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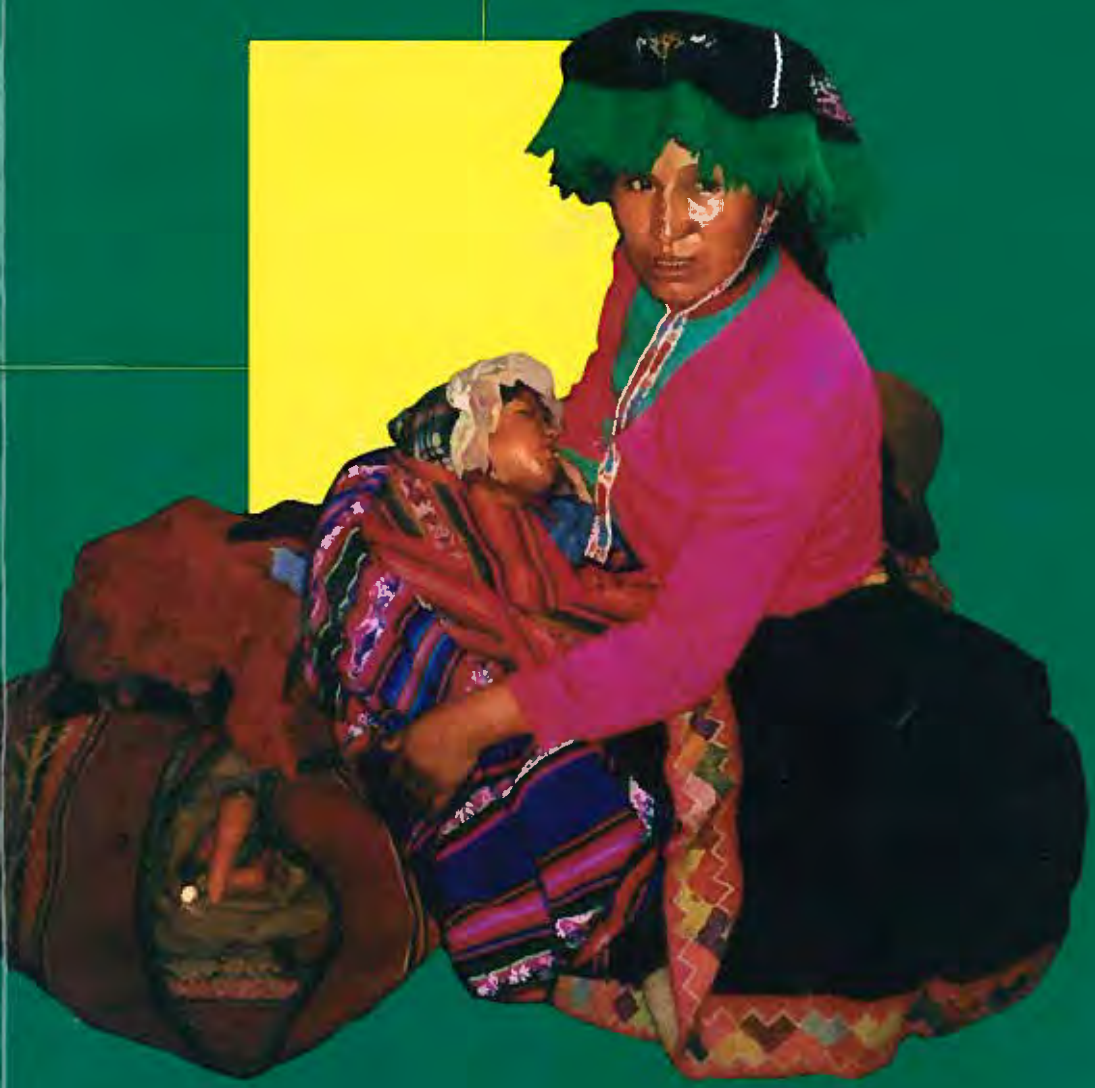
MICRONUTRIENT SERIES

