Plasma Hypoxanthine in Exteriorized, Acutely Asphyxiated Fetal Lambs

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Summary

Plasma hypoxanthine (HX) concentrations were measured in 16 acutely exteriorized fetal lambs during induced, graded hypoxia, and the values found were compared to established indicators of poor oxygenation in the fetus, such as oxygen saturation, blood gases, pH, base excess, and lactate. Highly significant correlations were found to all parameters of hypoxia except PaO_2 . When the duration of hypoxia was taken into account, the HX concentrations showed highly significant correlation to constructed variables of oxygen debt. In multiple correlation analysis, pH turned out as the strongest single variable, explaining 80% of the variance in HX concentration with the remaining parameters increasing the value to 87%. The highest concentrations of HX were obtained when hypoxemia was combined with acidemia or with a large fetomaternal PaCO_2 -gradient which correlated to a reduced cardiac output in the fetus. These findings appear to corroborate the conclusion that plasma HX concentration reflects tissue hypoxia in the fetal lamb.

Speculation

The need for a more objective and specific measure of perinatal asphyxia than the Apgar score is obvious. On the basis of our findings in experimental asphyxia in the sheep fetus, it appears that hypoxanthine measurements might be a useful parameter of tissue hypoxia in perinatal medicine.

According to several recent observations, the concentration of hypoxanthine (HX) in plasma appears as a theoretically interesting and clinically useful measure of impaired tissue oxygenation. Inasmuch as HX is a breakdown product of the energy-rich nucleotides of the cell, the level of this metabolite in body fluids should reflect the intracellular energy status during hypoxia.

Thus, the concentration of HX in umbilical plasma was associated with intrauterine asphyxia (13), and an elevated urinary excretion rate of HX was observed in neonates with birth complications leading to perinatal asphyxia (9). In experimental acute hypoxia in pigs, close correlations were found between plasma concentrations of HX and lactate or base deficit levels in blood (15). The HX concentration of cerebrospinal fluid was elevated in experimental hypoxia in dogs (19) and in neonates with asphyxia as well (10). Furthermore, the tissue concentration of HX were found to be raised during ischemic conditions in myocardium (1), brain (2, 18), and renal cortex (3).

The quantification of tissue hypoxia by HX measurements would be of special importance because lactic acid, a generally accepted measure of anaerobic metabolism, was found to increase during several conditions not associated with hypoxia (6, 12, 20).

The experimental work concerning HX has, however, until now mainly been performed on adult animals. We considered it of special interest to investigate the relationship between the HX

level and intrauterine asphyxia. In the present study, the metabolite has therefore been determined in the plasma of fetal lamb during induced, graded hypoxia. The values found have been compared to other signs of poor oxygenation, such as arterial oxygen saturation (SaO_2), arterial oxygen tension (PaO_2), pH, base excess (BE), and lactate. The role of impaired tissue perfusion due to failing circulation during progressing asphyxia leading to increasing tissue hypoxia was investigated by comparing the HX levels with the gradient of arterial carbon dioxide tensions (PaCO_2) between the fetus and the ewe. The PaCO_2 gradient across the placenta was thus taken as an indirect estimate of umbilical blood flow.

MATERIALS AND METHODS

EXPERIMENTAL DESIGN

The blood samples were collected from 16 acutely exteriorized fetuses from 16 ewes of mixed breed. The estimated gestational age ranged from 128 to 147 days (mean, 135 days; term, 145 to 150 days). The gestational age was estimated from fetal weight and crown-rump length using standard curves (8). Only the first fetus of each ewe was included.

The ewes were anesthetized (induction with thiopental, 5 mg/kg body weight, and maintenance anesthesia with chloralose, 35 mg/kg), tracheotomized, and ventilated with known gas mixtures. The fetus was exteriorized by cesarian section and placed on a thermostated table. Great care was taken to minimize disturbance of the umbilical circulation and to maintain body temperature and humidity. To avoid fetal breathing, the fetal trachea was cannulated and connected to a saline-filled bag. Maternal blood pressure was recorded through a catheter placed in the medial plantar artery of one foreleg. Fetal arterial blood pressure and heart rate were recorded continuously from a catheter in the right brachial artery via a Statham electromanometer. Arterial blood samples were taken from the same catheters. Fetal electrocardiogram was monitored from precordial leads, and in 8 of 16 fetuses, repeated measurements of combined cardiac output were made by thermodilution method (injection in vena cava inferior and thermistor in descending aorta).

