

VITAMIN D (Comment)**Breast milk**

Human milk contains relatively little vitamin D even when the mother is vitamin-replete, and the new born baby normally 'lives' off transplacentally acquired body stores for a period after birth. It is for the reason that some supplementation is widely recommended for both the mother and the baby during pregnancy and early infancy. Vitamin D is, nevertheless, toxic in excess, and the difference between a safe and a toxic dose is lower than for most other vitamins. The effect of low dose maternal supplementation (25 or 50 micrograms/day) only seems to have a very variable effect on the vitamin content of breast milk, but the breastfed babies of mothers taking 100 micrograms a day are generally very replete (Basile *et al.*, 2006). However, a pharmacological dose, of the magnitude sometimes given for hyperparathyroidism, could certainly produce dangerous hypercalcaemia in a breast fed baby. There could be few better examples of the motto at the front of this compendium – "all things are toxic; only the dose makes a thing not a poison" – a warning penned by Paracelsus some five hundred years ago.

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Rickets in infancy

Despite the ease with which it can be prevented, vitamin D deficiency still afflicts many children worldwide every year. Indeed there would seem to have been a resurgence of this problem in many countries with high living standards in the last twenty years. While rickets is the commonest presentation, infants may also present with hypocalcaemic symptoms. Tonic/clonic convulsions are often the first manifestation, and may appear at any time in the first six months of life. Heart failure is a rare but potentially fatal presentation (Maiya *et al.*, 2008). A proximal myopathy may cause delayed motor milestones and, in particular, delayed walking. Toddlers who have started to walk often present with bowed legs, and such children may also have swollen wrists and knees. An occasional child presents with a fracture because the bones have become thin and osteopenic.

While vitamin D deficiency is not, of course, the only cause of rickets (see for example the review article by Bajpai *et al.*, 2005), it is by far the most easily prevented and the most easily treated. Infants from certain ethnic groups are certainly at greater risk – black toddlers in the United States, middle eastern infants in Kuwait, south Asian and Afro-Caribbean infants in the UK. This is due to the fact that more ultraviolet sunlight is required to generate adequate vitamin D synthesis in dark skinned individuals (Holick, 2002). This can be a particular problem in northern latitudes (such as Canada, the UK and Scandinavia) where there is little ultraviolet radiation of the appropriate wavelength for many months of the year. However multiple reports have appeared from other countries, such as Saudi Arabia, India and Australia, where sunlight is plentiful. Here cultural practices (prolonged exclusive breast feeding compounded by forms of dress that limit the skin's exposure to light) seem the main aetiological factors.

Many countries have attempted to prevent such problems by ensuring that vulnerable groups receive dietary supplements of vitamin D during critical periods, such as pregnancy, lactation and infancy. It has long been held, both in Europe and in North America, that all children need at least 400 IU (10 micrograms) of vitamin D daily (Koo, *et al.*, 1993; Tsang, *et al.*, 1997) and this still remains the official view of the UK Department of Health. Women who are pregnant or breast feeding also need to ensure that their intake does not fall below this minimum. These recommendations have, however, been almost totally ignored for the last twenty years by most health professionals, as well as by the general public. Recommendations that Asian children in the UK should always be supplemented until they are five years old are also widely ignored, even though many are well known to have suboptimal levels at the age of two. Since a policy of daily supplementation seems hard to deliver thought should be given to offering an annual 150,000 IU autumn IM booster (Lawson and Thomas, 1999).

In fact, an intake of just 200 IU a day is probably all that is needed during infancy and childhood (Institute of Medicine, 1997), and there can be no doubt that sunlight has usually provided this in the past for most babies, even in the first few months of life. Doctors have, however, become increasingly aware that excessive exposure to ultraviolet light increases the risk of skin cancer, and there is some indirect epidemiological evidence to suggest that this risk may be more closely linked to early exposure than to

total exposure. While this remains a possibility, doubts will persist over the advisability of exposing young children to too much direct sunlight. Driven by these considerations the American Academy of Pediatrics has recently issued a "Clinical Report" reaffirming its view that *all* breast fed babies should receive supplemental vitamin D. Unfortunately, as the Academy note, this can only be achieved by using a multivitamin product at the moment because no commercial low-dose formulation exists that contains only vitamin D.

