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Determination of thiamine (vitamin B_1) in maternal blood during normal pregnancies and pregnancies with intrauterine growth retardation

T. Heinze and W. Weber*

Institute of Perinatal Medicine, Klinikum Rudolf Virchow,
Free University of Berlin, and Department of Obstetrics, Women's
Hospital Berlin-Neukölln, Berlin, West Germany
* Dept. of Clinical Pharmacology, Klinikum Steglitz, Free University
of Berlin

Summary: The concentration of thiamine (vitamin B_1) was measured in blood cells and plasma from mothers with normal pregnancy and from mothers whose pregnancy was complicated by intrauterine growth retardation (IUGR).

Thiamine concentrations were estimated by the thiochrome method using HPLC separation and fluorimetric detection according to Weber et al. (2). During normal pregnancies the thiamine values in blood cells fall in the 28th to the 39th week of gestation from 230 nmol/l to 170 nmol/l. In cases with severe IUGR there is only a slight decrease in the thiamine levels from 140 nmol/l in the 30th week of gestation to a level of 130 nmol/l in the 39th week of gestation.

During this period the thiamine values in plasma remain constant.

To compare the thiamine concentrations in normal pregnancies and in those with IUGR we separated the thiamine values in a group from 28/0 to 34/6 and one from 35/0 to 39/6 weeks of gestation. In both groups mothers with normal pregnancy had significantly higher thiamine levels in the blood cells than mothers whose pregnancy was complicated by IUGR ($p = 0.0001$ and $p = 0.0005$).

However, the thiamine values in plasma were not significantly different in normal pregnancies and pregnancies with IUGR. The results indicate that maternal thiamine deficiency might be one cause of IUGR.

Zusammenfassung: Der Gehalt an Thiamin (Vitamin B_1) wurde im mütterlichen Blut jeweils in den Blutzellen und im Plasma bei normalem Schwangerschaftsverlauf und bei Schwangerschaft mit intrauteriner Mangelentwicklung des Feten bestimmt.

Die Bestimmung der Thiaminkonzentration erfolgte mit der Thiochrom-Methode mittels HPLC-Trennung und anschließender fluorimetrischer Bestimmung nach der Methode von Weber et al. (2). Bei normalem Schwangerschaftsverlauf ist ein Abfall des Thiamingehalts in den Blutzellen von 230 nmol/l bis 170 nmol/l von der 28. bis zur 39. Schwangerschaftswoche zu beobachten. Bei schwerer intrauteriner Mangelentwicklung ist nur ein geringer Abfall des Thiamingehaltes von 140 nmol/l in der 30. Schwangerschaftswoche bis zu einem Gehalt von 130 nmol/l in der 39. Schwangerschaftswoche zu beobachten.

Demgegenüber bleiben die Thiaminwerte in Plasma annähernd konstant.

Um die Thiaminkonzentrationen bei normaler Schwangerschaft und bei schwerer intrauteriner Mangelentwicklung zu vergleichen, führten wir eine Einteilung in zwei Gruppen – eine von 28/0 bis 34/6 und eine von 35/0 bis 39/6 Schwangerschaftswochen durch. In beiden Gruppen waren die Thiaminwerte in den Blutzellen bei

normaler Schwangerschaft signifikant höher als bei intrauteriner Mangelentwicklung ($p = 0{,}0001$ und $p = 0{,}0005$). Die Thiaminwerte im Plasma unterschieden sich jedoch nicht signifikant bei normalem Schwangerschaftsverlauf und bei Schwangerschaften mit intrauteriner Mangelentwicklung. Unsere Ergebnisse deuten darauf hin, daß mütterlicher Thiaminmangel einen Grund für eine intrauterine Mangelentwicklung darstellt.

Key words: thiamine (vitamin B_1); pregnancy; intrauterine growth retardation (IUGR)

Schlüsselwörter: Thiamin (Vitamin B_1); Schwangerschaft; intrauterine Mangelentwicklung

Introduction

Low birthweight increases infant mortality; the lower the birthweight, the greater the perinatal mortality rate and the higher the incidence of brain disorders and mental retardation. The role of nutritional factors in the development of perinatal and postnatal growth retardation is still a point of controversy and not well understood. Baker et al. (4) found thiamine levels in the blood of low birthweight neonates to be the same as those in the blood of normal birthweight infants. Recently Roecklein et al. (1) suggested that thiamine deficiency may cause IUGR in rats. The results indicate that thiamine deficiency alone during in utero development in the rat contributes to intrauterine growth retardation (IUGR). They found that a lack of thiamine causes a reduction in body weight, in placental weight, and in liver weight, and therefore a higher brain liver ratio is considered as an indicator of IUGR. The present investigation was undertaken to determine the influence of low thiamine levels as a possible cause of IUGR of the fetus. We compared the thiamine levels in blood cells and in plasma of mothers with normal pregnancy and in cases with IUGR.