Periods of maternal and fetal hypoxia were instituted by ventilating the ewe with gas mixtures low in oxygen. Usually, the first period of hypoxia was induced by ventilation with 16% O_2 in N_2 for 20 to 40 min to bring the maternal PaO_2 from 11 to 15 kPa to 3.5 to 5 kPa. During the recovery period, 30% O_2 in N_2 was administered aiming at a return of fetal PaO_2 and PaCO_2 to normal values (8). Finally, a more profound period of second hypoxia was usually instituted by ventilating the ewe with 8 to 11% oxygen.

Apart from supplying samples for HX determinations, the fetuses were studied in three different kinds of experiments. The conduction of the experiments therefore varied somewhat in de-

sign. The problems studied in parallel with the present work were: (1) cardiac metabolism during hypoxia. These fetuses were thoracotomized, and repetitive small heart biopsies were taken. (Five of 16 fetuses belonged to this series); (2) the effect of beta-hydroxybutyrate on fetal brain metabolism. In these fetuses, beta-hydroxybutyrate was infused in amounts between 0.02 and 7 μ moles/min for 30 to 120 min IV (seven fetuses); (3) ECG changes in the fetal lamb during hypoxia in relation to beta-adrenoceptor stimulation and blockade. Infusions of small doses of isoprenaline and propranolol were given during these experiments (4 fetuses). However, propranolol was not given before the first hypoxic period. During first hypoxia, beta-blockade was not instituted in two cases, and in the remaining two fetuses, propranolol was injected at the end of this period after 25 (see Fig. 1) and 36 min, respectively.

Inasmuch as this study is, in fact, a by-product of three different studies, the three sets of experiments were analyzed separately with regard to HX concentrations during hypoxia. However, no statistically different values were found between the three groups. In the presentation of the results of this work, the 16 fetuses are therefore handled as one single group.

BLOOD GASES AND ACID-BASE STATUS

Arterial blood oxygen saturation, SaO_2 , was measured using a filter photometer (Radiometer OSM 2) together with hemoglobin concentrations. PaO_2 , PaCO_2 , and pH were measured immediately at 38°C with a Radiometer BMS 3, using standard electrodes. BE values were calculated using the Siggaard-Andersen nomogram at the prevailing hemoglobin concentrations. Blood lactate and glucose levels were measured using enzymatic methods (Biochemica Test Combination; Boehringer Mannheim, Germany).

HYPOXANTHINE DETERMINATION

HX concentrations were determined in 130 samples of arterial plasma from the fetal lamb. The number of samples in each experiment varied between 2 and 12 (median 7).

The method for determination of HX and xanthine in plasma with a PO_2 -electrode was previously described by Saugstad (14). It is based on the principle that oxygen is consumed quantitatively when HX and xanthine are oxidized to urate by xanthine oxidase. In this study, a Radiometer BMS 3 blood gas-monitor equipment was used. The volume of the measuring chamber was about 70 μ l. The chamber was filled with plasma to which catalase was added in proportion 20 μ l/ml, and a surplus of xanthine oxidase (10 μ l) was slowly injected into the upper part of the chamber with a Hamilton syringe. The solution was gently mixed by aspirating with the syringe 2 to 3 times. The PO_2 of the solution was continuously recorded by a potentiometer ink-recorder (Servogor model RE 511) at a paper speed of 0.5 mm/sec.

The fall in PO_2 ($=d\text{PO}_2$) after the addition of xanthine oxidase was calculated by extrapolation after the rapid phase of the

reaction was completed. Provided necessary precautions were taken (avoiding air bubbles in the solution and careful mixing of enzyme and solution), the method gave well-reproducible values within the range of interest. The standard error of measurements from double estimations in human plasma was calculated to 2.65 μ moles/liter within the range of 10 to 60 μ moles/liter.

The regression line for a standard curve in phosphate buffer was calculated to $d\text{PO}_2 = 0.64(\text{HX}) - 4.6$ within the concentration range 5 to 100 μ moles/liter ($r = 0.96$). In human plasma with added HX, the same relation gave $d\text{PO}_2 = 0.70(\text{HX}) + 9.0$ ($r = 0.99$). These values are in good agreement with the theoretically calculated relation $d\text{PO}_2 = 0.71(\text{HX})$, which we were using for calculations. However, the standard curves demonstrated less accuracy at HX concentrations less than 5 μ moles/liter. This was considered of minor importance because most samples during hypoxic conditions have concentrations exceeding this value. All samples were analyzed by Dr. Thiringer.

