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Pyridoxine supplementation during pregnancy, lactation and the first months of life: A review of the literature.

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Abstract

Background: Vitamin B6 plays a crucial role in the physiologic development and function of the central nervous system. Pyridoxal phosphate, the activated form of vitamin B6, acts as a coenzyme in approximately 100 reactions of human metabolism.

Objective: The aim of this review is to evaluate the effect of vitamin B6 supplementation during pregnancy, lactation and the first 6 months of life on the fetus, newborn and infant with the aim of verifying the effects of pyridoxine supplementation on fetuses and neonates and whether it could positively influence fetal and neonatal outcomes.

Methods: A literature search was conducted using PubMed as the medical database source. We selected original research studies, systematic reviews, review articles and case reports. We selected only articles in the English language. No limit was imposed on the year of publication of the studies.

Results: We included 34 publications published between 1975 and 2015, 19 concerning pyridoxine supplementation during pregnancy, 15 concerning pyridoxine supplementation during lactation. We did not find any studies concerning pyridoxine supplementation directly to neonates.

Conclusion: The beneficial effects of pyridoxine supplementation for pregnant and breast-feeding women have been widely demonstrated. We are convinced that providing pyridoxine supplementation directly to neonates could have a favorable effect on their neurological development.

Keywords: Vitamin B6, Pyridoxal phosphate, Pyridoxine supplementation, Pregnancy, Lactation, Neonatal outcome.

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Background

Vitamin B6 is a water-soluble vitamin with a crucial role in the physiologic development and function of the central nervous system (CNS) in newborns and infants [1,2]. Gyorgy first identified the vitamin in 1934 [3]. Naturally occurring forms include pyridoxal, pyridoxine and pyridoxamine, with their respective phosphates; in the human body, they are all converted into pyridoxal phosphate (PLP), the activated form of vitamin B6 [4]. PLP acts as a coenzyme in approximately 100 reactions involved in carbohydrate, lipid and protein metabolism, mainly the catabolic lysine pathway, myelin formation, steroid hormone formation and heme and neurotransmitter metabolism, mainly in the developing brain, such as serotonin, norepinephrine and gamma-amino butyric acid [1,2,5,6]. PLP is also involved in the immunological response, acts as an antioxidant and has a neuroprotective effect on rat neuronal cultures, suggesting a possible utilization in hypoxic-ischemic brain damage [6]. PLP activity depends on the presence of other cofactors, such as flavin, riboflavin, folate and tetrahydrobiopterin [6].

The most reliable indicator of vitamin B6 status in blood is PLP concentration [6,7]. Vitamin B6 is well absorbed through the gastrointestinal tract and is eliminated by the kidneys [1,6].

Natural sources of vitamin B6 include meats, fish, poultry and vegetables, such as potatoes and legumes, but it is destroyed by heating [1,4]. The bioavailability of vitamin B6 is almost 75%. The principal forms of vitamin B6 content in vegetables are pyridoxine, pyridoxine phosphate and pyridoxine glucoside (which have reduced bioavailability), while the main forms in animal food sources are pyridoxal phosphate, localized mainly in muscle, and pyridoxamine phosphate in low quantities [6].

The most common way to administer pyridoxine supplementation is orally; alternative ways of administration are intravenous, intramuscular and subcutaneous [1]. The bioavailability of pyridoxine supplementation is more than 90% [8].

Pyridoxal enters into the tissues and crosses the blood-brain barrier through a phosphorylated process [6].

PLP also plays an important role in the development of the fetal CNS. PLP is actively transported through the placenta in both directions but mainly toward the fetus: fetal plasma concentration of PLP is higher than maternal plasma concentration of PLP (ratio 5:1) [6,9]. There are no differences in PLP concentrations between term and preterm infants [8].

Objective

The objective of this study is to evaluate vitamin B6 supplementation during pregnancy, lactation and the first 6 months of life and its effect on the fetus, newborn and infant. Primary outcome is to verify whether pyridoxine supplementation could have positive effects on fetus and neonates. Secondary outcome is to verify whether pyridoxine supplementation could positively influence fetal and neonatal neurological outcomes, considering the crucial role of pyridoxine in human metabolism.

Methods

We identified original research studies and review articles concerning the supplementation of vitamin B6 during pregnancy, lactation and the first months of life. The PubMed database was used for this search. The search terms used were as follows: vitamin B6, pyridoxine, pyridoxal, pyridoxamine, pyridoxine phosphate, pyridoxine supplementation during pregnancy, pyridoxine supplementation during lactation, vitamin B6 supplementation in newborns, neonatal pyridoxine supplementation and vitamin B6 status. We selected only articles in the English language. No limit was imposed on the year of publication of the studies. We did not consider studies concerning therapeutic pyridoxine use, such as in pyridoxine-dependent epilepsies (PDEs), or studies concerning patients with chronic diseases.

