LACTATE IN THE HUMAN FETUS

M. Katz, E. Lunenfeld, I. Meizner, M. Mazor, B. Piura

Department of Obstetrics and Gynecology, Soroka University Hospital, Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer-Sheva, Israel

Introduction

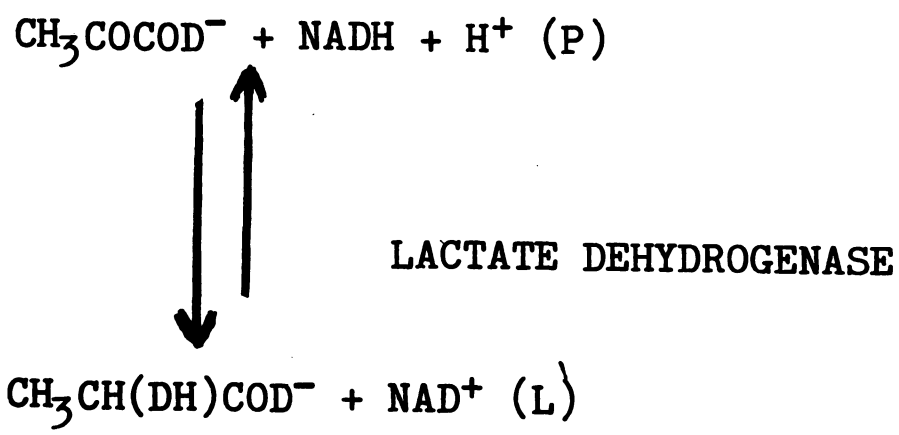
Lactic acid or α -hydroxyproprionic acid is an organic acid which belongs to the family of carboxylic acids. Lactic acid is found in juices of certain plants and in soil. In the human, lactate is produced by the skeletal muscle, skin, blood cells, brain and eye tissues during anaerobic glucolysis. Lactic acid was first isolated by a Swedish chemist, Carl Wilhelm Scheele, in 1780. In its pure form lactic acid is a colorless, crystaline substance, which melts at 18°C and is highly hydrophilic absorbing rapidly moisture from the atmosphere. The interest with lactate metabolism in the mother and fetus begins in the late twenties with the work published by Bell and Cunningham in the British Journal of Medicine, 1928 (1). The paper is called "The metabolism and acidity of fetal tissues and fluids". The authors found that umbilical cord blood lactate is twice as high as maternal venous. Three years later, in 1931, Eastman and McLane (2) reported that lactate values in umbilical cord at delivery are higher than in the fetus. They explain this rise by "lactate infusion" from the mother in cases of normal infants. As for cases with high lactate they believe that it is of endogenous production due to fetal asphyxia.

What is remarkable that their conclusions are mostly correct after more than 50 years and endless investigations. The formation of excessive amounts of lactic acid in response to acute metabolic demands in the face of temporarily inadequate tissue oxygen is a commonly recognized phenomenon. For example, during vigorous exercise there is an increase in muscular demand for oxygen and due to the oxygen deficit the energy requirement is supplemented by anaerobic metabolism of glucogen. The

release of energy is then accompanied by a rise in formation of lactic acid. Such source of energy is quite inefficient in terms of calorie production since for each gram molecule of lactic acid produced the free amount of energy is about ten times less than by the oxidation of the corresponding amount of lactic acid to carbon dioxide and water (3). But in a time of need, this is an extremely important mean of energy production which enables the organism to function, without harm, for brief periods of time in the absence of oxygen. To this forum, the capability to utilise anaerobic metabolism as a source of energy is of particular interest. We are dealing with an area in which our patient, the fetus, appears to be deprived physiologically of his normally low oxygen supply at frequent intervals during labor and delivery, and where, due to a multitude of pathologic processes, the fetal well-being may both depend as well as be jeopardized, by anaerobic metabolism and its by-products. The ability to produce lactate begins very early in fetal life, and Villee (4) in 1954 found evidence of lactate production in fetal tissues of seven weeks' gestation. The capability to breakdown glycogen to lactic acid in absence of oxygen was proven by Himwich et al (5) to be a protective measure that enables the immature fetus to survive temporary lack of oxygen. He placed a newborn rat in nitrogen and found that it survived more than expected and its lactate levels were high. After an injection of sodium fluoride or hypoglycemia induced by insulin, survival time was short and the lactate rise minimal.

