Vitamin A in pregnancy and lactation

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The consequences of variations in the supply of vitamin A during pregnancy and lactation, and the means by which vitamin A is transported from mother to foetus and to suckling offspring are summarized, followed by an account of some observations on a rural West African community, with a comment on their possible implications for human requirements.

Effects of deficiency on reproductive performance during pregnancy

Severe deficiency of vitamin A causes infertility, or impaired reproduction, in all vertebrate species which have been studied (Moore, 1957). The early studies on this impairment indicated that although the oestrous cycle is disrupted, and the vagina becomes permanently keratinized, the most characteristic results of deficiency are foetal resorption, stillbirths, and congenital malformations, rather than ovarian dysfunction or failure of fertilization or implantation. The complications of inanition, decreased resistance to infection, and other nonspecific effects of vitamin A deficiency made these observations difficult to interpret, until it was shown that retinoic acid would correct the systemic abnormalities, but failed to support vision and reproduction. In retinol deficient, retinoic acid-fed rats and guinea-pigs, the oestrous cycle and conception seemed normal, but the foetuses were resorbed (Thompson *et al.* 1964; Howell *et al.* 1967). The earliest abnormality was necrosis of the junctional zone of the placenta (Howell *et al.* 1964). Possible defects in steroid hormone production have been investigated, following the observations that in the absence of retinoic acid the reproductive performance of vitamin A deficient female rabbits was improved by progesterone administration (Hays & Kendall, 1956), and that conversion of pregnenolone to progesterone was depressed in retinol deficient, retinoic acid-fed rats (Juneja *et al.* 1966). However, neither oestrone nor progesterone overcame the defect in reproduction in retinoic acid-fed female rats (Coward *et al.* 1966; Calaustro & Lichton, 1968; Juneja *et al.* 1969). Juneja *et al.* (1969) found that the injection of pregnenolone or of 17-β-oestradiol in retinoic acid-fed rats reduced the resorption of foetuses, but could not support survival of the pups, or lactation in the dams. Ganguly *et al.* (1971*a*, *b*) observed reduced rates of ovarian secretion of progesterone, 20-α-hydroxypregn-4-en-3-one and pregnenolone in pregnant rats maintained on retinoic acid. Abnormalities in the vaginal cell cycle and ovarian function have more recently been observed in retinoic acid-fed rats (Sarada *et al.* 1977). Thus retinol deprivation probably can cause a disturbance of steroid hormone production, but the extent to which this is responsible for the overall impairment in reproductive capacity is not entirely clear.

When pregnancy is allowed to proceed to term in animals which are receiving marginal amounts of vitamin A, just sufficient to prevent total resorption of the foetuses, a high incidence of congenital malformations is observed. This has been shown in rats, rabbits, cows and pigs, and the nature of the defects depends on the timing and duration of the deficiency (Wilson *et al.* 1953; Palludan, 1966). In a study on hypovitaminosis A in eight pregnant Rhesus monkeys (O'Toole *et al.* 1974), abortions and xerophthalmia at birth were observed, but congenital malformations were not, and it was proposed that primate embryos may be less susceptible to injury by vitamin A deficiency than those of other mammals. A few instances of congenital malformations possibly attributable to vitamin A deficiency have been reported in human subjects (Sarma, 1959; Lambda & Sood, 1968), but there is little conclusive evidence that uncomplicated vitamin A deficiency can be teratogenic in humans.