STATISTICAL METHODS

Frequency distributions, means, and standard deviations were calculated by ordinary statistical methods. The Wilcoxon signed-ranks test and Student's t test were applied for testing significance of differences. The OSIRIS MDC program (11) was used for computing correlations and regressions. The stepwise multiple regression analysis was computed according to the BMDOR 2 program (5, 21).

RESULTS

HEMODYNAMIC PARAMETERS

Heart rate (FHR), mean arterial blood pressure (MABP), cardiac output (CO), arterial blood gases, lactate, and HX concentrations of the fetus prior to induction of hypoxia are given in Table 1. The hemodynamic variables in the present study are compared to those derived from a series of chronically instrumented lamb fetuses by Cohn *et al.* (4). Our values are given both for all 16 fetuses and for the 10 fetuses which had blood gas values within normal limits preceding hypoxic period I. The last mentioned 10 fetuses do not deviate from the reference material with regard to the circulatory parameters measured.

During hypoxic period I a slight increase of MABP was generally found, whereas FHR increased in 6, decreased in 3, and was unchanged in 7 cases. CO did not change markedly during moderate hypoxia, but decreased during severe degrees of hypoxia, especially in combination with beta-adrenoceptor blockade (Fig. 1). In these situations also, MABP and FHR fell, indicating failing cardiovascular function.

During the second hypoxic period, all fetuses were markedly affected both by the experimental procedures and hypoxia, demonstrating rapid deterioration of the circulation.

Table 1. Basal values for HR, MABP, combined CO, blood gases, lactate, and HX

Group	All fetuses (n = 16)	Fetuses compiled in Figure 2 (n = 10)	Cohn <i>et al.</i> (4) (n = 10)
HR (beats/min)	181 $\pm$ 10.3 ¹	164 $\pm$ 9.9	163 $\pm$ 8
MABP (mm Hg)	65 $\pm$ 1.5	63 $\pm$ 1.7	60 $\pm$ 4
CO (liter/min/kg)	0.57 $\pm$ 0.17 (n = 8)	0.54 $\pm$ 0.10 (n = 4)	0.48 $\pm$ 0.03
PaO_2 (kPa)	3.07 $\pm$ 0.15	3.20 $\pm$ 0.20	2.60 $\pm$ 0.13
PaCO_2 (kPa)	6.0 $\pm$ 0.24	5.60 $\pm$ 0.29	5.73 $\pm$ 0.27
pH	7.29 $\pm$ 0.03	7.35 $\pm$ 0.01	7.37 $\pm$ 0.01
SaO_2 (%)	59.7 $\pm$ 3.5	66.3 $\pm$ 3.9	
BE	-5.4 $\pm$ 1.2	-2.6 $\pm$ 0.9	
Lactate	4.5 $\pm$ 0.66	3.4 $\pm$ 0.73	
Hypoxanthine	15.1 $\pm$ 3.20	9.7 $\pm$ 1.28	

¹ Mean $\pm$ S.E.

Fig. 1. HR, MABP, combined CO, lactate, blood gases, and HX during periods of hypoxia and recovery phase in one fetus.

BLOOD GASES AND pH

During hypoxia, PaO_2 was lowered to minimal values ranging between 0.26 and 2.86 kPa (mean, 1.26, respectively, 1.28 kPa for hypoxic periods I and II), whereas PaCO_2 ranged between 4.2 and 17.5 (mean, 6.99 and 9.54, respectively). SO_2 fell to 12.7 ± 6.3 and $10.6 \pm 4.2\%$, respectively, at the end of the two hypoxic periods. pH was lowered to 7.14 during the first hypoxic period, whereas a more profound depression to 6.98 was achieved at the end of hypoxic period two (mean values).

BASE EXCESS AND LACTATE

A significant increase of lactate concentrations appeared after 10 min of hypoxia ($P < 0.01$) compared to initial values. Also, the further increase of lactate was significant for every 10-min period of hypoxia ($P < 0.01$). BE values decreased to -11.5 and -15.9 for each hypoxic period, respectively.