In his book on "Fetal and Neonatal Hypoxia" Saling concludes - "It is not oxygen but adequate sources of energy which are essential for cell survival. The fetus needs energy to maintain biochemical reactions and osmotic equilibrium" (6).

Before we proceed to discuss the specifics of lactate metabolism in the mother and fetus, please allow me a few physiologic considerations. Metabolically production of lactate is accompanied by the generation of an equivalent number of protons that are released into the body fluids. Those protons which are titrated by bicarbonate and non-bicarbonate body buffers, acidify the intracellular and extracellular environments. By contrast, metabolic removal of lactate consumes an equivalent number of hydrogen ions and thus restores the body's alkali reserve (Fig. 1).



This reversible reaction occurs in the cytosol and is catalysed by the enzyme lactate dehydrogenase (3). Lactate is formed when pyruvate reacts with reduced nicotinamide adenine dinucleotide and is converted back to pyruvate by reactions with the oxidized counterpart of the dinucleotide. Lactate is a metabolic end product and his only metabolic fate is oxidation back to pyruvate.

The intracellular (cytosolic) concentration of lactate is determined by three variables - concentration of pyruvate - produced mainly by anaerobic glycolysis; the ratio between reduced and oxidized nicotinamide adenine dinucleotide - which is also referred as redox (reduction/oxidation) state and the intracellular hydrogen ion concentration.

Lactic acidosis is defined as an acid base disorder in which accumulation of lactic acid reflects the disruption of normal balance between production and utilization. Metabolic acidosis may be caused by two mechanisms, as shown in Fig. 2.

$$\text{I)}\quad \text{PYRUVATE} + \text{DPNH}_2 \xrightleftharpoons{\text{LDH}} \text{LACTATE} + \text{DPN}$$

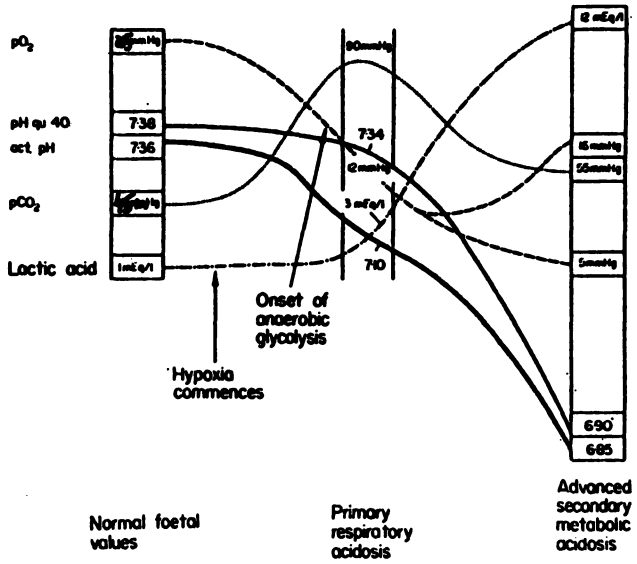
$$\text{II)}\quad \text{LACTATE} = [\text{PYRUVATE}] \times K \frac{[\text{DPNH}_2]}{[\text{DPN}]}$$

	MECHANISM	CAUSE	L/P RATIO
A.	INCREASED PYRUVATE	HYPOCAPNIA INFUSIONS OF BICARBONATE GLUCOSE & INSULIN CATECHOLAMINE	UNCHANGED
B.	ALTERATIONS OXIDATION DPN DUE TO TISSUE OXYGEN DEBT	HYPOXEMIA CIRCULATORY FAILURE	INCREASED

The first, which is essentially benign, results from an increase in pyruvate concentration with a parallel rise in lactate concentration and thus no change of the lactate/pyruvate ratio. Increase in pyruvate was found in response to hyperventilation and hypocapnia, alkalosis induced by infusion of bicarbonate, infusion of glucose and insulin and rise in catecholamines - on withdrawal of the stimulus pyruvate and lactate quickly will return to their normal values.