Teratogenic effects of hypervitaminosis A

Although the foetus is to some extent protected against the effects of excessive maternal intakes of vitamin A by homoeostatic mechanisms operating on circulating levels of retinol in the mother, there is, nevertheless, abundant evidence that excessive intakes by the mother can result in damage to the foetus, and especially in teratogenic effects during the critical periods of organ and limb development. This was first observed by Cohlan (1954) who produced abnormalities of the skull and brain in 54% of the offspring of maternal rats who were given 10 000 μg vitamin A from the second, third or fourth day to the sixteenth day of pregnancy. The nature of the abnormality depended on the gestational age at the time of administration (Giroud & Martinet, 1955; Giroud, 1960) and frequently took the form of anencephaly, cleft palate, anophthalmia, spina bifida, or syndactyly. Large doses of vitamin A on days 17–18 of gestation have been found to produce abnormal behaviour in the offspring without gross malformations (Hutchings & Gaston, 1974). Malformations have also been produced by excessive vitamin A intake in the guinea-pig, rabbit, hamster, mouse and pig, although there are clear differences in susceptibility between species and between variants of the same species in the response to high doses (Lorente & Miller, 1977; Seller *et al.* 1979). While there is good reason to believe that excessive vitamin A intakes may cause congenital defects in humans, and that the ingestion of large amounts during pregnancy is therefore inadvisable, there is little direct evidence or information to indicate the upper limit of safety. The observation (Gal *et al.* 1972) that maternal serum levels were higher, post-partum, in a group of mothers of infants with central nervous system defects than in those with normal babies is intriguing, but a causal relationship cannot necessarily be inferred.

Transfer of vitamin A from maternal stores to the foetus

In the rat, the foetal liver accumulates a small but remarkably constant amount of vitamin A during gestation, despite wide variations in maternal intake and liver

stores (Dann, 1932, 1934; Baumann *et al.* 1934; Henry *et al.* 1949; Moore, 1971). Takahashi *et al.* (1975) found that the concentration of vitamin A in the liver of neonates varied only 1·4-fold, over a 100-fold range of maternal liver concentration, corresponding to a 10-fold range of maternal intakes. At very low maternal intakes, however, the liver vitamin A concentration in the neonates was substantially reduced. The same group (Takahashi *et al.* 1977) found that the accumulation of vitamin A in the total conceptus followed a complex pattern. During the early stages (days 7–9) the vitamin accumulated to a high concentration, presumably in the placenta. From day 9 to 11 the concentration fell abruptly to less than 20% of that at the initial peak, and during days 11–14 both vitamin A and retinol-binding protein (RBP) accumulated in parallel, probably by transport of both components from the mother to the foetus. During days 16–20 the foetal liver started to synthesize RBP and to accumulate vitamin A, and foetal stores increased rapidly.

In cows, sheep, goats, dogs and cats, the newborn have liver vitamin A stores which are much smaller than those of the mother (Moore, 1957). In cows and pigs, large doses of vitamin A supplied to the mother increased the extent of placental transfer to a moderate extent. Large doses of carotene, in contrast, were entirely without effect on foetal vitamin A stores, and very little carotene *per se* was transferred to the foetal plasma.

These studies are consistent with the idea that the supply to the foetus is mainly from the retinol–RBP complex in maternal blood, which is buffered against considerable variations in maternal intake and is relatively insensitive to variations in maternal stores, except when they fall to very low levels.

There is a growing body of evidence for physiological inter-relationships between zinc and vitamin A, and three recent studies on rats have examined this question specifically in relation to foetal and neonatal development. In two of these, evidence was obtained for an interaction between Zn deficiency and the utilization of vitamin A. Duncan & Hurley (1978) showed an effect of Zn status on plasma vitamin A levels in both mothers and foetuses, and an interaction between the two nutrients in terms of number of implantations and the proportion of malformed foetuses. Huber & Gershoff (1975) found that the activity of alcohol dehydrogenase, especially in the retina, was diminished in the weanling pups of Zn deficient animals, thus implying a possible reduction in the conversion of retinol to retinal. However, no effect of Zn deficiency was observed by Apgar (1977) on the mobilization of maternal vitamin A stores for transfer to the foetal liver.

Measurements of human foetal liver vitamin A levels at autopsy have produced a rather wide range of values. The early studies were summarized by Moore (1957). Gal *et al.* (1972) found a range of values from less than 10 to more than 150 μg/g in livers of British infants near term. A wide range was also observed by Montreewasuwat & Olson (1979) in Thailand, although in this study, and that of Iyengar & Apte (1972) on foetuses from poorly nourished Indian women, there were few values above 50 μg/g, and mean values were of the order of 20 μg/g. Although foetal levels are generally lower than those of adults, it is difficult to be

certain, at present, about the quantitative relationship between maternal status and intake and foetal liver levels in humans, and whether they are as tightly controlled as they are in the rat. An early study by Toverud & Ender (1938) indicated that human foetal levels may be quite sensitive to variations in maternal intake, over the physiological range.