Safe vitamin A dosage during pregnancy and lactation

Recommendations and report of a consultation



World Health Organization

The Micronutrient Initiative

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Annexes

Abbreviations

CNS	central nervous system
DHS	Demographic and Health Surveys[1]
ENTIS	European Network of Teratology Information Services
GnRH	gonadotropin-releasing hormone
HIV	human immunodeficiency virus
HRP	Special Programme of Research, Development and Research Training in Human Reproduction
IU	international units
LAM	lactational amenorrhoea method
LH	luteinizing hormone
RBP-R	retinol-binding protein-bound retinol
RDA	recommended dietary allowance
RE	retinol equivalents
MSG	monosodium glutamate
UNDP	United Nations Development Programme
UNFPA	United Nations Population Fund
UNICEF	United Nations Children's Fund
VAD	vitamin A deficiency
WHO	World Health Organization

[1] DHS Demographic and Health Surveys Program, Columbia, Maryland 21045, USA.

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The Micronutrient Initiative (P.O. Box 8500, Ottawa, Canada K1G 3H9, tel. (613) 236.6163, fax (613) 236.9579) was established in 1992 by its principal sponsors — the Canadian International Development Agency, the International Development Research Centre, the United States Agency for International Development, the World Bank, the United Nations Children's Fund, and the United Nations Development Programme — to contribute to the sustainable control and elimination of micronutrient malnutrition.

Thanks are also due to Dr Barbara Underwood, formerly responsible for micronutrients in WHO's Programme of Nutrition, for organizing the consultation and participating in the preparation of its report, to Dr Bruno de Benoist for reviewing the manuscript, to Mr James Akré for editorial and organizational inputs, and to Mrs Eileen Brown for secretarial support.

Introduction

Vitamin A is essential for normal maintenance and functioning of body tissues, and for growth and development, including during pregnancy when the fetus makes demands on the mother's vitamin A stores, and during the postpartum period when the newborn is growing rapidly. Although the increased requirement during pregnancy is relatively small, in many countries where vitamin A deficiency (VAD) is endemic, women often experience deficiency symptoms such as night blindness that continue during the early period of lactation. In most cultures, the young infant depends on breast milk to obtain adequate amounts of the vitamin. Breast milk from deficient mothers is likely to contain insufficient vitamin A to build—or even to maintain—vitamin A stores in nursing infants. The fact that VAD is known to be associated with increased child mortality after six months of age is a convincing argument for improving maternal vitamin A nutrition as a child survival strategy. There may also be an additional direct benefit to maternal health, though this is not well documented.

Both severe VAD and vitamin A overload are teratogenic in animals and are associated with adverse reproductive outcomes. Although similar outcomes in deficient human populations are not documented, the possibility of risk must be considered. Providing a diet adequate in vitamin A—neither too little nor too much—is the safest solution to meeting needs during pregnancy and lactation. However, this is not easily accomplished in situations of poverty and where food with appropriate vitamin A content is in short supply and/or expensive. In such situations the recommended approach is to provide a vitamin A supplement during pregnancy at a dosage and frequency that will safely meet the needs of growing maternal and fetal tissue and will potentially build maternal body stores in anticipation of lactation. However, using high-dose vitamin A supplements to build maternal stores during pregnancy creates a dilemma because of the vitamin's potential teratogenicity during the early stages of pregnancy. The known teratogenic risk from excessive vitamin A taken in early pregnancy *may* extend to risk from excessively high doses taken during later periods of pregnancy, with possible non-teratogenic consequences on the subsequent behavioural and neuropsychological performance of the offspring. However, non-teratogenic developmental toxicity has not been confirmed. To avoid risk, an alternative to maternal high-dose supplementation during pregnancy is provision of a direct high-dose supplement to the mother during the early postpartum period, assuming that both approaches will improve vitamin A levels in breast milk and reduce mortality among nursing infants in the first years of life.

