis of severe intrapartum hypoxia indicates the presence of cord blood academia, and normal acid-base values thus refute this diagnosis. For pH, several reference intervals for cord arterial pH (ApH) have been published. However, our research group has previously shown that cord acid-base values vary with gestational age. We have also found that values below gestational age-adjusted reference values are better associated with depressed vitality at birth than values below fixed thresholds. Furthermore, even though it is arterial cord blood values that best represent the newborn’s metabolic condition at birth, it is often the umbilical vein that is sampled, as this is easier due to its larger size, and recent studies have demonstrated the usefulness of venous cord blood variables as proxies for cord arterial blood variables. Despite this, there is a lack of studies describing reference values for cord venous pH in preterm and term deliveries.

In addition, to determine the normal distribution of Apgar scores across different gestational ages, the present study aimed to establish gestational age-related reference values for pH in both arterial and venous cord blood at term and preterm deliveries.

2 | MATERIAL AND METHODS

Since the early 1980s, umbilical cord blood gases have routinely been determined at birth at the two maternity units of Skåne University Hospital in Malmö and Lund, a tertiary care hospital in Sweden. Arterial and venous umbilical cord blood were sampled immediately after birth in separate pre-heparinized 2-mL syringes and analyzed within 15 minutes using ABL 735 Radiometer blood gas analyzers (Radiometer A/S, Copenhagen, Denmark). These analyzers were used between 2001 and 2010 and were calibrated every day by an expert biomedical analyst. Blood gas data were automatically transferred from the hard drives of the analyzers to a computerized statistical program (STATVIEW® version 5.0.1; SAS Institute, Solna, Sweden).

A prerequisite for inclusion in the study was that all blood samples could without doubt be identified in the hard drives of the analyzers by their unique maternal personal identification number, site of sampling (arterial, venous), place of origin (labor and delivery ward) and time and date of analysis. Furthermore, all samples where the analyzer’s automatic quality check system reported an error due to poor calibration, temperature error, electrode instability, air bubbles at the electrode, etc., were excluded from the study. These strict criteria ensured optimal quality in our database.

Overall, 207,684 sample analyses were retrieved from the blood gas analyzers from 2001 to 2010. Samples not identified as originating from umbilical cord blood, not being paired as arterial-venous samples, not fulfilling the validation requirement that venous pH (VpH) should be at least 0.020 units higher than ApH, and where corresponding clinical data could not be retrieved, were excluded. By using maternal personal identification numbers for matching of clinical data from the regional Perinatal Revision South Register, we could identify 27,175 cases for the study. The study population represented 35.9% of the 75,793 deliveries during the period. Table 1 illustrates the demographic characteristics of the study population. Gestational age was routinely determined at an early second trimester ultrasound fetometry.

2.1 | Statistical analyses

Associations between continuous variables were investigated with simple linear and polynomial regression analyses. To minimize the influence of outliers, we also used weighted linear regression analysis when appropriate. The possible influence of more than one independent variable was investigated with multiple regression analysis. Median values and percentiles were calculated with the weighted average method for robustness against outliers. When skewed distributions appeared, logarithmic and exponential transformations were performed to gain the best goodness of fit. Analysis of covariance (ANCOVA) was used to elucidate the effect of mode of delivery on arterial and venous pH at birth. Statistics were performed with aid of the STATVIEW® computer software (version 5.0.1) and IBM SPSS Statistics for Windows, version 23.0 (IBM Svenska AB, Malmö, Sweden). Values are reported as mean ± standard deviation and median with 2.5th and 97.5th percentiles. A two-tailed P < 0.05 was considered statistically significant.

2.2 | Ethics approval

The study was approved by the Regional Research Ethics Committee in Lund, Sweden (Dnrs 2009/222 and 2012/5).
### TABLE 1  Distribution of 5-min Apgar score relative to gestational age