Much evidence links vitamin D deficiency in infancy to maternal vitamin D status. Fetal stores of vitamin D at birth are influenced by the mother's nutritional status, neonatal concentrations being 60-70% of maternal concentrations at birth, and inadequate fetal stores probably explain most of the children presenting with hypocalcaemic symptoms in the first six months of life. It is therefore important to target pregnant women, particularly from the ethnically vulnerable groups. Many different strategies have been proposed. Although a daily intake of 400 IU throughout pregnancy is often advocated, compliance is often poor (Brunvand *et al*, 1996) and this dose is inadequate in the absence of sunlight. A study of veiled Muslim women in Denmark concluded that even an intake of 600 IU a day was probably not enough to maintain 25-hydroxyvitamin D concentrations, and that 1000 IU a day might be more effective (Glerup, *et al.*, 2000). An intake of 25 micrograms (1000 IU) a day throughout the third trimester is certainly very effective (Brooke, *et al.*, 1980). Another strategy now widely adopted in France is to give a single large 100,000 or 150,000 IU intramuscular dose during the seventh month of pregnancy (Zeghoud, *et al.*, 1988).

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Concerns for the consequences of *sub-clinical* vitamin deficiency

Concern is starting to mount that unrecognized sub-clinical vitamin D deficiency during pregnancy and early childhood can have some unexpected long term consequences. An important longitudinal study has shown that children born to mothers who were sub-clinically vitamin D deficient during pregnancy developed less well-mineralised bones during the first 9 years of life (Javaid *et al.*, 2006). It is thought that routine vitamin D supplementation during the last trimester of pregnancy, particularly during the winter months, would almost certainly reduce the risk of these otherwise healthy children developing osteoporotic bone fractures in later life. This observational study clearly calls for replication in a formal controlled trial. A small study from Switzerland had already suggested that even the modest supplementation of breast fed babies in the first year of life (400 IU a day) improves bone mineral mass 7-9 years later (Zamora *et al.*, 1999).

A second concern is the belief that children who suffer sub-clinical vitamin D deficiency in early infancy seem to be at increased risk of developing type 1 diabetes, (a condition in which a poorly understood autoimmune process causes the progressive destruction of all the cells in the pancreas leaving the organ

unable to make insulin). This form of diabetes often manifests itself during childhood and has usually become apparent before the patient is 30. It is commonest in people of European descent, seems to be becoming progressively more common, and already affects two million people in Europe and North America. There are suggestions that by 2010 the condition will be 40% more common than it was a decade ago. Four observational studies and a cohort study have all now suggested that the risk is lower in children given supplemental vitamin D during infancy, and there is also some suggestion of a dose-response effect (Zipitis and Akobeng, 2008). Low levels are common in American children and commoner in children who have adverse cardiovascular risk factors (Kumar *et al.*, 2009; Reis *et al.*, 2009). Low serum vitamin D levels are strongly associated with hypertension, hyperglycaemia, and metabolic syndrome, independent of adiposity. Whether these things are causally linked remains to be established but the associations are suggestive.

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Babies with severe renal disease

Babies with severe renal disease often become hypocalcaemic. Damage to the proximal tubule can sometimes cause this, since this is the only body tissue capable of converting the 'provitamins' D₂ and D₃ into 1 α -hydroxycholecalciferol (the active hydroxylated vitamin). However, hypocalcaemia is often simply due to reduced renal phosphate clearance. This causes hyperphosphataemia, and this, in turn, causes the ionised calcium concentration to fall, both because 1- α -hydroxylase enzyme activity is inhibited and because of mass-action. Reducing the phosphate intake, by using a modified milk such as Kindergen (marketed by SHS International Ltd, Liverpool, UK) may be enough to correct this. Adding calcium to the diet may also help by increasing phosphate binding in the gut, thereby reducing phosphate absorption. In the young baby this can be done by adding small quantities of calcium carbonate to the diet. Give the family a 100 mg/ml suspension of calcium carbonate, instruct them to give the baby 30 mg/kg of this mixed in a whole day's feeds, and monitor the response.

