Changes in Magnesium, Total Calcium, Phosphorus, Copper and Zinc in Plasma and Erythrocytes from Newborns of Diabetic Mothers

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Zusammenfassung

In der vorliegenden Studie wurde das Verhalten der Plasma (Pl)- und Erythrocyten (Erc)-Konzentrationen an Magnesium (Mg), Gesamtkalzium (Ca), Phosphat (P), Kupfer (Cu) und Zink (Zn) bei 44 Neugeborenen diabetischer Mütter während der ersten fünf Lebenstage untersucht. Die bei der Geburt im Nabelschnurblut gemessenen Konzentrationen wurden mit entsprechenden Referenzwerten von 66 Neugeborenen gesunder Mütter verglichen. Während der ersten fünf Lebenstage ergaben sich signifikante Veränderungen für Erc-Mg, Pl-P, Pl-Cu und Pl-Zn. Verglichen mit den Kontrollen waren – ohne Berücksichtigung des Gestationsalters – im Nabelschnurblut der Neugeborenen diabetischer Mütter Pl-Mg, Pl-Ca, Erc-Cu und Erc-Zn signifikant erniedrigt, das Plasma-P hingegen signifikant erhöht. Die am stärksten diskriminierende Variable zwischen beiden Gruppen war das Pl-Ca gefolgt vom Pl-P.
Positive, signifikante *Spearman* Korrelationskoeffizienten ergeben sich zwischen kindlichen und mütterlichen Konzentrationen an Pl-Mg und Pl-Ca am Tage der Geburt ($p < 0.05$). Verschiedene Faktoren können diese signifikanten Variationen erklären: Magnesiummangel, immature Proteine, paradoxer funktioneller Hypoparathyreoidismus und erhöhte intestinale Kupfer-Ausscheidung.

Summary

Changes in plasma (Pl) and erythrocyte (Erc) concentrations of magnesium (Mg), total calcium (Ca), phosphorus (P), copper (Cu) and zinc (Zn) in 44 newborns of diabetic mothers during their first five days of life were investigated. Results in venous cord blood at birth were compared with those of 66 reference newborns. During the first five days of life, there were significant variations in Erc-Mg, Pl-P, Pl-Cu and Pl-Zn. Compared to control infants and without adjustment of the values for gestational age, Pl-Mg, Pl-Ca, Erc-Cu and Erc-Zn were significantly lower in cord blood from newborns of diabetic mothers, whereas Pl-P was significantly higher. The most discriminant variables between the two groups were Pl-Ca, followed by Pl-P. *Spearman* correlation coefficients between results for infants of diabetic mothers on the day of birth and their mothers were significantly positive ($P < 0.05$) for Pl-Mg and Pl-Ca. Several factors may account for these significant variations: magnesium deficit, protein immaturity, paradoxical functional hypoparathyroidism and increased intestinal copper elimination.

Résumé

L'évolution des concentrations plasmatiques (Pl) et érythrocytaires (Erc) du magnésium (Mg), du calcium total (Ca), du phosphore (P), du cuivre (Cu) et du zinc (Zn) de 44 nouveaunés de mères diabétiques au cours des cinq premiers jours de la vie a été analysée. A la naissance, dans le sang veineux du cordon, les résultats ont été comparés à ceux de 66 nouveaunés de référence. Au cours des cinq premiers jours de la vie, il y avait des évolutions significatives de Erc-Mg, Pl-P, Pl-Cu et Pl-Zn. Par comparaison aux enfants de référence et sans tenir compte de l'âge gestationnel, les résultats de Pl-Mg, Pl-Ca, Erc-Cu et Erc-Zn étaient significativement inférieurs dans le sang du cordon de nouveau-nés de mères diabétiques, tandis que la valeur de Pl-P était significativement augmentée. Les variables les plus discriminantes entre les deux groupes étaient Pl-Ca, suivi par Pl-P. Les coefficients de corrélation de *Spearman* entre les résultats des enfants de mères diabétiques le jour de leur naissance et ceux de leurs mères étaient significativement positifs ($P < 0.05$) pour Pl-Mg et Pl-Ca. Plusieurs hypothèses ont été évoquées pour expliquer les variations significatives observées chez les nouveau-nés de mères diabétiques: déficit en magnésium, immaturité protéique, hypoparathyroïdisme fonctionnel paradoxal et élimination intestinale du cuivre vraisemblablement augmentée.