Concern about potential teratogenesis has been raised because of recent data from a retrospective study of vitamin A intake among women in the USA. The study involved telephone interviews of women who presented for prenatal diagnosis and later gave birth to babies that had defects of structures purported to have an embryologic contribution from cranial neural crest cells (tissues associated with 13-cis-retinoic acid teratogenicity). These data suggest that total dietary intake above 15 000 IU, or above 10 000 IU if from supplements alone, increased the risk of these defects. These intakes are not uncommon in affluent populations that habitually consume more than the recommended dietary allowance (RDA) of vitamin A and also frequently consume vitamin supplements and/or rich sources of preformed vitamin A, such as animal liver. The study called into question the safety of giving supplements to fertile women whose habitual diets are either adequate or deficient in vitamin A.

WHO has received requests from its Member States, from UNICEF and from nongovernmental organizations (NGOs) for programmatic guidance on the safe use of vitamin A supplements by women of reproductive age. The Organization currently recommends that the relatively small increased need for vitamin A during pregnancy should be met through diet, or through a supplement not exceeding 10 000 IU daily throughout pregnancy. Because of the logistical difficulties associated with daily supplementation, some advocate a weekly or monthly supplement. There is, therefore, a need to review the risks and benefits to mother and fetus of frequencies and levels of vitamin A intake during pregnancy, and to assess their programmatic implications, keeping in mind the known long-term potential benefit of mortality reduction in the offspring.

Meanwhile, WHO, UNICEF and the International Vitamin A Consultative Group (IVACG) continue to recommend that, in areas of VAD endemicity, high doses of supplemental vitamin A (200 000 IU) be given to breast-feeding women during the infertile postpartum period which until recently was interpreted as lasting 4–6 weeks. It is well documented that following parturition the infertility period is influenced by breast-feeding practices. New data have become available from a multicentre study of the UNDP/UNFPA/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction (HRP) and from the Demographic and Health Surveys (DHS) concerning the return of menses relative to breast-feeding practices and country-specific contacts with the health system. There is a need to review these data and additional available information for their programmatic relevance for identifying opportunities for the safe provision of high-dose vitamin A supplements during the postpartum period.

In the light of the above considerations, WHO convened a consultation to consider both the safe dosage of vitamin A during pregnancy and the first six months postpartum, and the relevant policy and programme implications. This document presents the recommendations of participating experts in nutrition, teratology, reproductive physiology and population-based surveys, who have experience in both basic research and its public health applications.

The recommendations of the consultation appear first, and the scientific and programmatic considerations leading to these recommendations follow in the report of the meeting.

Recommendations for preformed vitamin A supplements for mothers during pregnancy and the first six months postpartum, and/or for their infants

Four scenarios were identified in which vitamin A supplements could be given through public health programmes and where safe dosage and frequency of administration need to be considered. These scenarios were:

1. Maternal supplementation during pregnancy.
2. Supplementation for mothers in the first six months postpartum.
3. Direct supplementation of infants before six months of age.
4. Supplementation both for mothers during the "safe" infertile postpartum period and for infants under six months of age.

1. Maternal supplementation during pregnancy

(Either during the first 60 days following conception when there is a teratogenic risk or after the first 60 days following conception, for women whose habitual intakes are above the RDA or below the RDA)

For fertile women, independent of their vitamin A status, 10 000 IU (3000 μg RE) is the maximum daily supplement to be recommended at any time during pregnancy.

Where VAD is endemic among children under school age and maternal diets are low in vitamin A, health benefits are expected for the mother and her developing fetus with little risk of detriment to either, from:

- either a **daily supplement** not exceeding 10 000 IU vitamin A (3000 μg RE) at any time during pregnancy;
- or a **weekly supplement** not exceeding 25 000 IU vitamin A (8500 μg RE). In this regard:
- a single dose > 25 000 IU is not advisable, particularly between day 15 and day 60 following conception (day 0);
- beyond 60 days after conception, the advisability of providing a single dose of > 25 000 IU is uncertain; any risk for non-teratogenic developmental toxicity is likely to diminish as pregnancy advances. In the case of a pregnant woman who may be reached only once during pregnancy, health workers should balance possible benefits from improved vitamin A status against potential risk of adverse consequences from receiving a supplement.