HYPOXANTHINE

Only minimal elevations of HX concentrations were found in plasma of the ewe during hypoxia, the highest value amounting to 20 $\mu\text{moles/liter}$ after 60 min of hypoxia (Fig. 2). Repeated measurements in additional 5 ewes showed no values exceeding 10 $\mu\text{moles/liter}$.

The increase of HX concentration in fetal blood with increasing time of hypoxia and decreasing SaO_2 is demonstrated by Figure 2. Figure 2 includes those 10 fetuses where SaO_2 and pH in arterial blood were within normal limits (7) before to institution of hypoxic period I (mean values in Table 1). Of the 6 excluded fetuses, one had SaO_2 30%, and five were acidotic with $\text{pH} \leq 7.30$, probably due to experimental procedures prior to the induction of hypoxia.

The basal values for HX prior to hypoxia ranged between 6 and 18 $\mu\text{moles/liter}$, mean, 9.7 $\mu\text{moles/liter}$. The rise of HX concentration with increasing time of hypoxia followed a linear course ($r = 0.59$; $P < 0.001$) in the fetuses compiled in Figure 2. During the first 10 min of hypoxia, however, the increase was only significant on a 5% level.

The 10 fetuses depicted in the Figure 2 responded to hypoxia

Fig. 2. The time relationship of plasma HX concentration and SaO_2 in 10 fetuses during first hypoxia. $\circ$, $\text{pH} \geq 7.30$; $\bullet$, $\text{pH} 7.15$ to 7.29 ; $\bullet$, $\text{pH} < 7.15$; $\blacktriangle$, highest value obtained from a ewe; $+$, fetus illustrated in Figure 1; $\dagger$, fetal death.

with moderate changes in the circulatory variables studied. However, after a period of 25 to 40 minutes of hypoxia, signs of failing circulation (decreasing MABP and CO) occurred in five fetuses. Therefore, the time period with stable circulatory variables was especially studied. In 9 of 10 fetuses, HX concentration increased during this time period, whereas the concentration was unchanged in the remaining case. This case is especially demonstrated in Figure 1, from which it is apparent that in this fetus HX concentration is not elevated by hypoxia alone, whereas a combination of hypoxia and circulatory failure (after beta-adrenoceptor block-

ade) causes a steep rise of HX. Concerning the increase of HX in the whole group of 10 fetuses, however, it was highly significant ($P < 0.001$) during the time period of hypoxia without signs of failing circulation.

The concentration changes of HX during recovery and hypoxic period II are illustrated by Figure 3. Despite of good arterial oxygenation measured by PaO_2 and SaO_2 , acidosis dominated, and 2 fetuses expired at the end of the recovery period. An additional slight, but statistically not significant increase in HX concentration appeared, the highest values occurring in the most acidotic fetuses.

CORRELATIONS BETWEEN HX AND OTHER HYPOXIA PARAMETERS

The whole material ($n = 130$) was subjected to a regression analysis with the hypoxia variables PaO_2 , PaCO_2 , SaO_2 , pH, BE, and lactate considered as independent variables, and HX considered as the dependent variable. With the exception of PaO_2 , all correlation coefficients turned out as highly significant (Table 2). Separate analyses of samples taken during hypoxic periods I + II ($n = 61$) and hypoxic period I ($n = 42$) improved all correlations between HX and other parameters, but the correlation to PaO_2 still remained insignificant.

Fig. 3. The time relationship of plasma HX concentration and SaO_2 during recovery phase and hypoxic period II. Same fetuses as in Figure 2. (9 and 7 surviving first hypoxia and recovery phase, respectively). Same symbols as in Figure 2.

Table 2 also includes three constructed parameters. The first two of these parameters are constructed by multiplying the "deficit" of PaO_2 and SaO_2 , respectively, with the elapsed time of hypoxemia according to the following calculations:

$$\begin{aligned}\text{PaO}_2\text{-debt} &= (2.8 - \text{actual PaO}_2) \times \text{duration of hypoxia} \\ \text{SaO}_2\text{-debt} &= (45 - \text{actual SaO}_2) \times \text{duration of hypoxia}\end{aligned}$$

PaO_2 of 2.8 kPa and SaO_2 of 45% were considered as the lower limits of normoxia (7). HX showed a significant correlation to the $\text{PaO}_2\text{-debt}$ only for hypoxic period I. For the same period of hypoxia, a significant correlation also existed between HX concentration and duration of hypoxia alone. When HX values were correlated to the parameter $\text{SaO}_2\text{-debt}$, significant correlations were obtained. The values from hypoxic period I, correlated better to $\text{SaO}_2\text{-debt}$ than to SaO_2 alone, whereas no differences were observed in the two other groups (Table 2).