Introduction

Little research has been undertaken to determine whether the combined effects of diabetes and pregnancy on maternal mineral metabolism lead to fetal variations [1–4]. Disturbances in the metabolism of minerals, particularly of essential trace elements, in the diabetic mother could cause fetal malformations [5–10]. The purpose of this study was to investigate changes in plasma (Pl) and erythrocyte (Erc) concentrations of magnesium (Pl-Mg, Erc-Mg), total calcium (Pl-Ca), phosphorus (Pl-P), copper (Pl-Cu, Erc-Cu) and zinc (Pl-Zn, Erc-Zn) in newborns of diabetic mothers during the first 5 days of life. Results in venous cord blood at birth were compared with those of a reference population, and the most discriminant variables between the two groups were determined.

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Subjects and Methods

Analyses were conducted from January 1989 to March 1991 in two groups of newborns. Parental consent was obtained for all 110 infants.

Subjects

The group of reference infants was composed of 66 white full-term babies (35 boys, 31 girls) born in the maternity ward of the University Hospital in Nantes, France. Mothers (19 to 40 years of age) were healthy and had no history of serious disease. All pregnancies were without complications and resulted in vaginal delivery. The Apgar score at 1 and 5 min was always 10. None of the infants had congenital malformation.

The group of infants from diabetic mothers was composed of 44 healthy babies (23 boys, 21 girls) born in the same hospital. The Apgar score at 5 min was always 10. None of the newborns presented congenital malformations.

Diabetic mothers (22 to 42 years of age) were recruited from the Nantes Diabetes Center. Diabetes was known before pregnancy in 27 type 1 (insulin-dependent) diabetes. Diabetes was diagnosed during pregnancy (WHO criteria) in 17 women (type 2). Patients with gestational diabetes mellitus required insulin therapy before the end of pregnancy. In case of type 1 diabetes, pregnancies were planned, and intensive treatment (multi-injection) was initiated before conception. Metabolic control during gestation was found to be satisfactory. At delivery, the percentage of glycosylated hemoglobin Hb A1 was on average elevated (8.68 ± 1.67 %). Cesarean section was frequently performed (60 %), contributing to a shorter ($P < 0.001$) gestational period in diabetic patients than in mothers of control subjects.

There were no maternal or perinatal complications. The paired mineral values in plasma and erythrocytes were determined at delivery in 15 mothers of these infants.

Assay techniques

Cord blood and blood obtained by heel puncture (day 2 and 5) were drawn into 2 ml Venoject tubes containing lithium heparin (Terumo, France, 78181 Saint Quentin en Yvelines Cédex, France) and then, without delay, centrifuged at 3500 x g for 8 min at 10 °C. Immediately afterwards, Mg, Ca and Zn concentrations were measured by flame atomic absorption spectrometry (Philips Pye Unicam SP9 model, Philips, France) according to previously described protocols [11]. Copper was analyzed by flameless atomic absorption spectrometry with Zeeman effect in plasma and erythrocytes diluted 50-fold with demineralized water (Perkin Elmer model 3030, Perkin Elmer, 78054 Saint Quentin en Yvelines Cédex, France). Phosphorus was determined by ultraviolet detection (340 nm) of ammonium phosphomolybdate (Biotrol kit, ref. A 2477, Biotrol, 75140 Paris Cédex 03, France). Sera (Biotrol-33 Plus, ref. Ao 2270) were used for the quality controls. For all the elements, intra- and interassay coefficients of variation were respectively < 2 % and 3 %. Accuracy ranged from 99 % to 102 %.