Where habitual vitamin A intakes exceed at least three times the RDA (about 8000 IU or 2400 μg RE), there is no demonstrated benefit from taking a supplement. On the contrary, the potential risk of adverse effects increases with higher intakes—above about 10 000 IU—if supplements are routinely ingested.

2. Supplementation for mothers in the first six months postpartum

(Single high-dose supplement above 25 000 IU, and usually at a level of 200 000 IU, during the safe period of postpartum infertility for mothers in vitamin-A-deficient areas)

At the population level

Mothers who are not breast-feeding will benefit from a high-dose supplement given safely during the first 28 days (4 weeks or 1 month) postpartum. Although the risk of conception beyond this point is poorly documented, normal fertility does not usually return for 5–10 weeks. Beyond 6 weeks, therefore, non-lactating mothers should be given no more than 10 000 IU daily. Direct supplementation of the non-breast-fed infant < 6 months of age, who is not given a fortified breast-milk substitute, with as much as 50 000 IU (15 000 μg RE) is the recommended safe intervention to meet the infant's need for vitamin A.

Mothers who are breast-feeding will benefit from a high-dose supplement given up to 60 days (8 weeks or 2 months) postpartum, as will their nursing infants—through higher levels of vitamin A in breast milk. The risk of pregnancy is related to menstrual status of the breast-feeding mother. If she has resumed menstruation she is regarded as fertile. If she is amenorrhoeic, the risk of pregnancy rises after 60 days, in some circumstances reaching 1%–2% by 6 months postpartum. In some very high-risk areas (e.g. where there is a high prevalence of clinical symptoms of VAD in mothers) where a high percentage of contact with the health system occurs within 8–12 weeks, the risk of extending the period for giving a high-dose supplement from week 8 to week 12 (estimated 2.8% conceptions) might be offset by important benefits to the mother (relief of symptoms) and the nursing infant (increased breast-milk vitamin A consumption and consequent increased likelihood of decreased risk of mortality).

For individuals

Mothers who are not breast-feeding, provide a supplement within 28 days of delivery; otherwise give a supplement directly to the infant.

Mothers who are breast-feeding:

- if using reliable contraception, give supplement anytime;
- if practising postpartum abstinence, give supplement anytime;
- if amenorrhoeic, give supplement up to 6 months postpartum;
- if not amenorrhoeic, give supplement to mother at time of next menstruation (an indication that conception has not occurred) or give supplement to child.

3. Direct supplementation of infants before six months of age

(In areas of endemic vitamin A deficiency)

Firm evidence of benefits to **breast-feeding infants** of direct supplementation before six months of age is insufficient. Studies are in progress to clarify the benefits/risks of single

supplementation at 50 000 IU (15 000 μg RE) at birth or thereafter, or multiple supplementation at 25 000 IU (7500 μg RE).

Infants who are **not breast-fed** and who are not given fortified breast-milk substitutes should receive a 50 000 IU supplement, preferably by about 2 months of age—otherwise at any time within the first 6 months of life. As an alternative, two doses of 25 000 IU can be given with an interval of a month or more in between.

4. Supplementation both for mothers during the "safe" infertile postpartum period and for infants under six months of age

There is currently insufficient information to make firm programmatic recommendations regarding risks and benefits to infants on the basis of this supplementation strategy. A WHO-sponsored trial is being conducted in three countries to clarify this issue and results should be available within the next year.