Results

We included 34 publications concerning pyridoxine supplementation during pregnancy and lactation, published between 1975 and 2015.

Concerning pyridoxine supplementation during pregnancy, we found 15 studies, 1 systematic review, 2 case reports and 1 review. Five studies examined the protective effects of pyridoxine on preventing congenital anomalies, and 2 studies examined the effect of pyridoxine on mothers during pregnancy. Six studies evaluated vitamin B6 supplementation during pregnancy and its effects on fetal and neonatal vitamin B6 status. One study reported the effect of an antenatal load of pyridoxine. Case reports indicated the teratogenic effects of high doses of pyridoxine supplementation during pregnancy. In contrast, 1 study reported a possible protective effect of maternal supplementation with high doses of pyridoxine. This review concerns the safety of pyridoxine supplementation.

Concerning pyridoxine supplementation during lactation, we found 15 studies. Two studies examined maternal and neonatal vitamin B6 status, 1 study examined the correlation between maternal supplementation and neonatal vitamin B6 status, and 2 studies evaluated vitamin B6 breast milk concentration. Six studies examined the correlation between neonatal vitamin B6 status and maternal vitamin B6 intake. Two studies investigated differences in the vitamin B6 concentrations of the breast milk of mothers of preterm and term infants. Two studies examined the correlation between the vitamin B6 intake of breast-fed infants and neonatal behavioral functioning.

We did not find any studies on the effects of pyridoxine supplementation on neonatal neurological outcomes or on pyridoxine supplementation directly to neonates.

Discussion

Vitamin B6 supplementation during pregnancy and lactation is a very widespread practice; almost all multivitamin preparations given during pregnancy contain pyridoxine. It has been demonstrated that pyridoxine supplementation reduces nausea and vomiting in pregnant women [10].

Pregnant women with celiac disease or hypertension, as well as women who use anticonvulsants, corticosteroids, or certain antibiotics (penicillamine, isoniazid, hydralazine and cycloserine) or who used oral contraceptives in the past could have asymptomatic pyridoxine deficits during pregnancy [11-14].

Blood PLP concentration indicates vitamin B6 status. There is no established reference range during the first 6 months [2]; ranges reported in the literature are 29-69 nmol/L on the first day of life and 23-51 nmol/L at 4 days of life [15], 25-78 nmol/L in the first 2 weeks of life [16], and 35-86 nmol/L at 6 weeks of life [17].

Vitamin B6 deficiency causes convulsions, depression, confusion, microcytic anemia and seborrheic dermatitis [7].

In animal models, severe maternal vitamin B6 deficiency could determine morphologic alterations and neurological problems, but no teratogenic effects have been demonstrated in humans [7].

Vitamin B6 Supplementation during Pregnancy

The recommended dietary allowance (RDA) of vitamin B6 during pregnancy is 1.9 mg daily [18]. During pregnancy, maternal vitamin B6 levels decrease, especially during the third trimester, but this decrease does not cause symptoms [1,7]. In contrast, fetal blood PLP concentration is higher than maternal blood PLP concentration during the second and third trimesters [7].

Several studies have demonstrated that pyridoxine supplementation during pregnancy has beneficial effects on the fetus, including a decreased risk of orofacial clefts, cardiovascular malformations, neural-tube defects, limb defects and urologic anomalies, as well as higher birth weights [5,19-23]. The usual therapeutic dose of pyridoxine does not have teratogenic effects [5].

It is not clear whether supplementation of high doses of pyridoxine could have teratogenic effects on fetuses; in the literature, two case reports described teratogenic effects [24,25]. Cohen and Benedich [26] reported a postnatal neurotoxic effect. In contrast, because of the physiological antagonism of glucocorticoid activity by PLP, McCarty [27] proposed that prenatal supplementation of high doses of pyridoxine could protect the fetus from an increased risk of hypertension, insulin resistance syndrome and coronary events due to an excess of glucocorticoid activity.

We found several studies concerning vitamin B6 supplementation during pregnancy and its effects on the vitamin B6 status of neonates.

In 1975, Clearly et al. [28] studied the effects of different dosages of daily vitamin B6 supplementation during pregnancy and evaluated maternal and fetal blood PLP levels; their results suggested that a daily vitamin B6 supplementation of more than 2 mg was necessary to maintain an adequate vitamin B6 status in mothers and, consequently, in fetuses.

In 1980, Ejderhamn and Hamfelt [29] demonstrated that infants whose mothers received vitamin B6 supplementation during pregnancy had a higher blood PLP concentration at 3 hours of life than infants whose mothers did not receive any supplementation and that vitamin B6 supplementation of 2-6 mg daily during pregnancy did not influence breast milk production.