Statistical analysis

The *Kruskal-Wallis* test was used to search for significant changes in variables during the first 5 days of life, the *Mann-Whitney* U-test for comparison of the means of the two groups of infants [12] and logistic discriminant analysis to determine the most discrim-

Tab. 1: Mineral Values in Plasma and Erythrocytes from Cord Blood and Heel Blood from Two Groups of Newborns (mean and SD).

	Pl-Mg	Erc-Mg	Pl-Ca	Pl-P	Pl-Cu	Erc-Cu	Pl-Zn	Erc-Zn
	mmol/L						µmol/L	
Newborns from normal mothers: cord blood (day 1) n = 66	0.85 (0.08)	1.76 (0.15)	2.48 (0.22)	1.57 (0.25)	5.58 (2.14)	12.9 (3.00)	16.0 (3.02)	40.4 (13.6)
Newborns from diabetic mothers: cord blood (day 1)	0.82 (0.14)[a] n = 37	1.71 (0.17) n = 44	1.96 (0.32)[b] n = 37	1.99 (0.40)[b] n = 33	5.15 (1.92) n = 25	10.9 (2.41)[b] n = 39	16.8 (5.66) n = 23	33.0 (18.3)[b] n = 44
Newborns from diabetic mothers: heel blood (day 2)	0.82 (0.13) n = 30	1.82 (0.17)[c] n = 32	1.88 (0.33) n = 30	2.34 (0.33)[c] n = 15	8.05 (3.00)[d] n = 24	10.7 (2.72) n = 27	14.1 (3.96) n = 12	32.8 (12.9) n = 32
Newborns from diabetic mothers: heel blood (day 5)	0.87 (0.16) n = 15	1.83 (0.22) n = 15	1.85 (0.36) n = 15	2.35 (0.20) n = 9	6.50 (1.89) n = 9	10.1 (3.47) n = 11	11.3 (1.36) n = 7	32.9 (9.89) n = 15
Changes in time (day 1 to day 5 of life) for newborns from diabetic mothers: *Kruskal-Wallis* test		$P < 0.05$		$P < 0.01$	$P < 0.001$		$P < 0.05$	

Comparison of results of newborns from diabetic mothers (day 1) vs results of 66 reference newborns (day 1):
[a] $P < 0.05$; [b] $P < 0.0001$ (*Mann-Whitney U* test).
Comparison of results of newborns from diabetic mothers on day 1 vs day 2:
[c] $P < 0.01$, [d] $P < 0.001$ (*Mann-Whitney U* test).

inant variables between the two groups of newborns on the day of birth [13]. A *Spearman* correlation was performed between the mineral results of newborns of diabetic mothers and the paired values of their mothers. All these statistical procedures were implemented using Systat software (Systat, Inc., Evanston, IL, U.S.A.).

Results

Results (not adjusted for gestational age) are summarized in tab. 1 and 2. As no statistically significant sex-related differences or any variations according to type 1 and type 2 diabetes mellitus could be determined for analytes and growth-related variables, all results for newborns of diabetic mothers were pooled. The number of results is less than 44 for most variables concerning infants of diabetic mothers since blood volume was often inadequate to perform all analyses, particularly in plasma. Moreover, blood specimens at day 2 and 5 were only obtained if they were absolutely essential for other examinations.

During the first 5 days of life of infants of diabetic mothers, Erc-Mg, Pl-P, Pl-Cu and Pl-Zn showed significant variations. In the venous cord blood of these newborns, Pl-Mg, Pl-Ca, Erc-Cu and Erc-Zn were significantly lower than in reference infants, whereas Pl-P was significantly higher. The most discriminant variables between the two infant populations were Pl-Ca, followed by Pl-P. When Pl-Ca is considered as the sole discriminant value, the allocation rule derived from the analysis procedure gives 86.3 % of newborns correctly classified. When both Pl-Ca and Pl-P are considered, this percentage is 89.5 %.