Report of the consultation
Safe vitamin A dosage during pregnancy and the first 6 months postpartum,
Geneva, World Health Organization, 19–21 June 1996

Objectives of the consultation

General objective

To review the available information and reach consensus on dosage and contact points during pregnancy and lactation when vitamin A supplements can be safely administered.

Specific objectives

1. To review evidence of VAD during pregnancy and/or lactation from countries WHO identifies as having a public health problem among children of pre-school age and to summarize information on programmes currently being implemented for this physiological stage.
2. To review available data on the length of postpartum infertility and how this is influenced by current and past breast-feeding practices, as well as other maternal/infant factors.
3. To review available data linking vitamin A to teratogenicity in humans from both deficient and excess intakes.
4. To review the demonstrated benefits of improved maternal vitamin A status during pregnancy and lactation compared with the benefits of direct supplementation of the infant during the first six post-gestational months.
5. To consider the programmatic implications of recommendations in the light of variations in women's contacts with health services during pregnancy and the first six months postpartum.

Vitamin A status during pregnancy and lactation

To provide guidance on safe and effective strategies for improving the vitamin A status of mothers and their infants, a review was presented of what is known about needs for vitamin A among pregnant women and their fetuses and among lactating women and their nursing infants. Although a small amount of vitamin A is essential for successful reproduction, too much—as well as severe deficit—is teratogenic. A brief summary of the information from the background review is presented as follows.

Vitamin A needs during pregnancy and lactation for the health of the mother and her fetus or infant (Dr Kathleen Rasmussen)

Among pregnant women, signs of VAD (night blindness) have been reported, particularly among those living on the Indian subcontinent. This problem is associated with poor socioeconomic status, high parity at young or old reproductive ages, and low intake of foods containing vitamin A. Vitamin A and related compounds are transferred from mother to fetus via the placenta. Studies in animals reveal that this transfer is sensitive to maternal vitamin A intake, both chronic and acute.Low doses (0.2-8.4 μmol, equivalent to about 200–8000 IU[1]) of vitamin A given to pregnant women increase their plasma retinol values. No birth defects have been reported with these doses, although none would be expected because in all studies they were given after embryogenesis was complete. The safe daily or weekly dose that can be given to pregnant women is not precisely known; it may depend in part on the woman's hepatic reserve of vitamin A. Massive doses of preformed vitamin A have not been routinely given to pregnant women so the effect of such a supplementation strategy on maternal and fetal health is unknown. However, it is clear that massive dosing with vitamin A should be avoided during the periconceptional period.

Among lactating women on the Indian subcontinent and in south-east Asia, signs of poor vitamin A status (night blindness) are reported, and low breast milk retinol values are found among Indian and Indonesian women. The problem is most likely to occur if the prior pregnancy was characterized by symptoms of night blindness. Vitamin A is transferred to milk from both retinol-binding protein-bound and chylomicra-associated vitamin A carriers, i.e. retinol and retinyl ester respectively. The chylomicra-associated vitamin A may be a particularly important route of transfer among women who receive chronic low doses of the vitamin (e.g. from food fortification programmes) as well as periodic acute high doses.

Both low daily doses and periodic massive doses of vitamin A increase the concentration of retinol in human milk. Massive doses, i.e. up to 312 μmol (300 000 IU), have been given to lactating women in the first few weeks postpartum with beneficial effects on both the mother and her nursing infant for at least the subsequent 6 months. The safe upper limit of the amount of vitamin that can be given at this time is not known. It could be higher than the 312 μmol that has been used successfully but additional studies, including monitoring of retinoid metabolites, are warranted before higher single dosages are recommended. If the infant is also to receive a

[1] Various units are used in the literature to refer to concentrations of preformed vitamin A. In this report, equivalent vitamin A (retinol equivalents [RE]) concentrations are defined as:

1 RE = 1μg all-trans retinol = 0.0035 μmol = 3.33 IU
1 μmol = 286 μg retinol = 951 IU.

In addition, most supplements are available as retinyl palmitate or retinyl acetate which have weight equivalence 1.83 and 1.15 respectively, greater than retinol (e.g. 60 mg retinol = 110 mg retinyl palmitate = 69 mg retinyl acetate, all with a potency of 200 000 IU).

supplement of vitamin A directly, this should be taken into consideration when calculating the amount to be given to the mother.