Subjects and Methods

Blood was taken at a different gestational age from 46 mothers undergoing clinical treatment because their fetuses were suspected of having IUGR. The diagnosis was based on ultrasound measurements. 19 of these fetuses suffered from severe IUGR and had very low birthweights ($p < 3$ according to Nickl's intrauterine weight standards (5, 6). Blood was taken once during pregnancy from 14 mothers, twice from four mothers and three times at different gestational ages from one mother. Ten of the fetuses had a slight IUGR and low birthweights ($p < 10$ according to Nickl (5, 6). In this group blood was taken once from five mothers, twice from four mothers and three times at different gestational ages from one mother.

However, 17 of the patients whose fetuses were suspected of having IUGR were delivered of normal weight babies. These 17 mothers and in addition 26 patients attending our antenatal clinic at the same time, who were later delivered of normal weight newborns, were taken to form a sufficiently large control group.

Blood samples were taken by venipuncture and thiamine concentrations were measured by the thiochrome method using HPLC separation and fluorimetric detection (2). We determined the thiamine values in plasma and in whole blood and calculated the thiamine levels in blood cells using the hematocrit. For statistics the Mann Whitney U Wilcoxon Rank Sum W Test and the Spearman Rank Correlation were used.

Results and Discussion

Table 1 shows the clinical data of patients and newborns. When considering the age of patients and the number of pregnancies, there is no significant difference in cases with IUGR and normal cases. The gestational age at delivery decreases slightly from 39 weeks to 37 weeks in normal cases and cases with severe IUGR caused by a higher rate of preterm babies in the group with severe IUGR. The average weight and the length of the newborns decrease as expected from 3 230 g and 50.1 cm in normal cases to 1 933 g and 44.0 cm in cases with severe IUGR. There was a corresponding decrease in the weight of the placenta.

Table 2 shows the fetal and maternal complications in pregnancy. Fetal complications indicated by a suspect CTG (cardiotocogram) are five times as high in cases with severe IUGR.

There are no great differences between normal cases and severe IUGR when considering most of the maternal complications in Table 2, but 31 % of the pregnancies with IUGR and only 7 % of the normal pregnancies are complicated by gestosis. Also the rate of preterm labors is higher in the group with IUGR (37 % as against 14 %).

Table 1. Clinical data of patients and newborns.

	normal cases n = 43	cases with slight IUGR n = 10	cases with severe IUGR n = 19
Age of patient, years	26.2 ± 5.6	27.4 ± 5.3	26.5 ± 6.1
Number of pregnancies	1.67 ± 0.8	1.36 ± 0.48	1.47 ± 0.5
Gestational age at delivery, weeks	39.1 ± 1.5	38.1 ± 0.6	37.24 ± 1.96
Weight of the newborn, g	3,232 ± 377	2,620 ± 109.6	1,933 ± 445
Length of the newborn, cm	50.1 ± 1.7	46.8 ± 1.66	44.0 ± 2.9
Loss of blood after delivery, ml	211 ± 191	172 ± 117.7	294 ± 215
Weight of the placenta, g	599 ± 122	533 ± 81.7	450 ± 193

Table 2. Fetal and maternal complications during pregnancy.

	normal cases n = 43		cases with slight IUGR n = 10		cases with severe IUGR n = 19	
	cases	%	cases	%	cases	%
Fetal complications during pregnancy						
Suspect CTG	4	9.3	1	10	10	53.0
Maternal complications during pregnancy						
Premature rupture of the membranes	9	20.9	2	20	3	15.8
Preterm labor	6	14.0	–	–	7	37.0
Green amniotic fluid	8	18.6	–	–	3	15.8
Diabetes mellitus	1	2.3	2	20	–	–
Gestosis (toxemia)	3	7.0	–	–	6	31.0

Table 3. Fetal and maternal complications during labor.

	normal cases n = 43		cases with slight IUGR n = 10		cases with severe IUGR n = 19	
	cases	%	cases	%	cases	%
Vaginal bleeding	4	9.3	1	10	9	47.4
Prostaglandin gel for cervix ripening	8	18.6	1	10	–	–
Arrest of labor	7	16.3	–	–	2	10.5
Fetal acidosis	1	2.3	–	–	5	26.3
Fever during labor	2	4.6	–	–	–	–
Infans mortuus or mal formations	–	–	–	–	1	5.3

In Table 3 the fetal and maternal complications during labor are indicated. The vaginal bleeding is significantly higher in the group with severe IUGR (48 % vs 9.3 %). Also the number of fetal acidoses indicating fetal hypoxia is more than 10 times as high in the cases with severe IUGR. One child in the IUGR group had a genetic malformation (microcephalie) and died two weeks after delivery.