The third constructed parameter, the " PaCO_2 -gradient" stands for fetomaternal PaCO_2 -difference. This variable was considered to reflect the circulatory conditions of placenta and probably other fetal organs. In the case of failing circulation, the PaCO_2 -gradient should increase on account of impaired placental perfusion, which would, furthermore, increase tissue hypoxia. This parameter was closely related to the fetal PaCO_2 value and showed the same correlation to HX concentration.

To test the hypothesis that the PaCO_2 -gradient reflects fetal circulatory conditions, these values were plotted against measurements of combined cardiac output (Fig. 4).

Fig. 4. The relation between the PaCO_2 -gradient (fetomaternal arterial PaCO_2 difference) and combined CO in 8 fetuses.

Table 2. Correlation matrix for HX and other hypoxia variables

	PaO_2	PaCO_2	SaO_2	pH	BE	Lactate	$\text{PaO}_2\text{-debt}$	$\text{SaO}_2\text{-debt}$	$\text{PaCO}_2\text{-gradient}$
All samples ($n = 130$)	ns ¹	0.62	-0.45	-0.87	-0.83	0.78	ns	0.42	0.59
Hypoxic period I + II ($n = 61$)	ns	0.63	-0.44	-0.90	-0.85	0.80	ns	0.40	0.58
1st hypoxia ($n = 42$)	ns	0.69	-0.47	-0.90	-0.87	0.83	0.45	0.63	0.70

¹ ns, non significant

Figure 4 demonstrates that below a critical level of blood flow, about 0.4 liter/min $\times$ kg, the PaCO_2 -gradient increases steeply when blood flow is reduced. On the contrary, an increase of CO_2 , even when severalfold, does not have any influence on it. Thus, it appears that a reduction of fetal cardiac output is associated with an increased PaCO_2 -gradient, which is closely related to increasing HX concentrations (Table 2).

The relations between HX concentrations, degree of hypoxemia, and the PaCO_2 -gradient are depicted in Figure 5. It is evident that a relation exists between low levels of arterial oxygenation and increased HX values. However, when arterial desaturation is combined with high PaCO_2 -gradients, there occurs a marked augmentation of the increase in HX concentration.

For the purpose of testing the relative significance of the different hypoxia parameters in the production of HX, a stepwise multiple regression analysis was computed on one hand for HX concentration and on the other hand for HX increase (Δ HX) as the dependent variables. The analyses included only data from hypoxic period I. All hypoxia parameters (except PaO_2) showed high intercorrelations. The listed variables together explained 87% of the variance for HX. The strongest single variable turned out to be pH, which alone explained 80% of the variance ($R = 0.90$). Additional significant information was added by the constructed variable SaO_2 -debt which explained another 4% of the variance. If pH was left out from the model, BE and PaCO_2 together explained as much of the variance as pH alone (80%).

If the constructed variables SaO_2 - and PaCO_2 -debt were left out from the model, lactate explained a significant part of the variance, amounting to an additional 3% upon the 80% explained by pH.

The multiple regression analyses with regard to Δ HX gave somewhat different results. The variable SaO_2 -debt made the most important contribution, explaining 66% of the variance and an additional 6% was supplied by BE. When only blood gas analyses and pH were included as independent variables, BE came out as the strongest variable with an explanation value of 40%, followed by SaO_2 (9%).

DISCUSSION

Quantification of the degree of fetal asphyxia would be desirable in the clinical situation. With presently used methods, it is, however, often difficult, especially in situations with prolonged or repeated periods of hypoxia. Plasma HX concentration as an indicator of the degree of tissue hypoxia has previously been advocated by several investigators. This recommendation is

Fig. 5. The relation between HX concentration and SaO_2 during hypoxic periods I + II in 16 fetuses. ○, PaCO_2 -gradient < 2.3 kPa; ◐, 2.3 to 3.2 kPa; ●, PaCO_2 -gradient $\geq$ 3.3 kPa.

founded on a theoretically attractive basis because HX is an intermediary breakdown product of energy-rich phosphates in the living cell.