The second mechanism which is caused by alteration of oxygenation, leads to a rise in lactate without a corresponding rise in pyruvate - changing thereby the lactate-pyruvate ratio in proportion to oxygen debt. In the human fetus lactic acidemia is a result of inadequate oxygen supply (6).

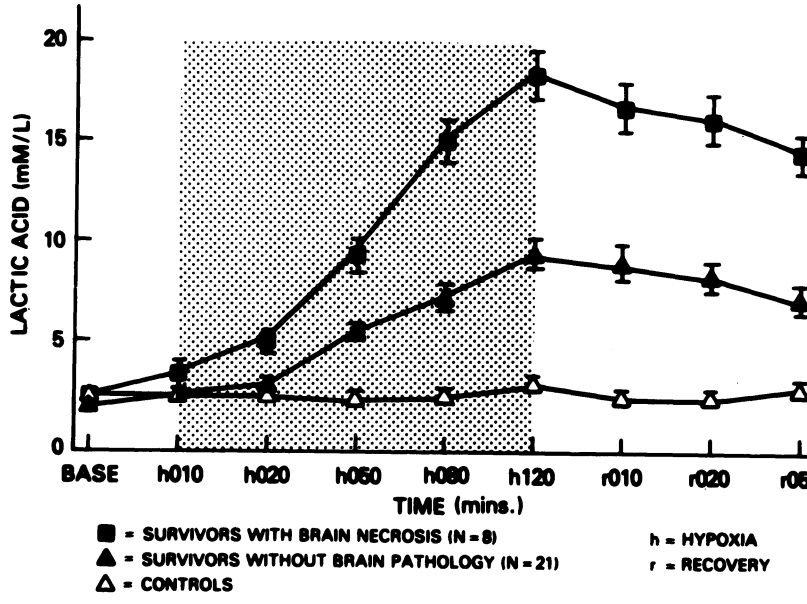
Fig. 3 taken from Saling's (6) book, summarizes the events that lead to fetal metabolic acidosis.



One has to keep in mind that a decrease in oxygen tension in the fetus even when small, may cause a shift of the oxygen dissociation curve, leading to a marked decrease of tissue oxygen saturation and content, and to excessive accumulation of lactic acid. The fetus has only limited capability to protect itself from high lactate levels, because fetal kidneys excrete fixed acids very slowly and the transfer to the mother is limited. Liver, renal cortex, heart and placenta are all lactate-consuming organs. They can use lactate - via pyruvate - as a substance for gluconeogenesis and oxidize it to CO_2 and water - provided the necessary amount of oxygen is available (3). In a study published in 1981 Myers et al (7) reported that in fetal monkeys, even though the primary cause of tissue injury was oxygen deprivation it was the degree of accumulation of lactic acid that determined the extent and severity of brain edema and necrosis (Fig. 4).

In those cases, if death does not result from brainstem compression or the development of cardiogenic shock shortly after resuscitation, survival with lifelong disability can be expected.

What are the normal acid-base characteristics of mother and fetus and how do they change in labor?



Low et al (8) in a paper published in the Am. J. Obstet. Gyn. in 1974 described the maternal and fetal acid-base, lactate and pyruvate characteristics during labor and delivery in 140 normal patients. Analysing maternal venous blood they found that there is a small decrease of buffer base with a twofold increase in lactate during the labor. The increase in lactate and decrease in pH occur at delivery (Tab. 1).

TABLE 1. The Acid-base, Lactate, and Pyruvate Concentrations in Maternal Venous Blood at the Onset of Labor, Middle of Labor, Second Stage, and Delivery.

	Onset of labor (No. = 28)		Middle of labor (No. = 33)		Second Stage (No. = 98)		Delivery (No. = 40)	
	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.
pH	7.408	0.03	7.433	0.05	7.423	0.06	7.	0.05
Pco_2(mm.Hg)	32.4	3.0	31.3	5.0	30.0	5.0	33.2	5.6
Buffer base (mEq./L.)	42.2	1.7	43.3	1.6	42.2	1.7	41.3	1.7
Lactate								
mmoles/L.	1.36	0.37	1.50	0.52	2.34	1.22	2.89	1.30
mg.%	9.9	2.7	10.8	3.7	16.7	8.5	20.7	9.5
Pyruvate								
mmoles/L.	0.14	0.03	0.14	0.03	0.20	0.08	0.22	0.08
mg.%	0.98	0.21	0.99	0.24	1.4	0.57	1.56	0.57
Lactate/pyruvate ratio	10.0		10.6		11.7		13.4	

In the normal fetus these data refer only to cord values at delivery, but this proves clearly that umbilical artery lactate is higher than this in umbilical vein (Tab. 2).