Human cord plasma retinol levels usually tend to be lower than the corresponding maternal plasma levels (Lund & Kimble, 1943*a*; Lewis *et al.* 1947; Venkatachalam *et al.* 1962), except when maternal levels are very low, when the relationship may be reversed (Lund & Kimble, 1943*a*; McLaren & Ward, 1962; Thomson *et al.* 1964). Vahlquist *et al.* (1975) found that RBP and thyroxine-binding prealbumin levels at birth, in a presumably well-nourished population, are about half the adult level. In two recent American studies (Brandt *et al.* 1978; Shenai *et al.* 1981), preterm infants had lower plasma retinol levels at birth than term infants. However, babies who were of low birth-weight but not premature had plasma retinol levels similar to those of normal birth-weight (Baker *et al.* 1977).

Lewis *et al.* (1947) found that 3000 μg vitamin A, or the equivalent amount of carotene, given daily during the final months of pregnancy, had no effect on plasma retinol levels in the neonate. Likewise, Byrn & Eastman (1943) and Neuwiler (1943) found that single large doses (up to 60 000 μg) given to the mother shortly before parturition did not increase cord plasma retinol levels. Venkatachalam *et al.* (1962) gave 9000 μg vitamin A/d throughout the last trimester of pregnancy to twelve malnourished Indian women who apparently had a very low intake from dietary sources, and observed significantly higher cord levels in them than in unsupplemented controls; it seems likely that their stores were severely depleted in the absence of supplementation.

Maternal status during human pregnancy

A number of studies have described night blindness, or impaired dark adaptation, in pregnant women receiving a diet which was likely to be inadequate in its vitamin A content. Most of the relevant studies have been summarized by Rodriguez & Irwin (1972); the impairment has usually been observed in the latter stages of pregnancy, and several studies have reported a spontaneous and rapid resolution almost immediately after parturition.

A decrease in plasma retinol levels during the course of pregnancy, or an increase post-partum, has been recorded in a large number of studies (Abt *et al.* 1942; Bodansky *et al.* 1943; Lund & Kimble, 1943*b*; Hoch & Marrack, 1948; Darby *et al.* 1953; von Lübke & Finkbeiner, 1958; Pulliam *et al.* 1962; Venkatachalam *et al.* 1962; McGanity *et al.* 1969; Basu & Arulanantham, 1973; Morse *et al.* 1975; Edozien *et al.* 1976). Only three studies failed to conform to this pattern (Al-Nagdy *et al.* 1971; Garcia *et al.* 1974; Gal & Parkinson, 1974). Although the concentration of vitamin E and other lipid-soluble components of plasma is increased during pregnancy (Knopp *et al.* 1978; Sauberlich, 1978), the control of vitamin A levels in plasma clearly differs from these by virtue of its association

with RBP and thyroxine-binding prealbumin. Since the decrease in vitamin A level parallels the decrease in serum albumin level which is observed during pregnancy (Hytten & Leitch, 1971), both albumin and RBP production may be controlled in the same way. Thus a moderate reduction in circulating retinol levels during pregnancy does not necessarily signify a depletion of body stores of vitamin A, and the spontaneous disappearance of the dark adaptation defect soon after parturition suggests a physiological adjustment at term, which allows more of the retinol–RBP complex to be released into the circulation.

Transfer from maternal stores to milk

Henry *et al.* (1949) studied the transfer of vitamin A from the mother to the suckling offspring in rats: they observed that large variations in maternal intake affected milk levels, and the transfer of vitamin A to the young, to a greater extent than variations in the size of maternal liver reserves. However, although the transfer rate may be independent of the size of the maternal reserve over a wide range, the liver reserves are usually the major contributor to the milk and the offspring. This was demonstrated in cows by Branstetter *et al.* (1973) and by Tomlinson *et al.* (1974), who also obtained evidence that retinol is transferred from the blood to the milk in preference to retinyl esters. Most of the retinol is re-esterified in the mammary gland and occurs as retinyl esters in the milk (Ganguly *et al.* 1947; Parrish *et al.* 1947). Vahlquist & Nilsson (1979) studied the transfer of vitamin A to the milk of rhesus monkeys and concluded that, unless their vitamin A intake was very high, 80–90% of the vitamin in their milk was derived from the circulating retinol–RBP complex, the remaining 10–20% being transferred from lipoprotein complexes of vitamin A or its esters. Ross (1982) demonstrated retinol esterification by isolated mammary gland microsomes from lactating rats, and provided further evidence that the retinyl esters in milk are derived from non-esterified retinol in the blood. Thus the transfer from the circulating retinol–RBP complex, in both the placenta and the mammary gland, must involve surface receptors for RBP which have not yet been studied.