| Gestational age (wk) | Number of cases | Percentiles | 5  | 10  | 25  | 50  | 75  | 90  | 95  |
|----------------------|-----------------|-------------|----|-----|-----|-----|-----|-----|-----|
| <28                  | 74              | 3           | 4  | 6   | 7   | 9   | 10  | 10  | 10  |
| 28                   | 23              | 1           | 5  | 7   | 8   | 10  | 10  | 10  | 10  |
| 29                   | 28              | 5           | 7  | 8   | 9   | 10  | 10  | 10  | 10  |
| 30                   | 39              | 5           | 5  | 8   | 9   | 10  | 10  | 10  | 10  |
| 31                   | 66              | 6           | 7  | 9   | 10  | 10  | 10  | 10  | 10  |
| 32                   | 69              | 6           | 7  | 9   | 10  | 10  | 10  | 10  | 10  |
| 33                   | 119             | 7           | 7  | 9   | 10  | 10  | 10  | 10  | 10  |
| 34                   | 212             | 7           | 8  | 9   | 10  | 10  | 10  | 10  | 10  |
| 35                   | 375             | 7           | 8  | 9   | 10  | 10  | 10  | 10  | 10  |
| 36                   | 651             | 8           | 9  | 10  | 10  | 10  | 10  | 10  | 10  |
| 37                   | 1607            | 9           | 9  | 10  | 10  | 10  | 10  | 10  | 10  |
| 38                   | 4553            | 9           | 9  | 10  | 10  | 10  | 10  | 10  | 10  |
| 39                   | 6530            | 9           | 9  | 10  | 10  | 10  | 10  | 10  | 10  |
| 40                   | 7360            | 9           | 9  | 10  | 10  | 10  | 10  | 10  | 10  |
| 41                   | 4037            | 9           | 9  | 10  | 10  | 10  | 10  | 10  | 10  |
| 42                   | 1381            | 8           | 9  | 10  | 10  | 10  | 10  | 10  | 10  |
| >42                  | 51              | 9           | 9  | 10  | 10  | 10  | 10  | 10  | 10  |
| **Total**            | **27 175**      |             |    |     |     |     |     |     |     |

### TABLE 2  Reference values for pH in the umbilical cord artery and vein relative to gestational age at birth (n = 18 584)

| Gestational age (wk) | Umbilical artery pH | Umbilical vein pH |
|----------------------|---------------------|-------------------|
|                      | 2.5th percentile | Median | 97.5th percentile | 2.5th percentile | Median | 97.5th percentile |
| 34+0                 | 7.112               | 7.284          | 7.424               | 7.163               | 7.333          | 7.466               |
| 34+3                 | 7.113               | 7.285          | 7.423               | 7.164               | 7.336          | 7.467               |
| 35+0                 | 7.113               | 7.285          | 7.422               | 7.165               | 7.339          | 7.468               |
| 35+3                 | 7.114               | 7.285          | 7.421               | 7.166               | 7.341          | 7.468               |
| 36+0                 | 7.114               | 7.285          | 7.419               | 7.166               | 7.344          | 7.468               |
| 36+3                 | 7.113               | 7.284          | 7.418               | 7.165               | 7.345          | 7.468               |
| 37+0                 | 7.113               | 7.282          | 7.416               | 7.165               | 7.346          | 7.468               |
| 37+3                 | 7.112               | 7.281          | 7.415               | 7.164               | 7.346          | 7.467               |
| 38+0                 | 7.111               | 7.278          | 7.412               | 7.162               | 7.346          | 7.467               |
| 38+3                 | 7.110               | 7.276          | 7.411               | 7.161               | 7.345          | 7.466               |
| 39+0                 | 7.108               | 7.273          | 7.408               | 7.158               | 7.343          | 7.465               |
| 39+3                 | 7.107               | 7.270          | 7.406               | 7.156               | 7.341          | 7.463               |
| 40+0                 | 7.105               | 7.266          | 7.404               | 7.153               | 7.338          | 7.462               |
| 40+3                 | 7.103               | 7.262          | 7.401               | 7.150               | 7.335          | 7.460               |
| 41+0                 | 7.100               | 7.257          | 7.398               | 7.146               | 7.331          | 7.458               |
| 41+3                 | 7.098               | 7.253          | 7.396               | 7.143               | 7.327          | 7.456               |
| 42+0                 | 7.094               | 7.246          | 7.393               | 7.138               | 7.321          | 7.453               |
| 42+3                 | 7.091               | 7.241          | 7.390               | 7.134               | 7.316          | 7.451               |

### 3 RESULTS

Table 2 illustrates the distribution of 5-minute Apgar scores across different gestational weeks in the series of 27 175 validated cases. There were too few newborns before 28 weeks for robust calculation of percentiles in individual weeks and we thus merged those into one group. Simple linear regression analysis showed a negative association between umbilical cord ApH and gestational age ($P < 0.001$, ...
r^2 = 0.022); quadratic and cubic linear regression analyses showed a better r^2 value (both P < 0.001, r^2 = 0.025).