Spearman correlation coefficients were significantly positive ($P < 0.05$) between Pl-Mg results of infants of diabetic mothers on the day of birth and those of their mothers ($r_S = 0.576$; $n = 13$), and between their respective Pl-Ca values ($r_S = 0.584$; $n = 13$). As indicated in fig. 1 and 2, *Spearman* correlation coefficients between Pl-Mg and Pl-Ca were not significant in these newborns ($r_S = 0.081$; $n = 37$) and their mothers ($r_S = 0.444$, $P < 0.10$; $n = 15$). In the 15 diabetic mothers, the means and standard deviations of Pl-Mg and Pl-Ca were respectively 0.67 ± 0.08 mmol/L and 1.66 ± 0.21 mmol/L.

Tab. 2: Variables Concerning the Two Groups of Newborns (mean and SD).

	Newborns from normal mothers, n = 66		Newborns from diabetic mothers		
Mother's age (years)	27.8	(4.91)	30.8	(4.70),	n = 43
Duration of gestation (weeks)	39.5	(1.39)	37.8	(1.85),	n = 44[a]
Birth weight (kg)	3.32	(0.41)	3.25	(0.55),	n = 43
Birth height (cm)	49.4	(1.94)	49.0	(2.19),	n = 35
Head circumference (cm)	34.4	(1.28)	34.4	(1.74),	n = 38

[a]t-test ($p < 0.001$)

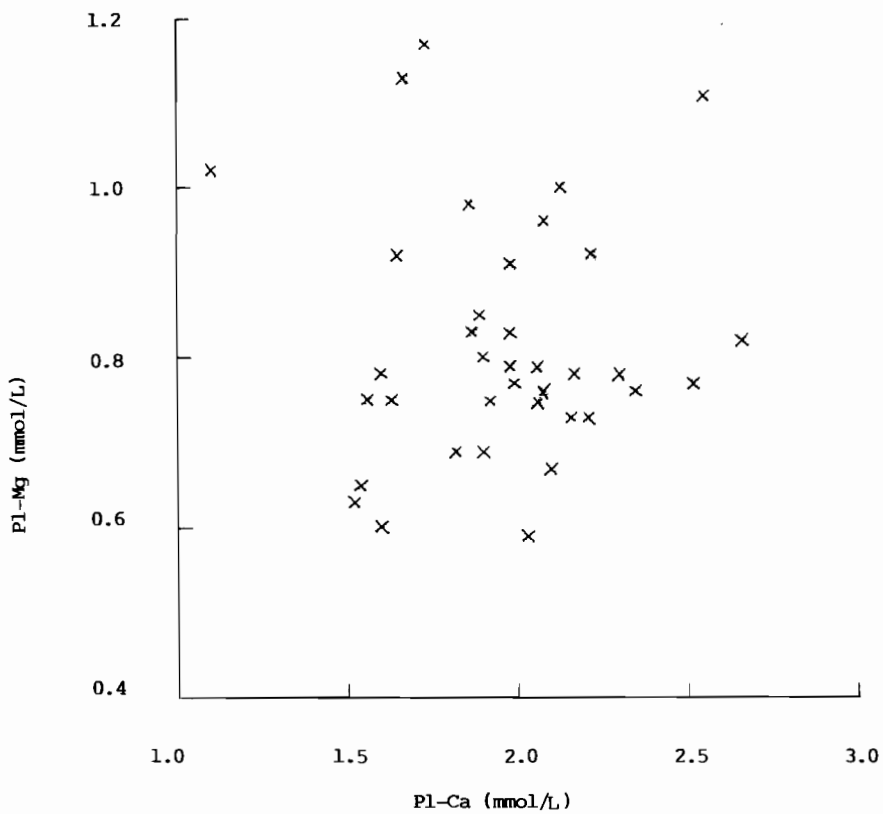

Fig. 1: Scattergram for Pl-Mg and Pl-Ca in newborns of diabetic mothers (cord blood, n = 37).

Discussion

Although many studies have dealt with the effects of pregnancy or diabetes mellitus on mineral metabolism, little attention has been paid to the combined effects of diabetes and pregnancy [14]. The placental filter constitutes an impassable barrier for maternal or fetal insulin [15, 16]. Moreover, neither parathyroid hormone (PTH) nor calcitonin can cross the placenta [4, 16–18]. In the normal fetus, the reaction to physiologic hypercalcemia involves a calcitonin increase and a PTH decrease, which are apparently favorable to skeletal growth [16, 18].