The twofold increase in lactate concentration in the normal fetus, with a parallel increase in the lactate-pyruvate ratio indicates a minor degree of tissue oxygen debt in the fetus. Low's data were thereafter confirmed by extensive work of Dellenbach (9), Smith (10) and many others.

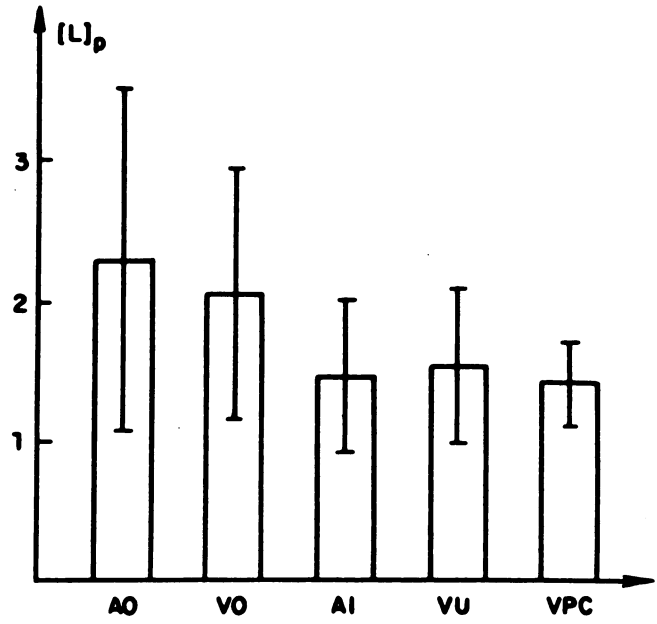
One may, therefore, conclude that minor acid base changes occur during normal delivery and lead to a rise in lactate levels with a consequent drop

TABLE 2. The Acid-base Characteristics in Fetal Capillary Blood One Hour Prior to Delivery and the Acid-base, Lactate, and Pyruvate Concentrations in Umbilical Vein and Artery Blood at Delivery

	Late first stage (No. = 10)		Delivery - vein (No. = 140)		Delivery-artery (No. = 133)	
	Mean	S.D.	Mean	S.D.	Mean	S.D.
pH	7.313	0.05	7.340	0.05	7.270	0.05
PCO_2 (mm.Hg.)	45.0	7.0	39.6	5.5	50.7	6.8
Buffer base (mEq./L.)	42.2	2.0	42.8	2.0	41.1	2.5
Lactate						
mmoles/L.			2.81	1.18	3.29	1.39
mg.%			19.4	8.1	22.7	9.6
Pyruvate						
mmoles/L.			0.18	0.05	0.19	0.05
mg.%			1.2	0.36	1.3	0.35
Lactate/pyruvate ratio			16.0		17.0	

in pH in both mother and fetus. Dellenbach et al. (11) followed the acid base changes and lactate concentration in arterial and venous blood of 60 patignts, at term, during elective Cesarean section. In each case they obtained simultaneously samples from maternal iliac artery, uterine vein, antecubital vein, umbilical artery and umbilical vein. What they found is that the level of maternal lactate is identical regardless of the sampling site. The gradient of lactate was always positive between fetus and mother and umbilical artery and umbilical vein, indicating that the human fetus produces lactic acid and that a part of lactate disappears when it crosses the placenta (Fig. 5).

Schneider et al investigated the influence of type of anesthesia used for elective Cesarean sections on lactic acid concentration in mother and fetus in 22 patients with general and 9 with epidural anesthesia. The first blood sample was taken 15 minutes prior to anesthesia, then the second at the delivery of the newborn (Fig. 6).