Swanson *et al.* (1968) found that the rate of loss of liver vitamin A by milk cows on a depletion diet was about the same as that found by Hayes *et al.* (1968) for steers, and that there was no difference in depletion rates between high- and low-yielding cows. Thus the drain on liver stores through milk secretion may be lower than predicted from the amount secreted in the milk, perhaps through more efficient utilization or conservation.

The levels both of vitamin A and of carotenoids are very substantially higher in colostrum and early milk than those in mature milk in all species studied. Colostrum is essential for survival and normal development of the calf and, whereas plasma retinol levels were only 3·4 μg/100 ml before suckling, they rose to 15 μg/100 ml after the first day's suckling (Moore & Berry, 1947). In humans, the vitamin A concentration in colostrum is two- to five-fold higher than that in mature milk (Lesher *et al.* 1945; von Lübke & Finkbeiner, 1958; Kon & Mawson,

1950) and for carotenoids there is at least a five-fold difference. The carotenoid pigments present in human milk are, however, a relatively poor source of vitamin A: Thompson *et al.* (1942) showed that α- and β-carotene together contributed only 23% of the total pigment, with xanthophyll contributing 47%, lycopene 9% and unidentified pigments 21%.

Breast milk vitamin A concentrations, and their response to vitamin A supplementation, in human populations

Relatively few studies have compared breast milk vitamin A levels with intake of retinol or retinol equivalents by lactating women, or have compared directly the breast milk concentrations in well-nourished and poorly-nourished communities. It is therefore not easy to obtain a clear picture of the relationship between intake and breast milk vitamin A levels. Since all but the most recent studies have been reviewed by Rodriguez & Irwin (1972), only a brief summary will be given here.

During World War II, a detailed study of breast milk composition was carried out by Kon & Mawson (1950) in the UK. One of the populations studied lived in a poor area of London (Shoreditch) and their mean intake of retinol equivalents, from contemporary surveys, was about 850–950 μg/d. The other was a relatively prosperous community in Reading, whose intake was probably higher, but unfortunately is not recorded. Per unit volume of milk, the community in Reading had a higher vitamin A level than the community in Shoreditch (460 μg/l compared with 380 μg/l respectively), but when expressed per g fat, the level was identical in the two communities. The authors have clearly demonstrated that there exists a complex interrelationship between vitamin A content, total fat content and milk yield, and it is likely that at least part of the difference between communities that is apparent from other studies may be attributable to differences in fat content.

A recent study of mature breast milk from lactating women in five towns in England and Wales (Department of Health and Social Security, 1977) has found a mean vitamin A content of 600 μg/l, which is very similar to the level found by Macy's group (Kaucher *et al.* 1945; Lesher *et al.* 1945) in the breast milk of American women, whose mean intake was about 2 500 μg retinol equivalents/d.

Gebre-Medhin *et al.* (1976) compared breast milk vitamin A levels between Swedish mothers, whose intake of retinol equivalents was considered 'ample' but is not recorded, and those of two groups of Ethiopian women, one of whom was considered to have a poor diet, relatively deficient in vitamin A, although the mean intakes observed (Gebre-Medhin & Gobezie, 1975) were in the region of 800 μg/d. Over the same period of lactation (0·5–6·5 months post-partum), the Swedish mothers' milk contained, on average, 467 μg retinol/l, whereas that of the poorer group of Ethiopians contained significantly less: 298 μg/l. The difference in breast milk levels was matched by a comparable difference in plasma RBP levels. In addition, the poorer group of Ethiopian subjects had more free, non-esterified retinol in their milk than the Swedish subjects. Intriguingly, Fredrikzon *et al.*

(1978) have observed that the milk of primates, including man, contains a latent lipase which can be activated by bile salts in the duodenum, and which may assist the hydrolysis of retinyl esters in the intestine of the infant. This could be of particular importance for infants with low endogenous lipase activity, since retinyl esters must be hydrolysed before they can be absorbed.