Infants are born with low hepatic reserves of vitamin A. These reserves normally increase 60-fold in the first 6 months of life in response to the vitamin A delivered in breast milk which is the primary – if not the only – source of vitamin A in their diets. It is safe to supplement infants by supplementing their mothers. It is also safe to supplement infants directly. Massive doses of up to 52 μmol (50 000 IU) have been given to newborns; in one study this dose reduced infant mortality. Other studies of the same or lower doses, given two or more times somewhat later after birth but before 6 months of age, failed to show a reduction in mortality or morbidity among populations where breast-feeding predominates.

Insufficient information is currently available to evaluate the safety and effectiveness of dosing both a mother and her nursing infant concurrently.

The relation of maternal vitamin A status to other conditions

Breast milk composition

Maternal diet influences the level of several vitamins and minerals in breast milk, including vitamin A (Table 1). Epidemiologic studies of vitamin-A-fortified food products, such as monosodium glutamate (MSG) and sugar, and intervention trials using high-dose supplementation for mothers soon after birth, demonstrate the association between diet and breast milk. Transfer of vitamin A from maternal blood to breast milk is regulated primarily by levels of maternal retinol-binding protein-bound retinol (RBP-R), and possibly also chylomicra-solubilized retinyl esters soon after supplementation with high doses of vitamin A. Most retinol in breast milk is in the form of retinyl esters and is related to the fat content of breast milk. Low maternal zinc status, protein-energy malnutrition (PEM), and situations that activate an acute-phase response (e.g. infectious diseases) all reduce levels of RBP and as a consequence cause reduced serum levels of vitamin A, i.e. RBP-R, which could limit the retinol transferred to milk.

Table 1. Nutrients in breast milk most affected and least affected by maternal diet

Nutrients most affected	Nutrients least affected
Fatty acids	Protein
Vitamin A	Lipid
Vitamin D	Carbohydrate
Vitamin E	(lactose)
Vitamin K	Calcium
Thiamin	Magnesium
Riboflavin	Folate
Vitamin B_6	Iron
Vitamin B_{12}	Zinc
Selenium	Copper
Iodine	Manganese

Iron-deficiency anaemia

Haemoglobin response to iron supplementation is suppressed among anaemic subjects who are also deficient in vitamin A. Data from the WHO global data bank on anaemia among women of reproductive age, including those pregnant and lactating, showed considerable overlap with

countries where VAD occurs among children of pre-school age. Presumably these are countries where women also are likely to have inadequate vitamin A status. For example, the highest prevalence of anaemia in pregnant women—up to 78%—occurs in south-east Asia where the prevalence of VAD is also highest. This relationship was recently demonstrated among iron-deficient, lactating women in Indonesia; VAD depressed their haemoglobin response to iron supplementation by about 30%.

Participants at the consultation noted that in many parts of the South-East Asia Region, particularly in India, the reason for the high prevalence of anaemia is the low bioavailability of food-iron from habitual diets and from programmes that limit supplemental iron doses. Under these circumstances—which are also likely in some other regions with a high prevalence of anaemia—bioavailable iron is essential for correcting anaemia. Providing vitamin A alone, therefore, will not contribute to resolving the anaemia problem unless there is concurrent improvement in the quantity of bioavailable iron.

