Umbilical Ascorbic Acid Levels in Fetal Distress

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Summary Umbilical arterial and venous blood samples were obtained at birth immediately after clamping the cord in 38 infants. Simultaneously, maternal arterial samples were collected. Arterial blood samples were analyzed for acid-base blood gas content and venous blood samples were analyzed for plasma ascorbic acid levels. The umbilical plasma ascorbic acid level was significantly higher when compared with maternal plasma levels (172.9±39.2 vs. 57.8±21.0 μmol/liter, p<0.0001). Correlations between maternal ascorbic acid levels and umbilical cord levels proved to be insignificant. Umbilical ascorbic acid levels in the 2 groups of infants characterized by the presence or absence of fetal distress showed significantly higher levels in the fetal distressed group (17 infants) when compared to the non-distressed group (21 infants)—191.9±36.0 vs. 157.4±34.6 μmol/liter, p<0.005. The use of an umbilical cord ascorbic acid cut-off point of 95.8 μmol/liter gave a sensitivity of 76% and a specificity of 67% as predictors for the presence or absence of fetal distress (p<0.025). The results of the present study demonstrate a substantial increase in ascorbic acid levels in infants exposed to intrapartum fetal distress, without any clinical sign of such insult at or after birth.

Key Words asphyxia, fetal distress, neonate

The premature brain is exceptionally rich in ascorbic acid and as such has probably an important regulatory role in ascorbic acid homeostasis. Adlard et al. (1) demonstrated decreased brain ascorbic acid concomitant with elevated serum ascorbic acid in severely asphyxiated rats; the inference being that hypoxic-ischemic insult to the brain resulted in an efflux of ascorbic acid into the circulation. Arad and Eyal (2), investigating premature infants with brain hemorrhage, found higher plasma ascorbic acid levels in those infants with massive intraventricular hemorrhage. Brain hemorrhage in premature infants is usually accompanied by hypoxic-ischemic episodes and these traumatic factors certainly can lead to minor or major brain damage. Again, the inference is that the damaged brain releases large
amounts of ascorbic acid into the circulation.

Intrapartum fetal distress may be a sign of fetal oxygen deprivation which can lead to brain damage and frequently precedes an asphyxiated neonate at birth. At times, intrapartum fetal distress is often unaccompanied by asphyxial signs at birth and the question is asked whether such fetal distress can lead to intrapartum brain insult without any clinical signs of such damage at or after birth. If so, then it could be that in such cases, the demonstration of elevated ascorbic acid levels could well be used to answer the question.

That being so, we investigated umbilical plasma ascorbic acid levels at birth in non-asphyxiated neonates where one group evidenced intrapartum fetal distress, and a second group had a completely normal intrapartum course unaccompanied by any fetal distress.

Thirty-eight women admitted to the delivery suite of the Assaf Harofeh Medical Center, Zerifin, Israel, in active singleton labor were randomly enrolled into the study.

During each labor, the fetal heart rate was continuously monitored by a Hewlett-Packard 8040 cardiotocograph (Hewlett-Packard, Boeblingen, Germany) via a fetal scalp electrode. Fetal distress was diagnosed by the presence of late decelerations (uniform decreases in fetal heart rate exceeding 20 beats/min below the base-line rate) and/or severe variable decelerations (irregular decreases in fetal heart rate below 60 beats/min, decreases in fetal heart rate exceeding 60 beats/min below the base-line, or decreases in fetal heart rate exceeding 60 seconds in duration) with or without base-line variability changes (absence of variability, variability less than 6 beats/min, sinusoidal pattern). By these criteria fetal distress was present in 17 labors and these infants constitute the fetal distress group. In 21 labors there were no signs of fetal distress and these 21 infants constitute the control group.

Umbilical arterial and venous blood samples were obtained immediately after clamping the umbilical cord in all 38 infants. Simultaneously, maternal radial arterial blood samples were collected after informed consent was obtained. These specimens were collected anaerobically into preheparinized polyethylene syringes and analyzed immediately for acid-base blood gas content using an automated pH/blood gas analyzer (Instrumentation Laboratory 1306 Analyzer, Instrumentation Laboratory, Lexington, U.S.A.). Umbilical venous and maternal arterial plasma were analyzed in duplicate for ascorbic acid levels by the method of Roe and Kuether (3). All infants were assessed at 1 and 5 min of age by the Apgar method (4) and the results expressed as a score for each time period where maximum and minimum scores are 10 and 0, respectively. A 1 min Apgar less than 4 points and/or a 5 min Apgar score less than 6 points indicate asphyxia. All infants with Apgar scores equaling or exceeding these values were not birth asphyxiated. Gestational age was determined using the Ballard method (5). Clinical data were collected on the 38 mother-infant pairs.

To study the effect of stress as evidenced by fetal distress on fetal plasma
ascorbic acid levels, comparisons were made between clinical characteristics and umbilical venous acid-base gas content, in the fetal distress group and the control group.