Breast milk vitamin A levels of 200 μg/l or less have been recorded in poorly nourished communities, where xerophthalmia is common among children (Meulemans & de Haas, 1936; Gopalan, 1958; Belavady & Gopalan, 1959; Venkatachalam *et al.* 1962). Butte & Calloway (1981) observed mean retinol levels of 329 μg/l in Navajo women whose median intake was calculated as 750 μg/d.

Studies of the response of breast milk vitamin A to vitamin A supplements have, for the most part, been confined to relatively short-term supplementation, usually with large doses of vitamin A, and there are not many studies on subjects whose body stores were likely to have been low at the start of supplementation. Supplements of up to 3000 μg/d given to nine malnourished Indian women for periods of 1·5 to 9 months, failed to produce a consistent increase in their breast milk vitamin A levels (Belavady & Gopalan, 1960). Kon & Mawson (1950) likewise were unable to detect an effect of a supplement providing 900–3600 μg vitamin A for 1 week–3 months during pregnancy, but were able to produce an increase of 40–70% in the vitamin A concentration in the fat of breast milk of women who were given 7200 μg vitamin A/d for 9 d immediately following parturition.

From the studies described above, it is clear that maternal deficiency during pregnancy and lactation in human subjects can give rise to impaired function; in particular, abnormal dark adaptation responses during pregnancy and a reduction in breast milk vitamin A concentration. However, further information is still needed on the quantitative relationship between these impairments and maternal intake of vitamin A and its precursors. In particular, it is not clear whether a prolonged period of intake approaching the recommended dietary allowance (RDA) in a population whose intakes are usually much lower, confers any measurable advantage. The following preliminary account of studies currently in progress in a West African rural community describes an approach to these questions.

Observations on the vitamin A status of pregnant and lactating women in a West African rural community

Intensive studies are currently being undertaken of a subsistence farming community in the village of Keneba, The Gambia, in order to clarify the role of nutritional status, with respect to a variety of nutrients, on maternal progress during pregnancy and lactation, and on the factors which affect the growth, and other aspects of health, of the weanling child. Clear evidence of an energy deficit, especially during the rainy season, has been obtained (Paul *et al.* 1979; Prentice *et al.* 1981); riboflavin deficiency is present, with clinical signs appearing during the rainy season (Bates *et al.* 1981); and vitamin C intakes and blood levels are extremely low during the latter part of the rains and the early part of the dry season (Bates *et al.* 1982).

A survey relating to vitamin A in neighbouring parts of the Sahel region of West Africa (Le Francois *et al.* 1980), has indicated that there are large differences in intakes of vitamin A precursors between different regions. Thus, in two villages in the northern part of Senegal, the mean intake was estimated to be only 40% of the RDA (World Health Organization, 1967), whereas in the southern region of Casamance, where red palm oil is plentifully available, intakes as high as 387% of the RDA were encountered.

In Keneba, palm oil is not freely available, since it is not produced in the immediate locality, and it is too expensive for the villagers to purchase in substantial amounts. Analysis of typical palm oil-containing sauces prepared in the village revealed a mean carotene content of about 50 μg/g. The other major contributions to carotene intake are from mangoes, available at the end of the dry season in May and June, which were found to contain on average 16 μg/g, and from leaf sauces, used during the rainy season, which contained on average 15 μg/g. Smaller amounts of carotene were derived from oranges, pumpkins and from groundnut sauces containing tomatoes and peppers.