[L]p
3
2
1
AO
VO
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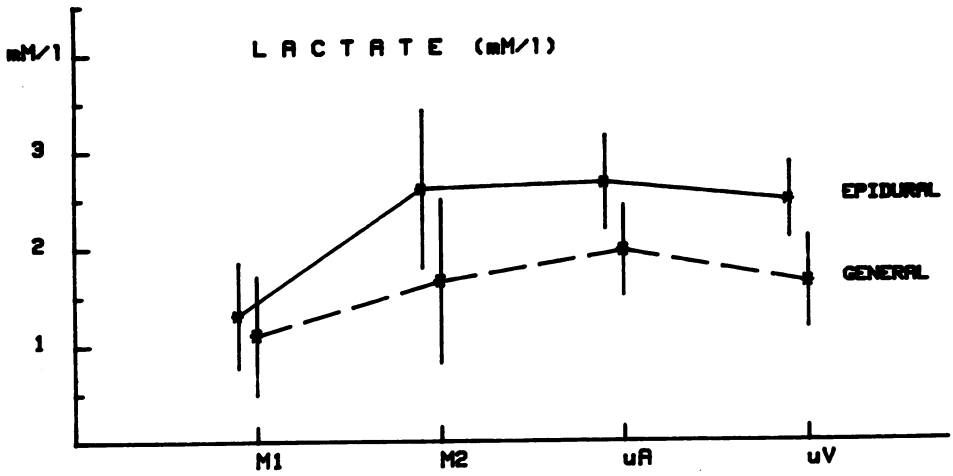

mM/l
LACTATE (mM/l)
3
2
1
M1
M2
uA
uV
EPIDURAL
GENERAL

Lactate levels in mother rose in both types of anesthesia, most probably during induction time, but the increase was more significant in those with epidural than with general anesthesia.

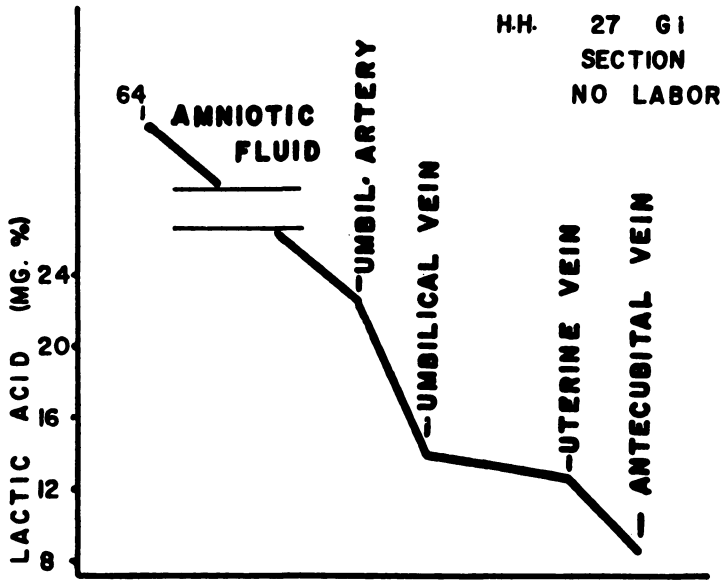
One can only speculate that the possible explanation for this rise would be an increased lactate production due to temporary tissue hypoxia and stimulation of lactate metabolism as a result of stress or anxiety. In their study umbilical artery lactate and vein lactate were higher than maternal which shows once more that without labor, under a steady state the fetus produces lactate, and because of placental permeability a slow but constant flow of lactate from the fetus to the mother follows.

Moll (13) studied the accumulation and disappearance of lactate in the fetus of a guinea pig who also has a hemochorial placenta and according to him where fetal oxygenation is optimal placental transfer and fetal utilization of lactate are almost equal. Otey et al (14) suggested that the placenta serves as a buffer for the fetus. Low (15) in 1979 states that based on his work the changes of lactate and pyruvate that occur in mother and fetus during labor are parallel but independent. He based this statement on the fact that maternal lactate in normal and "complicated" pregnancies was quite similar whereas the "complicated" group had a much higher fetal lactate level than the normal.