HIV-1 infection

There is evidence among HIV-infected pregnant women in Africa that suggests poor vitamin A status (serum retinol <1.05 μmol/l [30 μg/dl]). In Kenya, Malawi and South Africa, where vitamin A status has been assessed in these women, it is estimated that 52–63% are in poor status. In Malawi, poor status is associated with increased vertical transmission of HIV-1, higher infant mortality, low birth weight and increased maternal mortality. In Kenya, HIV-infected lactating women with severe VAD (serum retinol <0.70 μmol/l [20 μg/dl]) are at increased risk of having HIV-infected cells in their breast milk. However, these findings do not establish a causal role for VAD in HIV transmission because low serum vitamin A could be a marker of infection severity or other risk factors.

To establish causality, clinical trials are needed where vitamin A supplements are given to HIV-infected pregnant women. At least three such trials are known to be in progress—one each in Malawi, South Africa and the United Republic of Tanzania. In all three trials, a daily dose of vitamin A or placebo is given during the third trimester of pregnancy. The Malawi study provides 10 000 IU retinyl palmitate (5500 μg RE) while the South African and Tanzanian studies provide 5000 IU (2750 μg RE) retinyl palmitate and 30 mg beta-carotene. At delivery, women in all three studies will receive 200 000 IU (110 mg RE) of vitamin A or a placebo.

Concern has been expressed about the safety of vitamin A supplementation in HIV-1 infected women. One *in vitro* study showed that retinoic acid increased replication of HIV-1, while another *in vitro* study, using different cell-culture conditions, showed decreased replication. The question as to whether vitamin A increases the HIV-1 viral burden is important because many women in vitamin-A-deficient countries who may be targeted to receive supplementation could be infected with HIV. A preliminary study from South Africa showed no increase in HIV-1 viral burden when pregnant women were given a low daily dose of vitamin A in the third trimester of pregnancy and 200 000 IU at delivery. These findings require verification.

Participants identified concerns that need additional research because of important programmatic implications. These included:

- how the transfer of vitamin A to breast milk can be optimized;
- what maternal conditions (e.g. other nutrient deficits or diseases) can interfere with transfer;
- whether the vitamin A concentration in the mammary gland affects the content of vitamin A in breast milk;
- whether retinyl-ester, or retinol-metabolite, spikes in breast milk correspond to spikes in blood chylomicra-solubilized retinyl esters and, if so, how long the levels remain elevated.

The programmatic concern of the latter question is whether there should be a period after maternal high dosing during which breast-feeding should be postponed to minimize any unknown, but potential, risk to the infant from unphysiologically high concentrations of retinoid metabolites.

Country experiences

Brief presentations were made of programme experiences in Bangladesh, Gambia, India and Morocco. The presentations and subsequent discussions illustrated the wide variation in situations where supplementation programmes are, or may need to be, implemented on behalf of pregnant and lactating women.

Bangladesh

In Bangladesh, there is currently no national vitamin A supplementation programme that includes women routinely. Nearly 80% of deliveries in rural areas are in the home with no contact between health workers and mothers before 8 weeks postpartum. Only about one-third of the home deliveries are attended by trained birth attendants. Under these conditions, it is programmatically difficult to supplement pregnant and lactating mothers safely through a nationwide programme implemented through the routine health services. It could be possible programmatically to add a vitamin A capsule supplement to a "safe delivery kit" or "cord kit" where these are used. Limited experience using this approach in the Matlab area in Bangladesh has been positive. However, before this approach can be recommended on a broad scale, cost-effective studies should be carried out.

India

Data from India indicate that, unlike anaemia, vitamin A deficiency in pregnancy is not associated with increased maternal morbidity and mortality. There is at this time, therefore, no programme for universal supplementation to pregnant women. Most deliveries in rural areas take place at home and there is no specific maternal health contact point in the first 8 weeks after delivery when large-dose vitamin A supplementation can be given safely. India does not, therefore, have a policy encouraging targeted supplementation to lactating women who contact

health services prior to 8 weeks postpartum. Currently infants' vitamin A needs are directly addressed by providing 100 000 IU at 9 months at the same time as the measles immunization.