Fig. 1 shows the estimated mean daily intake of retinol equivalents from home foods by lactating women in Keneba for the period, May 1978–May 1980 (A. A. Paul and E. Robin, personal communication).The mean intake over the whole period was 427 μg/d, nearly all of which was derived fom carotene; the amount of preformed vitamin A in the diet being extremely small, since meat, dairy products

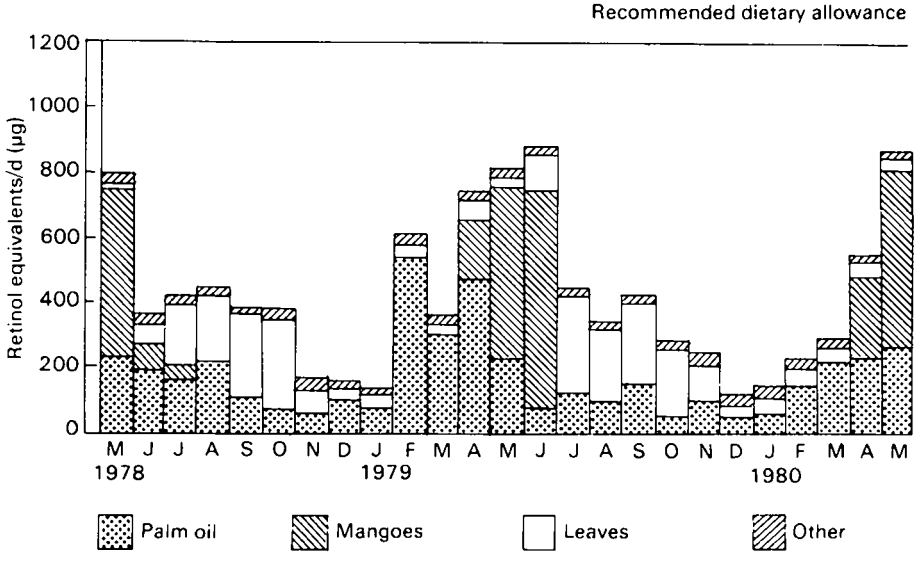

Fig. 1. Daily intake of retinol equivalents by Gambian women during lactation. Over the 2-year period, food intakes were measured for 1 d every week in a total of 130 subjects, of mean age 28·2 years and mean parity 5·0 at the outset.

For further information about the subjects and dietary assessment methods, see Prentice *et al.* 1980.

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and fatty fish are rarely available to the villagers. Thus intake is only 35% of the RDA for lactating women (World Health Organization, 1967; Department of Health and Social Security, 1979). Since most of the mothers in Keneba breast-feed their infants for 18 months or more, producing on average 600 ml milk/d throughout this period (Prentice *et al.* 1980), and since they usually become pregnant again as soon as each child is weaned, they have little opportunity to replenish depleted body stores between pregnancies. The mean intake of retinol equivalents by the pregnant women, 462 μg/d, was 62% of the RDA.

Parallel observations carried out on pregnant and lactating Caucasian women living in Cambridge, England revealed, as expected, a much higher intake of retinol equivalents, approximately 66% of which was derived from preformed vitamin A. Sixty-two subjects studied during pregnancy had a mean intake of 1849 μg/d (median, 1603 μg/d); forty-seven studied during lactation had a mean intake of 1855 μg/d (median, 1628 μg/d): (A. A. Paul and A. E. Black, personal communication).

From May 1979 onwards, a food supplement was offered to all the lactating mothers in Keneba, consisting of groundnut-based biscuits and a vitamin-fortified tea drink (Prentice *et al.* 1980). The amount consumed by each mother was recorded every day, and the mean intake of retinol from the supplement was calculated to be 1250 μg/d, all as preformed vitamin A. Thus the mean intake of retinol equivalents in the supplemented subjects should have fulfilled the RDA throughout the year, including those months when the intake from home foods was lowest.

Blood samples were obtained from each subject every 6 weeks during pregnancy, then within a few days post-partum and at 6 weeks, 12 weeks and every 3 months thereafter during lactation (Prentice *et al.* 1980). Fig. 2 shows the mean plasma retinol concentrations observed at successive stages of pregnancy, and for the pre-supplement and post-supplement groups separately, at successive stages of lactation. The significant downward trend ($P<0.01$) seen during the course of pregnancy is similar to that recorded in previous studies. There was also an unexpected downward trend during the course of lactation both in the pre-supplement and in the post-supplement groups ($P<0.01$), but the difference between these two groups was not significant at $P<0.05$, and there was no progressive increase with time in plasma retinol levels of the subjects who were receiving the supplement. When plasma samples from thirty-one supplemented lactating subjects were compared with samples from sixty unsupplemented lactating subjects from neighbouring villages, 16 months after the introduction of the supplement in Keneba, no significant difference in retinol levels was observed. The plasma retinol levels found in the Cambridge mothers were, however, substantially higher than those found for the Gambian mothers, during both pregnancy and lactation.