Previous reports of elevated HX concentrations in plasma concerned adult animals (dog and pig) in hypoxic or anoxic conditions (1, 15-17). We considered the acutely exteriorized fetal lamb preparation a suitable model to test the hypothesis and that the HX concentration in the fetal plasma would reflect the degree of tissue hypoxia.

Our results demonstrate a progressive increase of HX concentration during hypoxemia as well as an accumulated augmentation of the HX values with repeated periods of hypoxic stress on the fetus. (Figs. 1, 2, and 3). The question whether hypoxemia in itself produces an elevation of the HX concentration or if secondary circulatory events are necessary is elucidated by the reaction to the first hypoxic period in the 10 fetuses in Figure 2. These fetuses had both hemodynamic and blood gas variables compatible with normal before the institution of hypoxia (Table 1). The increase of HX during the period of hypoxia without signs of circulatory failure was highly significant, which indicates that hypoxia alone is sufficient to affect the purine metabolism. In the present study, the HX level of fetal plasma correlated significantly with other parameters of hypoxia. A poor correlation was, however, found to the prevailing degree of oxygenation of the arterial blood (Table 2). On the other hand, a highly significant correlation was found to the constructed parameter of oxygen-debt, which was a product of the deficit in arterial oxygen saturation and the duration of hypoxia.

The dominating correlation found in the whole material was that between HX and pH. The latter variable is often considered as the best single measure of intrauterine hypoxia. It appears that the measurement of PaO_2 does not convey as much information about progressive alterations in tissues during hypoxia as pH measurement. This is quite reasonable because pH changes gradually with the duration of hypoxia, whereas PaO_2 rapidly falls to low levels to stay largely unchanged during the rest of the hypoxic period.

The highest levels of HX occurred when hypoxemia was combined with low pH (Figs. 2 and 3) or with large difference between maternal and fetal PaCO_2 (Fig. 5). Because maternal PaCO_2 was kept reasonably constant with the ewe on artificial ventilation, a large PaCO_2 -gradient, which in this case actually equals a high fetal PaCO_2 , indicates impaired gas transport over the placenta and thus probably reduced umbilical blood flow. The demonstration of an inverse relationship between the PaCO_2 -gradient and the combined cardiac output below a critical level of blood flow (Fig. 4) suggests a reduced umbilical blood flow concomitant with a raised PaCO_2 -gradient. In the fetal lamb, 40 to 45% of combined cardiac output perfuses the placenta, and this proportion is increased during asphyxia (4). Inasmuch as in our experimental set-up, high feto-maternal PaCO_2 -differences thus reflect a general deterioration of organ perfusion, the findings of particularly high HX concentrations in combination with large PaCO_2 -gradients (Fig. 5) further corroborate the conclusion that plasma HX concentration in the sheep fetus reflects tissue hypoxia.

The high concentrations of HX found in acidotic fetuses during recovery periods are probably due to the washout of HX from peripheral to central circulation when organ perfusion is improving and could thus be considered as a measure of "cumulative hypoxia" or hidden hypoxanthinemia.

In accordance with previous findings in adult animals (15) HX also correlated well with other metabolic parameters of oxygen debt, i.e., lactate concentrations and BE (Table 2).

The present results do not single out any of these measures of oxygen debt as superior to the others. From a theoretical point of view, HX is attractive to favor as a factor reflecting the energy state of the cell. Lactacidosis may be present for other reasons than oxygen lack, as in the cases of fetuses and neonates with intrauterine growth retardation. These children combine the inherent tendency to intrapartum asphyxia with elevated lactate levels for metabolic reasons (12).

Further investigations are required considering the contribution of different organs in the production of HX and the elimination of the substance, before a more exact evaluation of the role of HX in the diagnosis and quantification of perinatal asphyxia can be made. The relative contribution of brain, myocardium, liver, and placenta would thereby be of special interest as well as the rate of elimination of HX from fetal plasma.

In summary, the present study appears to demonstrate that plasma HX concentration increases during periods of oxygen lack and particularly the combination of oxygen lack, acidosis, and poor tissue perfusion will cause a marked augmentation of the HX concentration. Inasmuch as fetal asphyxia is characterized by the same events all leading to tissue hypoxia, the concentration of plasma HX in the fetus might well turn out a valuable parameter of perinatal asphyxia.

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