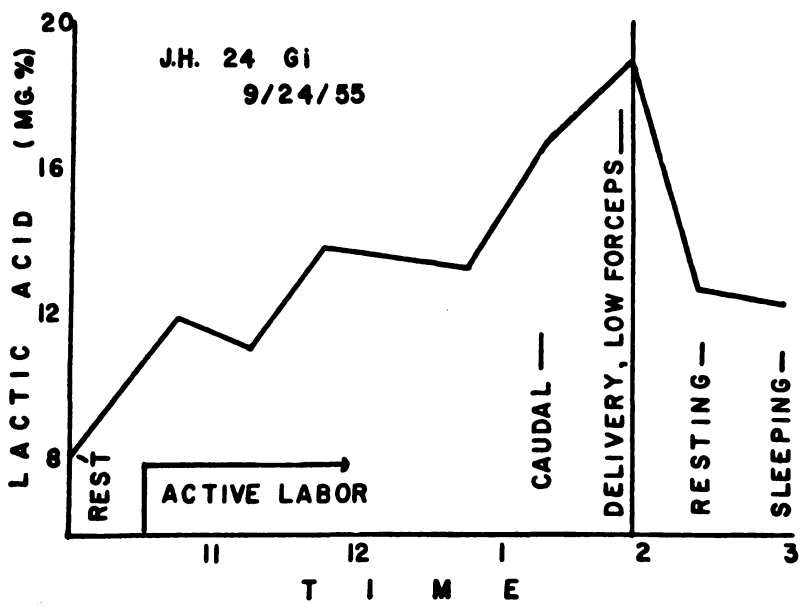
Lactic acid is present in high concentration in amniotic fluid - Raiha (16) believes that this high concentration is a result of fetal excretion and probably due to glycolysis. High activity of lactic dehydrogenase was found in amniotic fluid by Lapin and Freeman (17) (Fig. 7).

In summary, based on human observations and animal studies, it seems that little, if any, lactate and pyruvate are crossing the placenta. If transplacental transfer exists it will be by diffusion and it is, therefore, logical that the movement will be from the fetus to the mother.

Increase in lactate in fetus and mother, most probably occurs independently. We know now that maternal lactate rises during labor and delivery and the question is what is the cause of this rise and at which stage of labor does it happen.



Hendricks (18) found that there is a gradual increase of lactate during active labor with a peak level at time of delivery (Fig. 8).

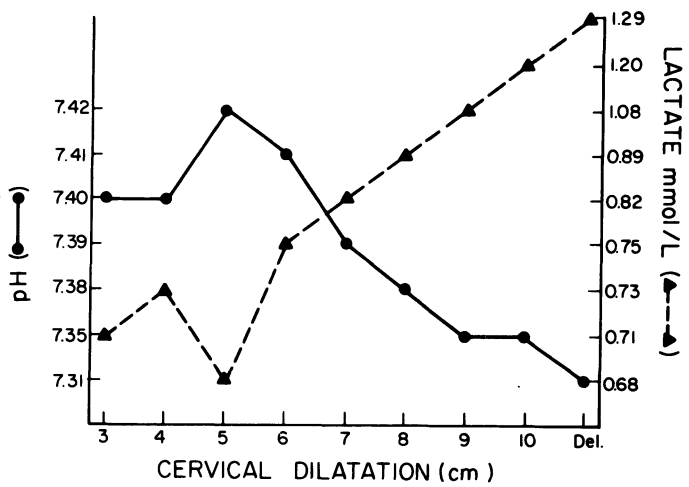


According to Hendricks it may be assumed that at least a major portion of the progressive rise in lactic acid concentration is on the basis of activity of the uterus and/or its contents.

If Hendrick's conclusion is correct, it should point to a state similar to what one can see during exercise when muscular work leads to oxygen utilization greater than supply and as a result, to excessive lactate accumulation.

In order to assess the energy expenditure in normal labor we did the following:
25 healthy parturients were attached by a mouth piece to a metabolic cart which measured every 10 min. for 5 mins. duration, oxygen consumption, CO_2 production, heart rate and respiration rate. At cervical dilatation of 3,6,8 and 10 cm, venous blood samples were obtained for lactate and pH. The mean results of 17 patients are presented (19). (Fig. 9).