To test further the hypothesis that marginal vitamin A deficiency might exist in the unsupplemented Gambian mothers, especially during late pregnancy, studies of

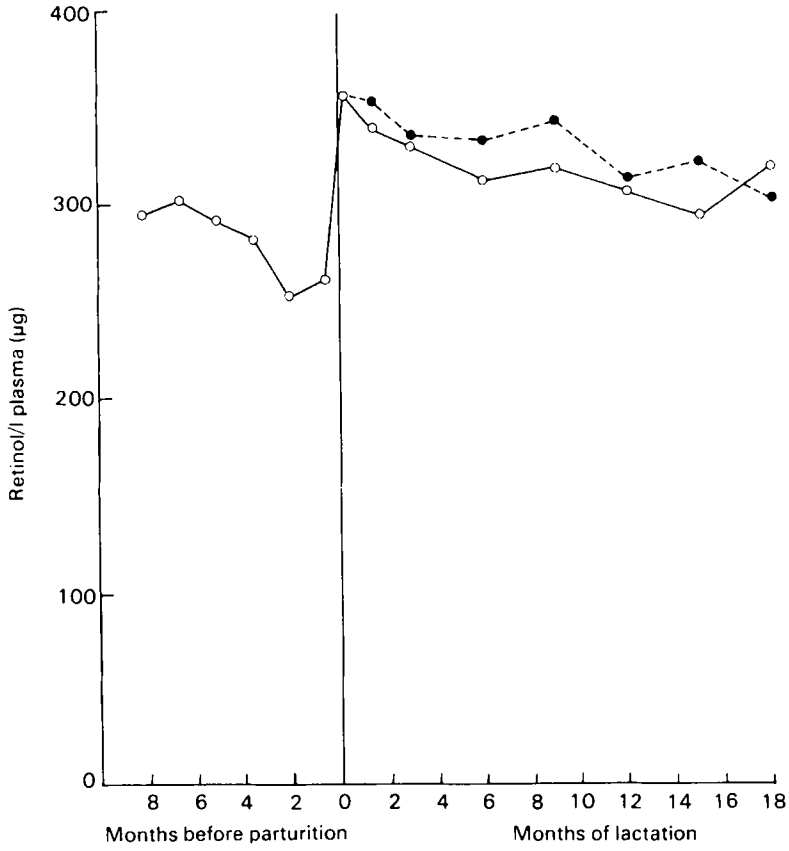

Fig. 2. Plasma retinol levels during the cycle of pregnancy and lactation in Gambian women. ○, Unsupplemented subjects; ●, subjects who were receiving a vitamin-fortified tea and biscuit supplement during lactation. Plasma retinol concentration was measured by the method of Thompson *et al.* (1971). The analyses cover the period: May 1978–May 1980 in Keneba; the mean number of subjects at each stage of pregnancy being 67 (range 18–95), the mean number of unsupplemented subjects during lactation being 29 (range 12–37), and of supplemented subjects, 47 (range 32–55). The mean standard deviation for plasma retinol was 80 μg/l.

their dark adaptation response were carried out during 1981, using a Friedmann Visual Field Analyser (Clement Clarke International Ltd, London). This was done on groups of thirty-seven pregnant Gambian mothers from a village where no supplement had been introduced, and on eighty-nine from Keneba, where by this time all the pregnant and the lactating mothers had been receiving the tea and biscuit supplement from a very early stage of pregnancy. The test was also carried out on Gambian and Caucasian members of Medical Research Council staff, whose age range was similar to that of the Gambian women, but whose nutritional and health status were generally better than those of the village population. The dark adaptation response was, on average, slightly but significantly better in the Medical Research Council staff members than in the Gambian mothers ($P<0{\cdot}01$), but the supplemented mothers in Keneba showed no improvement over the

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mothers in the unsupplemented village; indeed there was a slight trend in the opposite direction (L. Villard, personal communication). Of the thirty-seven unsupplemented mothers, only one had a response which was marginally below the normal range specified by the manufacturers of the instrument, and this was not considered to be significantly abnormal.