Since the aim of the study was to estimate “normal” pH reference values, all newborns with Apgar scores less than the median score were excluded from statistics on pH (i.e., exclusion of newborns with a 5-minute Apgar score below 7 for <28 weeks, below 8 for week 28, below 9 for weeks 29-30, and below 10 for ≥31 weeks; see Table 1). This step ensured inclusion of only “vigorous” newborns. Using linear regression, there was only a minimal change in the estimates for ApH vs gestational age (all P < 0.001, r^2 = 0.022 and 0.023, respectively).

The effect of mode of delivery was evaluated using ANCOVA (Table S1), showing significantly higher ApH in newborns delivered by elective (n = 2069) than emergency cesarean section (n = 2197), and significantly lower ApH in newborns delivered by vacuum extraction or forceps (n = 21 350) vs spontaneous vaginal delivery (n = 21 350) (P < 0.001 for all estimates). Since mode of delivery significantly affected ApH, we restricted our statistical analyses to include only spontaneous, non-instrumental vaginal deliveries. As a result of this sorting, the number of newborns in gestational weeks 28-33 became too few (n = 86) for robust estimations of reference values in these weeks.

The final series for calculation of pH reference values comprised 18 584 newborns with a complete panel of ApH, VpH and Apgar score equal to or greater than the median value at 5 minutes after spontaneous vaginal delivery at ≥34 gestational weeks (Figure 1).

Simple linear and polynomial regression analyses showed that for both ApH and VpH, the quadratic and cubic models to calculate pH ranges relative to gestational age were better than the simple model (P < 0.001 for all calculations; ApH: simple r^2 = 0.012, quadratic and cubic r^2 = 0.013; VpH: simple r^2 = 0.005, quadratic and cubic r^2 = 0.008). Logarithmic and exponential transformation of values did not improve the goodness of fit of either ApH or VpH. It was not possible to achieve a robust distribution to calculate reference values from standard deviation (SD) distributions, so we based the estimates on percentiles only. In addition, due to sensitivity to outliers and thus unsteady estimates of the 2.5th percentiles, weighted quadratic regression analyses were performed to estimate percentiles (Figures 2 and 3). A linear decline in both ApH and VpH was

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**Figure 1** Flowchart showing 27 175 newborns for description of Apgar score distributions and stepwise exclusions of cases to final series of 18 584 newborns included in calculations of arterial and venous umbilical cord blood pH reference values.

**Figure 2** The 95% reference interval of 18 584 vigorous newborns with median and percentile values of umbilical cord arterial pH relative to gestational age (P < 0.001).

**Figure 3** The 95% reference interval of 18 584 vigorous newborns with median and percentile values of umbilical cord venous pH relative to gestational age (P < 0.001).
observed with advancing gestational age. Median pH at 34\(^{\text{th}}\) weeks of gestation was 7.308 in the umbilical artery and 7.347 in the vein. At 42\(^{\text{nd}}\) weeks, median arterial pH was 7.246 and venous pH 7.319.

### 4 | DISCUSSION

This study determined the normal distribution of 5-minute Apgar scores in preterm, term and post-term newborns in an unselected population of 27,175 newborns. We know of no other similar large study. When not stratified by mode of delivery, the median 5-minute Apgar score was 7 before 28 weeks, 8 at 28 gestational weeks, 9 at 29-30 weeks, and 10 from 31 weeks onwards. As the study population was a good representation of the total population, the lower median scores in moderately and extremely preterm newborns may reflect differences in maturity rather than depressed vitality. Inevitably, Apgar scoring is to some extent subjective and the generalizability of our results is thereby limited by interobserver\(^{16}\) and regional differences.\(^{17}\)

This study also defined gestational age-related reference values for pH in arterial and venous umbilical cord blood in a series of 18,584 vigorous preterm, term and post-term newborns after spontaneous vaginal delivery. During the progress of gestation, we found that both arterial and venous median pH fitted a slightly downward quadratic linear regression curve. By meticulous purging from the database of non-optimal blood gas analyses, ensuring the highest standard of data quality, we believe these reference values are well suited for use in clinical practice and research.

We chose to calculate pH values with three decimals, as reported by the blood gas analyzers, because rounding-off decimals would introduce bias in the statistical calculations.\(^{18}\) However, both the second and third decimal values are uncertain, since the standard drift tolerance of the pH potentiometer electrode is ±.020.\(^{19}\) On the other hand, in a substantially large sample, upward and downward drifts would neutralize one another.