Differences between maternal and cord ascorbic acid level were analyzed using the unpaired Student t-test. The Fisher exact test or chi-square test with Yates' correction when appropriate were used to compare proportions between groups. The Pearson correlation coefficient was utilized to test for correlations between ascorbic acid levels, acid-base variables and other variables in maternal and umbilical cord blood. The ability of a particular umbilical venous ascorbic acid cut-off point (for all values exceeding the chosen point) to include all cases of fetal distress—the sensitivity—was calculated by the method of Galen and Gambino (6), as was the specificity which refers to the same chosen point below which all cases without fetal distress are included. Sensitivity and specificity are provided as percentages. The use of sensitivity and specificity provides predictive value of the umbilical cord ascorbic acid levels vis-a-vis fetal distress.

All results are expressed as mean ± standard deviation unless otherwise indicated. A level of significance was set at 0.05.

Selected clinical and laboratory characteristics of the two groups are provided in Table 1. None of the 38 infants had abnormal Apgar scores, i.e., no birth asphyxia was evidenced. However, the fetal distress group had slightly lower Apgar scores as opposed to the control group and this difference was statistically significant. Additionally the mean pH value in the fetal distress group was significantly lower than that in the control group. Umbilical venous ascorbic acid levels were higher in the fetal distress group. Mean values were 191.9 and 157.4 μmol/liter in each group, respectively, and these differences reached statistical significance.
Table 2. Clinical features and plasma ascorbic acid levels in mothers of fetal distress group and mothers of the control group.

| Variable                        | Fetal distress group (N=17) | Control group (N=21) |
|---------------------------------|-----------------------------|----------------------|
| Age (years)                     | 28.05±5.25                  | 24.33±9.15           |
| Cigarette smoker (≥10/day = smoker) | 6                           | 8                    |
| Previous deliveries             | 1.4±2.2                     | 2.4±2.7              |
| Mode of delivery*               |                             |                      |
| S                               | 10                          | 12                   |
| V                               | 5                           | 7                    |
| CS                              | 2                           | 2                    |
| Ascorbic acid level (µmol/liter) | 65.2±24.9                   | 52.1±14.2            |

*S, spontaneous; V, vacuum extraction; CS, cesarean section. The differences were tested utilizing the chi-square test or unpaired Student t-test.

Table 3. Predictive value of umbilical venous ascorbic acid level vs. fetal distress.

| Fetal distress | Present | Absent |
|----------------|---------|--------|
| Umbilical ascorbic acid level (µmol/liter) | >95.8 | 13 | 7 |
|                  | ≤95.8   | 4      | 14 |
| Sensitivity      |         | 76%    |
| Specificity      |         | 67%    |

Sensitivity—an index of the diagnostic test's ability to detect fetal distress when it is present is 13/(13+4)=76%. Specificity—the ability of the diagnostic test to correctly identify the absence of fetal distress 14/(7+14)=67%. Relation between umbilical ascorbic acid levels and fetal distress was significant (p<0.025).

Table 2 provides certain clinical features pertaining to the mothers of the two groups. The table also indicates the maternal ascorbic acid value in each group. The mean maternal ascorbic acid value in the fetal distress group (65.2 µmol/liter) was slightly higher than that of the control group (52.1 µmol/liter), but the difference did not achieve statistical significance. No statistically significant correlation was found between maternal ascorbic acid levels and age, cigarette smoking, previous deliveries and mode of delivery.

The mean combined (the 2 groups) umbilical ascorbic acid level was significantly higher as compared with the maternal level (172.9±39.2 vs. 57.8±21.0 µmol/liter, p<0.0001). However, a statistically significant correlation between these two levels could not be demonstrated.

Table 3 indicates the predictive value of the umbilical venous ascorbic acid level relative to fetal distress, when the entire group of 38 infants was considered. The median value of umbilical venous ascorbic acid level for the entire study group was 95.8 µmol/liter. This value was taken as the cut-off point. Sensitivity and
specificity at this point were 76% and 67%, respectively ($p < 0.025$). On an individual basis however, 4 fetal distressed infants had ascorbic acid levels less than the cut-off point while in 7 non-fetal distressed infants, ascorbic acid levels exceeded the cut-off point.

Active materno-fetal transfer of ascorbic acid *via* the placenta results in higher levels in the newborn (7, 8). Our study confirmed this materno-fetal gradient and the lack of correlation between maternal and fetal levels.

The present study has demonstrated that a group of infants whose intrapartum course was complicated by fetal distress, had higher ascorbic acid levels than a control group with a normal intrapartum course. Furthermore, umbilical venous ascorbic acid levels above 95.8 μmol/liter were associated with intrapartum fetal distress with a sensitivity of 76%. In our study, birth asphyxia was absent. This would indicate that the fetal distress was mild. This however does not negate the possibility that mild fetal distress may produce minimal brain damage with resultant efflux of ascorbic acid.

Further investigation into ascorbic acid kinetics and its relationship to fetal distress, in particular when accompanied by severe birth asphyxia and brain damage, are in order and would provide more understanding regarding our findings.

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