The vitamin A content of samples of foremilk from the different groups of subjects was measured, and gave the following mean values (± standard deviations) (μg/l): unsupplemented Gambian mothers, 525±160 (*n* 38); supplemented Gambian mothers, 535±214 (*n* 27). Thus there was no indication from these measurements that the Gambian subjects were secreting less vitamin A in their milk than the UK subjects, or that the Gambian breast milk levels were responsive to supplementation.

Although these observations do not entirely rule out the possibility of a functional defect, related to marginal vitamin A deficiency in the unsupplemented Gambian subjects, the likelihood now appears relatively low, especially since there was no detectable improvement in any of the indices measured after a prolonged period of supplementation.

Requirements and recommended dietary allowances of vitamin A during pregnancy and lactation

Both the World Health Organization (1967) and the Department of Health and Social Security (1979) recommend a daily intake of 750 μg retinol equivalents for adult men and women, based mainly on the vitamin A deprivation–repletion study of Hume & Krebs (1949), which indicated that an intake of 390 μg retinol is the minimum protective dose needed to maintain clinical and functional normality in male subjects. The recommendation of 750 μg/d was intended to provide a generous safety margin to allow for individual variation in requirements and to maintain liver reserves. A more recent deprivation–repletion study (Sauberlich *et al.* 1974) indicated that the minimum requirement of male subjects may be close to 600 μg/d by some criteria, such as the reversal of cutaneous lesions and abnormal electroretinograms.

It is not known whether the requirements of men and women are identical. The evidence relating to this question has been discussed in some detail by Moore (1957); it is clear that there exists a hormone-dependent sex difference in the way in which vitamin A is handled, and there is some less clearcut evidence from human epidemiological studies, that males tend to become deficient more readily than females. There is also evidence from rat experiments that females may be able to utilize carotene more readily than males (Murray & Erdody, 1971). In the USA (Food and Nutrition Board, National Research Council, 1980), a higher recommendation is made for men than for women on the basis of the difference in body size (1000 and 800 μg/d respectively).

The World Health Organization (1967) considered that no increase in the RDA is required during pregnancy, since over the entire span of human pregnancy, only

about 25 μg additional retinol/d is needed to accumulate substantial foetal liver reserves, which can be met without increasing the amount recommended. Thirty years ago, an increase from 750 to 900 μg/d was recommended during pregnancy in the UK (British Medical Association, 1949–50), and currently in the USA an increase from 800 to 1000 μg/d is recommended. The World Health Organization (1967) and the current UK and USA recommendations all agree on 1200 μg/d for lactation, on the basis that in a well-nourished population the average milk output is 850 ml/d, with an average retinol content of 49 μg/100 ml. This implies, of course, that the intake of a lactating subject should be 50–60% greater than the intake of a non-lactating subject, which is considerably greater than the increment in energy requirement.

For lactating women in communities like the one we are studying in The Gambia, where preformed vitamin A is virtually absent from the diet, there will frequently be a wide gap between the RDA and the actual intake of retinol equivalents, assuming that a 6:1 conversion value from carotene to retinol (World Health Organization, 1967) is applicable. Even if an adjustment were made on the basis that the mean daily milk output by Gambian mothers is about 600 ml, the shortfall is still considerable, and the intake is not much greater than the minimum considered necessary to maintain normal function in male subjects. It appears, however, that vitamin A status probably is not seriously impaired, and is not significantly responsive to a considerable period of supplementation, with an amount of vitamin A that is ample to overcome the theoretical dietary shortfall.

It is possible, therefore, either that the safety margin in the RDA for lactating women is relatively high, or that the 6:1 conversion ratio from carotene to retinol equivalents is inappropriate for foods such as palm oil-containing sauces and mangoes, or that the subjects can utilize the available carotene with high efficiency, which may be associated with their sex, their physiological status, or with a process of adaptation to relatively low intakes. Any of these explanations would, of course, imply that the apparent shortfall in intake does not impose a physiological disadvantage and is not, therefore, a significant nutritional handicap in this community.

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