A major strength of the current study was the meticulous inclusion criteria by which all samples that did not fulfil the standards of the blood gas analyzers’ quality check system were discarded. This even included rejection of all analyses where not only the pH electrode but also electrodes for pO\(_2\), pCO\(_2\) and lactate showed poor calibration and instability. Most such electrode errors are not shown on the paper printouts from the analyzer and are detected only when the hard drive of the analyzer is explored. We therefore believe our study series was of optimal analytical quality. Furthermore, the pH values were not obtained from any manually managed obstetric database but were extracted from the hard drives of the analyzers and transferred directly to the statistical computer programs. This eliminated the possibility of human error in retrieving the data.

The possibility of late cord clamping resulting in "hidden acidosis" (acidemia, hypercapnia, high base deficit and lacticemia), was something we could not control for in the design of the current study. Late cord clamping could also potentially result in a falsely high pO\(_2\) if the newborn started to breathe before the cord was clamped. Thus, the possibility of "physiologically" false values could not be controlled for.

All operative deliveries and newborns not showing a normal vitality were excluded in the study design, since we were not interested in describing pH values for adverse outcomes. When investigating population-based reference values, the exclusion of all diseased individuals is a vital component in the study design.\(^{20}\) In light of the current study, a 5-minute Apgar Score below the gestational age-related median value differentiated vigorous from non-vigorous newborns. Despite the large series, we could not create reference values for premature newborns before 34 gestational weeks as there were too few cases to perform robust statistics. This can be explained not only by our strict inclusion criteria, but also by the fact that preterm newborns are often growth-restricted and often delivered by cesarean section.\(^{21}\) We aim to explore this issue in a future study.

There is no global consensus on the definition of umbilical cord blood acidemia. It has been defined as fixed umbilical artery pH cut-offs from <7.00 to <7.20,\(^{22}\) irrespective of gestational age, but it is well known that pH decreases with progression of pregnancy.\(^{6,8,23}\) Maternity units in Sweden define a cord artery pH <7.10 as academic, since this value corresponds to the mean value of −2 SD in the population.\(^{24,25}\) The American College of Obstetricians and Gynecologists and the National Institute for Health and Clinical Excellence recommend the use of an arterial pH <7.00 as a clinically useful fixed cut-off to identify neonates at high risk for serious neonatal morbidity and mortality.\(^{26,27}\) However, our research group has previously established that gestational age-adjusted values of pH, base deficit and lactate in cord blood at birth are better associated with the newborn’s vitality than are fixed cut-off values.\(^{10}\)

Malin et al\(^{22}\) found a strong association between low cord arterial pH and short-term and long-term adverse outcomes, with a clear dose-response relation. It is, however, important to be aware that statistical definitions of low pH values in cord blood based on population studies do not necessarily reflect biological adverse effects of tissue acidosis in the individual. It seems that only in combination with decreased vitality is a low cord pH predictive.\(^{28}\) Furthermore, at moderate degrees of acidemia, where pH is <7.10 but >7.00, a neuroprotective mechanism may be triggered: at this ApH level, Dennis et al\(^{29}\) found no neurodevelopmental delay at 4.5 years of age and Svirko et al\(^{30}\) even found that lower arterial pH from stressful vaginal deliveries correlated to higher literacy and non-verbal intelligence score at ages 6-8 years.

A clinical implication of our findings is that gestational age-related reference values reflect better than static reference values the normal maturity processes and physiological changes occurring with advancing gestational age. During the progress of pregnancy, the fetus develops a mixed metabolic and respiratory “academia”.\(^{3} \) The respiratory component is explained by an increasing "carbon dioxide load" from the growing fetus, whereas the etiology of the metabolic component is as yet unknown. When deciding what is normal and what is abnormal, gestational age-related reference values for cord pH might make a difference in neonatal management and in the assessment of insurance and litigation cases.
5 | CONCLUSION

The study determined the distribution of Apgar scores at 5 minutes across different gestational ages in a series of 27 175 newborns, a good representation of the total obstetric population. The median Apgar score increased with the progress of gestation and was 10 from 31 weeks onwards.

Based on a robust clinical material with validated paired arterial and venous umbilical cord blood samples from 18 584 births, gestational age-related reference values for pH from vigorous newborns were calculated. Both arterial and venous pH were found to decrease linearly with increasing gestational age, from a median of 7.308 at 34-ga to 7.246 at 42-ga in the cord artery. One might regard such a decrease of only 0.062 pH units as unimportant, but in terms of hydrogen ion concentration, it represents an increase by 15% from 49.204 to 56.755 mol/L over the time period.

CONFICT OF INTEREST

The authors declare no conflicts of interest.

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