Figure 1 demonstrates the thiamine levels in blood cells in cases with normal birthweight compared with those with severe IUGR during the second half of gestation.

There is a drop of about 20 % in the median values of the normal cases from the 28th week of gestation to the 39th week of gestation from a

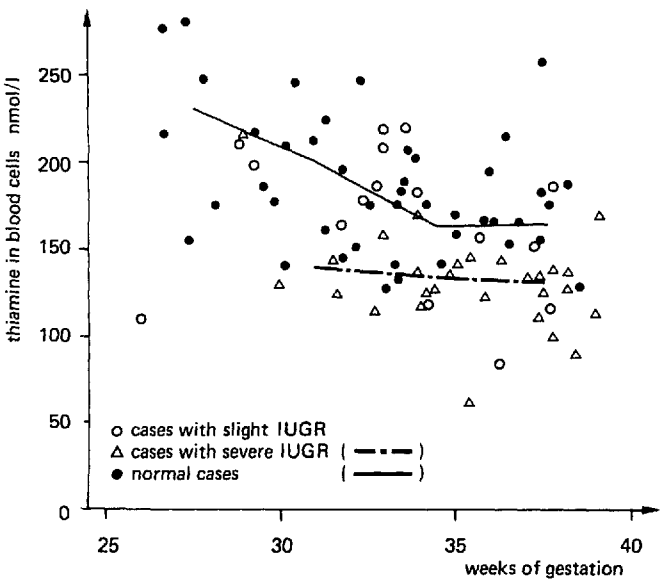

Fig. 1. Thiamine concentrations in blood cells in cases with normal birthweight (●), with severe IUGR (△), and with slight IUGR (○) during the second half of gestation.

thiamine level of about 230 nmol/l to 170 nmol/l thiamine in the 39th week of gestation.

In cases with severe IUGR there is only a slight decrease in the thiamine levels from 140 nmol/l in the 30th week of gestation to a level of 130 nmol/l in the 39th week of gestation.

The thiamine levels in cases with severe IUGR are considerably lower than those in cases with normal birthweight. At the end of gestation we obtain nearly the same slope in both cases, but there is a nearly parallel shift to lower values of about 40 nmol in cases with IUGR.

In cases with slight IUGR we find a great spreading of B_1 values. Because of the small number of values a statistical interpretation is not indicated.

Figure 2 shows the thiamine values in plasma. Here there is no change in the thiamine level of normal cases during the second half of gestation and there is also no significant difference between the thiamine levels in pregnancies with eutrophic and those with hypotrophic fetuses. However at the end of gestation (> 36/0 weeks), there is a slight drop of the plasma thiamine in cases with severe IUGR.

Thiamine values in cases with slight IUGR show a great variation too, a statistical interpretation has not been undertaken because of the small number of values.

Figure 3 involves a comparison between eutrophic fetuses and fetuses with severe IUGR. We made a division into two groups. One group from the 28/0 to 34/6 weeks of gestation and the other from 35/0 to 39/6 weeks of gestation. In both groups there are significant differences between babies with normal birthweight and small for date babies. In the group 28/0–34/6 weeks of gestation we received for eutrophic fetuses a median, m = 185

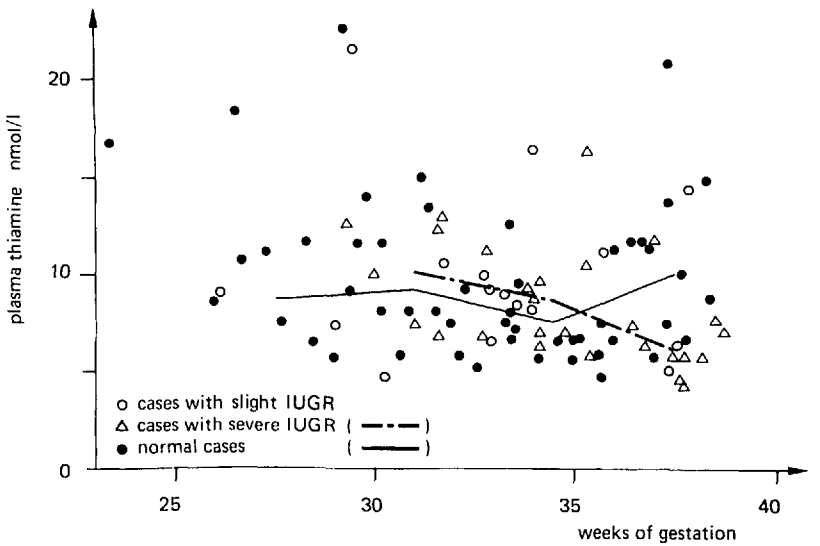

Fig. 2. Thiamine concentrations in plasma in cases with normal birthweight (●), with severe IUGR (△), and slight IUGR (○) during the second half of gestation.