Our results for decreased Pl-Mg and Pl-

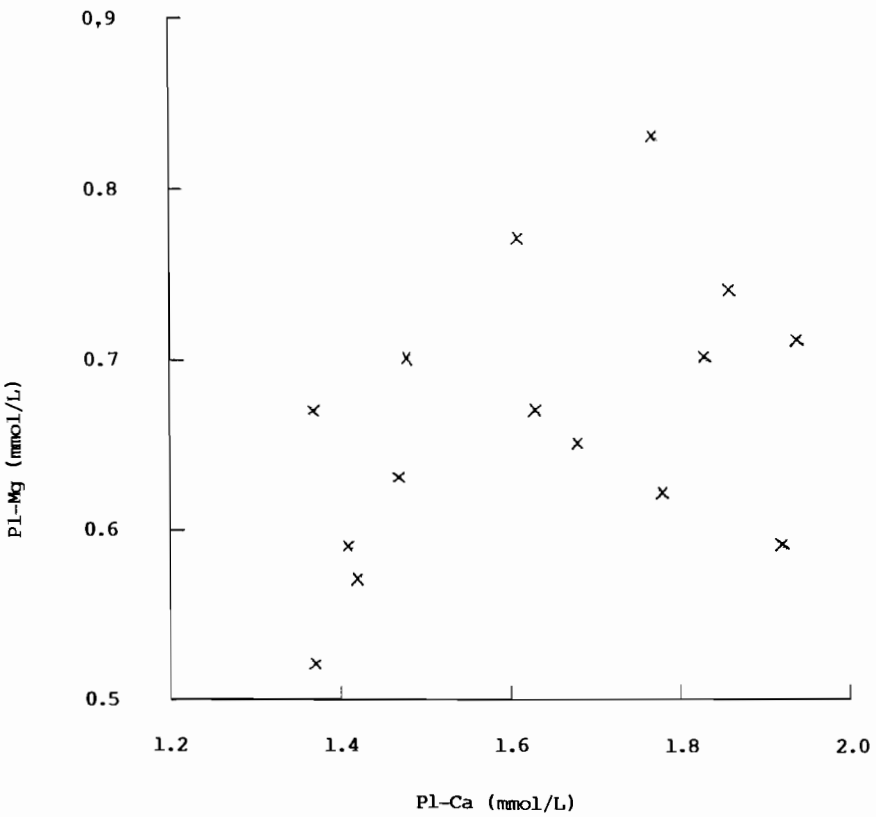

Fig. 2: Scattergram for Pl-Mg and Pl-Ca in diabetic mothers, n = 15.

Ca and increased Pl-P in cord blood from newborns of diabetic mothers as compared to control infants are in agreement with those of various authors [4, 17–22]. However, *Kuoppala* [7] found similar cord blood serum-P and -Mg concentrations in groups of newborns from diabetic and control mothers. It has been reported that the general Pl-Mg decrease in infants of diabetic mothers is related to the frequency of maternal Mg deficit and to neonatal hypocalcemia and hyperphosphatemia secondary to paradoxical functional hypoparathyroidism (PTH protein immaturity) [4, 17, 19, 21–23). Furthermore, mild hypomagnesemia, which does not improve at day 2, and Pl-Ca, which decreases until day 5, may be the best indicators that PTH remains low in these newborns [4]. Their hypocalcemia could reduce the number of centers of ossification [7, 20]. Moreover, our findings for reference infants indicate that the most significant regressors accounting for Pl-Mg were Pl-P followed by Pl-Ca, both of which were positively correlated ($P < 0.05$) with Pl-Mg. It would thus seem that mineral metabolism depends not only on complex, interdependent hormonal mechanisms but also on the external and internal maternal environment at the stressed period of delivery [17, 18, 23, 24].