MATERNAL METABOLIC PROFILE IN RELATION STAGES OF LABOR AND DELIVERY(mean values)



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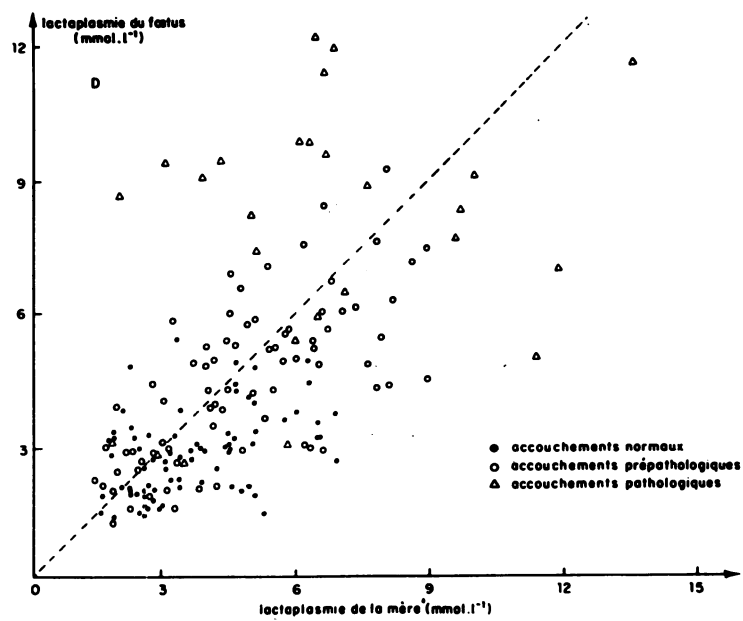
Oxygen consumption seems to double during contraction, but returns to precontraction levels in about 30 sec. Maternal glucose levels remained stable throughout labor. The pH dropped by 0.05 pH units and the lactate levels were almost stable until the second stage of labor, during which the rise was in a range of 40-50%.

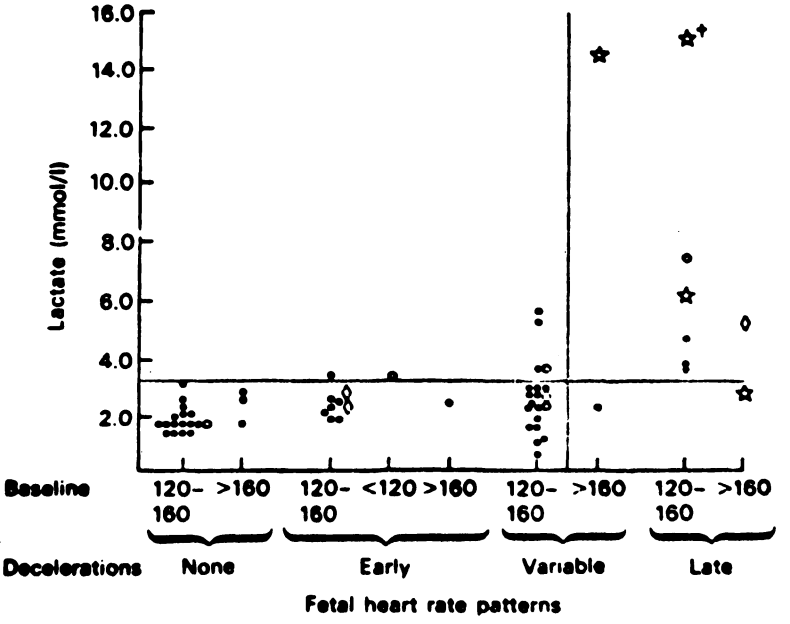
Based on our data we tend to believe that the major contributor to the rise in maternal lactate is not only the uterus but also maternal skeletal and abdominal muscles, participating in the process of delivery.

In a prospective study of 254 patients who had a vaginal delivery of a singleton fetus, we found that the mean maternal venous lactate levels during latent phase was 0.85 $\pm$ 0.14 mmol/L, and rose at delivery up to 2.14 $\pm$ 0.28 (range from 1.34 - 5.40). The mean umbilical artery lactate was 2.87 and umbilical vein 2.31 mmol/L (20).