Only if the plasma calcium concentration remains low even after the plasma phosphate concentration has been brought down to the lower end of the normal [normal range 1.5 – 2.9 mmol/l], is it usually necessary to start treatment with 20 nanograms/kg of alphacalcidol by mouth once a day. The dose given is then increased gradually until the ionised calcium concentration is in the upper half of the normal range [1.18 to 1.38 mmol/l in late infancy]. Such treatment should *not* be started while the plasma phosphate concentration is still high, because soft tissue structures soon start to calcify when the plasma calcium and plasma phosphate levels are both simultaneously high. The renal medulla is often the first tissue affected. Marked arterial calcification can also occur. When long term supplementation is necessary the alphacalcidol dose needs to be adjusted periodically so as to keep the parathyroid hormone concentration normal, or close to normal.

Note that alphacalcidol cannot be diluted and that the smallest measurable dose is 100 nanograms. If a small dose than this proves necessary the best solution is to give the drug less than once a day.

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Toxicity

An accidental overdose of alphacalcidol can be very dangerous, causing vomiting, lethargy and severe hypercalcaemia. The use of a diuretic such as furosemide, together with a high IV fluid intake, can help to bring the serum calcium level down, and minimise the risk of permanent renal damage. Treatment with the oral bisphosphonate, alendronic acid (5 or even 10 mg once a day), may also speed recovery.

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Other recent reports of vitamin D deficiency in infancy

Reports of children developing rickets during infancy while being breast fed by asymptomatic but vitamin-deficient mothers continue to appear with monotonous regularity from many different parts of the world. We seem to live in a schizophrenic civilisation. One half of the population has come to believe that taking a few vitamin pills is capable of curing or preventing a host of ills. The other half seems to believe that,

since breast milk is best for babies, it cannot be right, proper or necessary to offer any baby so fed any further dietary supplement. The fact that it is almost impossible to find a commercial product that contains an appropriate dose of vitamin D for daily use that does not also offer several other totally unnecessary vitamin supplements, only serves to make the education of the general public still harder. There can be few better examples of the way the major drug companies put their own interests ahead of those of the general public. This totally unchecked commercial marketing trick simply serves to further reinforce the unfounded belief that multiple vitamin supplements are of benefit for a whole range of conditions in adult life as well as in infancy. Those who discovered the anti-rachitic powers of vitamin D eighty years ago would be amazed (and saddened) to see how little importance the average midwife, obstetrician or paediatrician places on the prevention of this condition.

For a whole series of reports, not only from countries in Europe where sunshine is limited, but also in tropical and sub-tropical countries, see the following papers. Problems have been reported both in dark skinned and in light skinned babies, and the number of reports seems to have grown quite rapidly in the last ten years. Despite this nothing has yet been done in most countries to reduce the number of women who end up starting to breast feed after delivery when they themselves remain sub-clinically vitamin deficient because no attention was ever paid to this issue during pregnancy. The current advice of the UK's National Institute of Clinical Excellence, that "....(pregnant) women may choose to take 10 micrograms of vitamin D per day, as found in the Healthy Start multivitamin supplement", is not particularly helpful. Neither has anything been done to make the general public aware of the value of making sure that all breast fed babies receive a regular small daily dose of vitamin D of a magnitude similar to that offered to every artificially fed baby. Nor has anything been done to coerce any of the large multinational drug companies into providing a simple, inexpensive, low dose daily supplement that does not contain a range of other unnecessary supplements.

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SINGLE DOSE PROPHYLAXIS IN PREGNANCY

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SINGLE DOSE SUPPLEMENTATION (“STOSSTHERAPY”) FOR YOUNG CHILDREN

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VITAMIN D DEFICIENT HEALTH FOODS

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