The significant positive correlations between Pl-Mg results of newborns of diabetic mothers and those of their mothers, and between their respective Pl-Ca values, are not easy to explain. The fact that cord blood phosphate, magnesium and calcium concentrations are usually higher than maternal concentrations suggests that fetal homeostasis of these elements is at least partially independent of maternal factors [4, 25]. Fetal parathyroids are functional [4]. The higher fetal concentrations favor the notion of active transport mechanisms across the placenta [23, 25]. It has recently been demonstrated that maternofetal transfer of Mg, as well as of Ca is dependent on placental metabolism [25]. Moreover, the mechanism of Mg transport across the placenta may be independent of active Ca transport. However, the fact that maternal serum Mg concentrations have a considerable influence on fetal values [23] may account for the positive correlations obtained by us. These data, independently of the mechanism involved, support the view of *Spätling* et al. that Mg should be supplemented during pregnancy [26].

There has been little research into changes in Mg, Ca and P during the first days of life owing to difficulties in obtaining sufficient blood samples. The changes in these variables noted by *Tsang* et al. [19] and *Salle* et al. [27] in infants of diabetic mothers differ from our results and those reported by *Pitkin* [18] and *Nelson* et al. [28] for reference newborns.

Few studies have concerned Cu and Zn in newborns of diabetic mothers. Generally, in diabetic patients, Pl-Zn is decreased, whereas Pl-Cu is higher than in control subjects [2, 3]. Similarly, Pl-Zn is normally lower and Pl-Cu higher in normal pregnancy at term [5, 10, 29–33]. Results for serum Zn and Cu similar to ours have been found in reference infants [31, 32, 34]. As in our study, *Wibell* et al. [10] found no differences at birth in serum Zn concentration between newborns of diabetic mothers and reference newborns. In normal control newborns, changes comparable to those found by us during the first days of life in infants of diabetic mothers have been reported for serum Cu and Zn [35]. Furthermore, the Pl-Zn/Pl-Cu ratio in our study was higher (3.26) in cord blood from newborns of diabetic mothers than in reference newborns (2.87). A rise in this ratio is considered to be a risk factor in the pathogenesis of atherosclerosis, which can begin in childhood [3, 4, 8, 36]. Contrary to the results of *Yasodhara* et al. [33] and *Kapu* et al. [37], we did not find significant correlations between maternal and cord Pl-Cu or Pl-Zn.

To our knowledge, no previous studies have investigated Erc-Zn and Erc-Cu in newborns of diabetic mothers. In our study these variables remained at values quite significantly lower than

reference values during the first 5 days of life. The fact that Erc-Zn is primarily associated with the carbonic anhydrase metallo-enzyme (EC 1.4.2.1) suggests that the lower Erc-Zn values in infants of diabetic mothers correspond to lower concentrations of carbonic anhydrase [5, 8]. In erythrocytes, Zn increases the affinity of hemoglobin for oxygen and produces an „antisickling" effect on membrane, thus reducing hemolysis [38]. Copper intervenes in various enzymes, notably in the superoxide dismutase of erythrocytes (EC 1.15.1.1) [39]. Moreover, it is known that disturbances of Cu metabolism in newborns can cause anemia, leukopenia and even bone disorders with retardation in ossification [39]. It is of interest to note that Pl-Ca was positively correlated ($P < 0.001$) with Erc-Cu and Pl-Cu ($P < 0.05$) in the cord blood of our reference infants. The low Erc-Cu concentrations in newborns of diabetic mothers might be due to ceruloplasmin liver protein immaturity and/or increased Cu intestinal elimination in infants more afflicted with jaundice than were reference newborns.

It may be concluded that Pl-Mg, Pl-Ca, Erc-Cu and Erc-Zn in venous cord blood of newborns of diabetic mothers were significantly decreased, whereas Pl-P was significantly increased compared to reference infants. The variables permitting the best discrimination between the two groups of infants were Pl-Ca followed by Pl-P. Several factors may account for the significant variations observed in newborns of diabetic mothers during the first 5 days of life: magnesium deficit, protein immaturity, paradoxical functional hypoparathyroidism and increased intestinal copper elimination.

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