When Haberey et al (21) compared maternal and fetal lactate levels in labor, they found an almost linear correlation between those two, throughout labor and delivery in normal cases. Maternal values remained persistently lower also in those defined as prepathological and pathological cases in which fetal lactate rose significantly - thus once more providing proof that fetal metabolic acidosis during labor and delivery is very unlikely to be secondary to lactate produced by mother (Fig. 10).



When lactate levels assessed in capillary scalp blood smaples were related to fetal heart rate patterns it was shown by Young (22), Smith (10) and Katz (20) that a high correlation exists between cardiotocographic indicators of fetal asphyxia and hyperlacticemia (Fig. 11).



We then looked upon the relation between meconium stained amniotic fluid and lactate levels. The results were interesting but not surprising - lactate in umbilical artery and vein was in the normal range when light meconium was seen.

In the 22 patients (out of 254) who had thick meconium, lactate was 4.15±1.2 mmol/L in the umbilical artery and 2.76±1.27 in umbilical vein. The difference in lactate levels in the two groups of meconium was statistically significant (p 0.01). This finding supports the view that thick meconium is indeed a sign of fetal hypoxia (23).

There is one more subject, quite controversial, which we would like to address, and it is that of duration of second stage of labor - and its impact on neonatal well-being. The second stage is characterized by uterine contractions that are both frequent and prolonged. During those contractions there is a marked reduction in placental perfusion.

Beard and Morris (24) and many other investigators found a decrease in base excess and fall in scalp capillary pH during second stage, and Wood et al (25) had shown that prolongation of expulsion period is associated with maternal and fetal acidosis. Out of 254 cases in our study we had accurate data on duration of second stage in 148 patients (20).

In 101 patients in whom second stage lasted from 1 to 75 minutes maternal lactate levels were ascertained, showing a rise in values which were statistically not significant.

The changes with duration of second stage were significant in umbilical artery and umbilical vein (Tab. 3).

TABLE 3. Umbilical and Maternal Lactate (mmol/l) by Duration of the Second Stage of Labor and Parity

	Duration of second stage (min)			
Blood sample	1-15	16-30	> 30	P*
Umbilical artery				
Primiparae	2.4 (1.7-4.2) (n = 18)	2.9 (1.0-5.5) (n = 18)	3.1 (1.8-6.5) (n = 26)	<0.025
Multiparae	2.4 (0.8-5.2) (n = 54)	2.6 (1.6-4.2) (n = 17)	2.9 (1.5-9.8) (n = 10)	<0.023
Umbilical vein				
Primiparae	2.6 (1.3-3.5) (n = 21)	2.7 (1.4-4.8) (n = 19)	3.2 (1.6-7.2) (n = 27)	<0.015
Multiparae	2.2 (0.8-4.6) (n = 54)	2.8 (1.5-5.7) (n = 17)	2.9 (1.5-2.9) (n = 10)	<0.013
Maternal vein				
Primiparae	3.1 (2.1-4.3) (n = 18)	3.5 (2.5-7.4) (n = 10)	3.5 (1.7-6.5) (n = 21)	NS
Multiparae	3.0 (1.3-6.7) (n = 40)	3.4 (1.8-5.4) (n = 9)	4.0 (3.7-4.4) (n = 3)	NS

Results are medians (range), n is the number of samples

*Statistical analysis used Kruskal-Wallis one way ANOVA.

Although in this study the changes in pO_2 and pCO_2 were less marked than those in pH and lactate we know from the work of Huch et al and Pearson that during second stage there is a decline in oxygen supply to the fetus leading to a mild respiratory acidosis of the fetus which resolves quickly after delivery. It is therefore important to avoid excessive prolongation of second stage of labor during which lactic acid accumulation and metabolic acidosis may develop.

Studies done by Smith (10), Low (8) and Young (22),as well as our own prove that lactic acid measurements are as good predictors of neonatal outcome as scalp pH. The availability of a quick assessment using micro samples of scalp blood should enable us to diagnose the development of oxygen deficit maybe even before significant drop in scalp pH. It is our belief that lactate measurements in labor in the fetus and mother should be added to the armamentarium of means of surveillance in labor and delivery.

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