In 1981, Schuster et al. [30] studied maternal vitamin B6 status and its correlation with infant status at birth; they found that infants born from mothers with lower vitamin B6 levels presented lower Apgar scores at birth.

In 1983, Temesvari et al. [31] studied the effects of antenatal supplementation of pyridoxine on the blood oxygen affinity and prolactin levels in newborns and their mothers. These researchers administered 100 mg of pyridoxine intramuscularly or orally to pregnant women at term who were not supplemented earlier and evaluated the *in vitro* oxygen affinity and prolactin levels in both maternal and newborn blood. These authors found that the blood oxygen affinity increased moderately in mothers and significantly in newborns after pyridoxine supplementation, but there were no modifications of prolactin blood levels in mothers and newborns and no modifications of daily breast milk production. On the basis of their results, these researchers hypothesized that maternal pyridoxine supplementation during labor could have positive effects on the postnatal adaptation of newborns by increasing blood oxygen transport.

In 1985, Reinken and Dockx [32] compared the vitamin B6 content in milk during the first 75 days after birth in 16 women delivering preterm and 24 women delivering at term; all the mothers were supplemented with 5 mg of vitamin B6 daily from the second trimester of pregnancy to birth. These authors found that the milk of women delivering preterm had significantly higher vitamin B6 content than the milk of the at-term group. These authors concluded that vitamin B6 supplementation during pregnancy was crucial. In our opinion, these results suggest that preterm infants need higher vitamin B6 supplementation than at-term infants.

In 1989, Hamfelt et al. [33] studied blood PLP levels in the first weeks of life; they found lower levels in the blood and milk of women who were not supplemented during pregnancy and a decrease in blood PLP levels of exclusively breast-fed infants during the first two weeks of life.

In 1999, Chang [34] studied the effects of pyridoxine supplementation during pregnancy on maternal and neonatal vitamin B6 status at birth and neonatal growth; he gave a daily supplementation with 0, 1, 2 or 3 mg of pyridoxine to 209 pregnant women and examined their newborns. He found that maternal and neonatal blood PLP concentrations correlated positively with maternal supplementation and that neonates whose mothers received 2 mg daily of pyridoxine presented better growth; thus, he concluded that a daily supplement of 2 mg pyridoxine was adequate.

In 2015 Salam et al. [1] published a systematic review concerning the effects of pyridoxine supplementation during pregnancy and labour on maternal and neonatal outcomes; the authors concluded that there were no enough evidences to detect clinical benefits of pyridoxine supplementation in pregnancy and labour.

We suggest that correct pyridoxine supplementation during pregnancy could have beneficial effects on fetal outcomes, mostly in fetuses with PDEs.

Vitamin B6 Supplementation during Lactation

Pyridoxine supplementation during breastfeeding is very important. The dietary reference intake of vitamin B6 for women during lactation is 2 mg daily [35]. The vitamin B6 concentration in human milk reflects maternal pyridoxine intake [2]. The forms of vitamin B6 in breast milk are pyridoxal phosphate and pyridoxal [6]. During the first days after birth, vitamin B6 levels in breast milk are low and increase during the subsequent weeks [7]. Numerous studies have demonstrated a strong correlation between maternal blood PLP and vitamin B6 content in breast milk.

Several studies have been conducted to evaluate sufficient vitamin B6 supplementation to maintain adequate vitamin B6 levels in breast milk.

In 1976, West and Kirksey [36] and in 1982, Reynolds et al. [37] demonstrated that maternal consumption of 2.5 mg of pyridoxine daily during lactation did not provide sufficient RDA of vitamin B6 for their infants.

In 1985, Udipi et al. [38] studied the vitamin B6 concentration of the milk of preterm and term mothers during the first month of lactation; their results showed lower levels of vitamin B6 in the milk of preterm women, suggesting a possible need for infant supplementation.

In 1985, Styslinger and Kirksey [39] evaluated the vitamin B6 concentration of the breast milk of women who did not receive vitamin B6 supplementation versus women who received 2.5, 10 or 20 mg of pyridoxine daily; they found that the vitamin B6 concentration of the breast milk of mothers who were not supplemented was lower than that of the breast milk of supplemented mothers. In the group of supplemented mothers, vitamin B6 concentration in breast milk increased proportionally with the augmentation of supplementation.