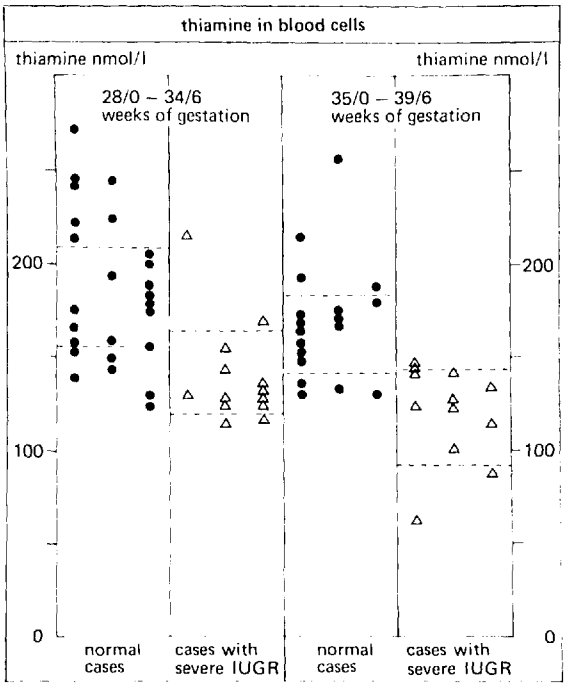

Fig. 3. Comparison between eutrophic fetuses and fetuses with severe IUGR. Dotted lines indicate 95 % confidence intervals.

nmol/l, a confidence interval, 95 % CI = 155–210 nmol/l, and for hypotrophic fetuses m = 137 nmol/l, 95 % CI = 120–162 nmol/l (p = 0.0001).

In the group 35/0–39/6 weeks of gestation we received the following results: m = 165 nmol/l, 95 % CI = 140–182 nmol/l for eutrophic fetuses and for hypotrophic fetuses m = 125 nmol/l, 95 % CI = 92–142 nmol/l (p = 0.0005).

We undertook the same comparison for the thiamine levels in plasma and found no significant difference between eutrophic and hypotrophic fetuses (p = 0,86). However, in the group from 35/0 to 39/6 weeks of gestation the thiamine levels in plasma are slightly lower than those in eutrophic pregnancies (p = 0.077).

In plasma thiamine is available only as free thiamine and as thiamine monophosphate TMP. Both forms can enter the intracellular space, but only free thiamine is phosphorylated to the biological-active thiamine diphosphate TDP, which represents the main form of the vitamin (7). TDP is intracellularly trapped due to its charged diphosphate group. To leave the cell, it has to be dephosphorylated (see Fig. 4).

The results show that mainly during normal pregnancy there is a drop in the total thiamine levels in blood cells. Towards the end of gestation the intracellularly stored TDP is reduced by the increased requirement of the growing fetus.

The thiamine levels in plasma remain constant in the second half of gestation. This might be explained by the fact that plasma thiamine

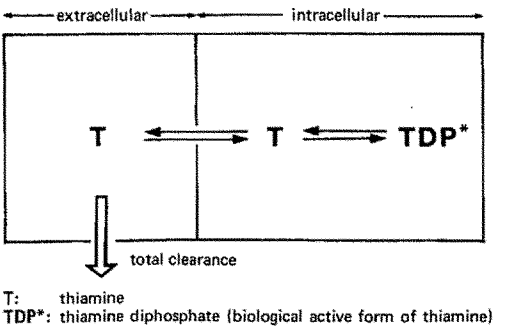

Fig. 4. Pharmacokinetic model for thiamine.

representing the transport form of the vitamin is affected only when the intracellularly stored thiamine is reduced considerably. That might be the case in severe IUGR where a slight decrease of the plasma thiamine occurs towards the end of pregnancy. Here the already reduced intracellularly stored content of thiamine is affected by the growing consumption at the end of pregnancy. It is possible that an existing thiamine deficiency is exacerbated by the increasing fetal requirement.

Our results indicate that thiamine deficiency might be one cause of IUGR. That does not agree with the results of Baker et al. (4) who used a protozoological method for thiamine determination and found no statistically significant differences in circulating vitamin B_1 levels between mothers giving birth to normal or low birthweight babies.

Vir et al. (3) using the transketolase activity for thiamine determination also found no correlation between thiamine status and anthropometric measurements of neonates. This might be caused by the unspecific and unsensitive methods that they used.

We suggest vitamin B_1 supplementation in cases of severe intrauterine growth retardation especially at the end of gestation.

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Anschrift des Verfassers:

Dr. Dr. T. Heinze, Institut f. Perinatale Medizin, Freie Universität Berlin, Mariendorfer Weg 28, 1000 Berlin 44 (FRG)