In 1986, Borschel et al. [40] compared the growth and blood PLP concentrations of healthy term breast-fed infants, whose mothers received 2.5 or 25 mg of pyridoxine supplementation, to the growth and blood PLP concentrations of healthy, term, formula-fed infants. There were no significant differences in growth, but the authors found significantly higher levels of blood PLP concentrations in the formula-fed group; they demonstrated that blood PLP levels correlated with vitamin B6 intake only in the first months of life and that these levels tended to decrease subsequently. The different blood PLP levels in breast-fed and formula-fed infants could be due to the different forms of vitamin B6 content in breast milk and formula: breast milk contains principally pyridoxal, while formula contain pyridoxine [2,6,41].

In 1990, Chang and Kirksey [42] demonstrated that a supplementation of 2.5-4 mg of pyridoxine daily was sufficient to maintain an adequate maternal vitamin B6 status and an adequate vitamin B6 breast milk concentration.

In 1990, McCullough et al. [43] demonstrated that infant behavior assessed by the Brazelton Neonatal Behavioral Assessment Scale was significantly correlated with maternal vitamin B6 status.

In 1992, Kang-Yoon et al. [44] published a study in which the authors gave 2 or 27 mg of pyridoxine to mothers during the first 28 days of lactation and gave 0.4 mg of pyridoxine daily to a subgroup of breast-fed infants whose mothers received 2 mg of pyridoxine daily. These authors found a direct correlation between the pyridoxine intake of mothers and infant pyridoxine status. These authors also found a lower vitamin B6 concentration in the milk of mothers of preterm infants than in the milk of mothers of term infants [45].

In 1996, Heiskanen et al. [46] studied the vitamin B6 status of mothers and their breast-fed infants, dosing blood PLP concentration at 2, 4, 6, 7.5, 9, 10, 11, 12 months after birth. Half of the mothers received pyridoxine supplementation during pregnancy, and all of them received 1 mg of pyridoxine daily during lactation. These authors found that infant vitamin B6 status was higher than maternal vitamin B6 status. In fact, infant status was independent of maternal status during the first 4 months and after 6 months of life, human milk alone could not be sufficient to maintain adequate vitamin B6 status in some infants.

In 2002, Chang and Kirksey [2] studied the effects of different levels of maternal vitamin B6 supplementation in breast-fed infants. These authors examined 47 healthy infants born at term whose mothers received 2.5, 4, 7.5 or 10 mg of vitamin B6 daily. These authors evaluated vitamin B6 concentrations in their breast milk at 1, 2, 3, 4, 5 and 6 months of life, cord blood PLP concentration at birth and maternal and infant blood PLP concentration at 1, 4 and 6 months of life. Their results showed that mothers who received supplementation of 2.5 mg of pyridoxine presented a lower concentration of pyridoxine in their breast milk than mothers who received higher dosages. Chang and Kirksey [2] also found that the vitamin B6 intake of the infants was significantly correlated with maternal supplementation even after the introduction of formula and weaning, but none of the infants received the daily RDA of vitamin B6 for the first 3 months. From 4 to 6 months, only the group of infants whose mothers received 10 mg of daily supplementation met the RDA of vitamin B6, but all the groups received the adequate intake (AI) for vitamin B6 in the first six months of life. These authors concluded that there was a need for a re-evaluation of the RDA of vitamin B6 for mothers during lactation. In the same study, neonatal blood PLP concentration was directly proportional to maternal supplementation, and it was significantly related to maternal PLP concentration. The authors did not find differences in growth, suggesting that vitamin B6 status did not influence growth in the first 6 months of life. A reduced gain in length has been reported in the literature for breast-fed infants with low vitamin B6 status from 6 to 9 months of life [47].

In 2002, Ooylan et al. [48] studied the effect of maternal vitamin B6 intake on vitamin B6 content in breast milk and the effect of vitamin B6 content in breast milk on infant neurobehavioral functioning using the Brazelton Neonatal Behavioral Assessment Scale. These authors found that women with higher vitamin B6 intake had significantly higher blood PLP levels, and infant neurobehavioral functioning was positively correlated with the vitamin B6 content in breast milk.

Vitamin B6 Supplementation during First Month of Life

The recommended dietary allowance (RDA) of vitamin B6 for the first 6 months of life is 0.3 mg daily (1989), while the AI is 0.1 mg daily [2,35]. In the literature, there are no studies on pyridoxine supplementation directly to neonates during first months of life. Further studies are needed to evaluate the possible effects of such supplementation.

Conclusion

The beneficial effects of pyridoxine supplementation for pregnant and breast-feeding women have been widely demonstrated. Considering that pyridoxine plays a crucial role in the development and functioning of the neonatal brain, we are convinced that providing pyridoxine supplementation directly to neonates could have a favorable effect on their neurological development. Further studies are needed to demonstrate our hypothesis.

Code of Ethics

The study conformed to the ethical guidelines of the 1975 Declaration of Helsinki as revised in 2000.

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