Immunization-linked vitamin A supplementation programmes during infancy need to be reinforced by joining them with growth monitoring or similar programmes that provide periodic contact when the supplement can be delivered. Contacts for supplement delivery are necessary where diets remain inadequate to ensure the potential benefit of mortality reduction throughout the vulnerable pre-school years. Maternal needs, of course, will not be met safely through infant immunization contacts unless coupled to a BCG or maternal tetanus toxoid booster within 8–12 weeks of delivery. However, opportunity for targeted supplementation should be sought for those lactating women who *do* come into early contact with the health system, i.e. by 8 weeks from delivery.

Gambia

In Gambia, in spite of a low and seasonably variable dietary intake of vitamin A, almost none of which is preformed, there is little biochemical evidence (e.g. moderately low serum retinol values) or functional evidence (e.g. night blindness) of deficiency among pregnant and lactating women. Both serum levels and breast-milk retinol levels, however, responded modestly to a small, i.e. less than 1 RDA, supervised daily dose of vitamin A over a period of several months. In this scenario, the data suggest that a dietary increment in vitamin A activity, rather than supplements, could control any subnormal vitamin A status. One potential diet-based programme considered appropriate to the area is improved year-round availability of vitamin A though increased supply of sun-dried mangoes in rural communities.

Morocco

Morocco represents yet another scenario. No recent information is available on the vitamin A status of different potentially vulnerable groups in the country. Before considering a programme, therefore, a systematic review (a situation analysis) is required to identify the target populations for which programmes may be needed (children, pregnant and lactating women, or both), and to find out the health service coverage or access to services of the identified target group(s) (e.g. the percentage of women followed at antenatal clinics, the distribution of home or assisted deliveries, and antigen-specific immunization coverage of children). On the basis of this information, programmes can be designed that efficiently utilize health institutions and other health service contact points that achieve the broadest coverage of the target group during the period of its vulnerability. Only then will it be possible to tailor the dose and frequency of administration to the existing infrastructure for safe delivery of vitamin A to vulnerable groups.

Countries where vitamin A intakes habitually exceed the RDA

Several countries in Europe, as well as Japan and the USA, have expressed concern about the possible adverse effects of too much vitamin A because large numbers of their populations regularly consume the vitamin in excess of the RDA. The consumption of liver during

pregnancy has been of particular concern. A recent study in the United Kingdom (1) was cited that compared equivalent amounts of vitamin A (i.e. 50 and 150 mg, about 165 000 and 500 000 IU) given as a supplement or as cooked calf liver resulting in markedly different metabolism. Peak serum values of potentially teratogenic metabolites from liver were several-fold lower and occurred later than when supplements were given. The consultation reviewed a report from France which is thought to exemplify this type of situation.

Nutrition surveys in **France** indicate that vitamin A intakes, especially among women of reproductive age, are likely to be above adequate levels with the possible exception of a growing number of people in precarious economic situations. About 60% of dietary vitamin A is from carotenoids, the remaining coming from preformed sources. Some foods containing preformed vitamin A (e.g. animal livers), although not widely consumed, have potential for raising total intakes to levels that could be teratogenic for some pregnant women who consume liver frequently. Concentrations as high as 100 000 IU/100 g liver (30 000 μg RE/100 g), or occasionally even higher, are reported in France. This is the consequence of supplements added to the diet of these animals. Recently the situation prompted France and the European Union to reduce the amount of vitamin A provided in animal feed and, as a consequence, vitamin A concentrations in animal liver have been effectively reduced. This control measure is, therefore, being continued.

Vitamin A supplements are also a source of concern in France because their consumption appears to be increasing. To further protect against teratogenic risk and hypervitaminosis A, a recent decision was made to limit the potency of vitamin A supplements available to the public to a maximum of one RDA, i.e. 1000 μg/unit. This is a precautionary measure since there has been no increase in teratogenic events reported in France that could be related to an excessive vitamin A intake for a period when an increase in the vitamin A food supply may have occurred. This conclusion was reached following a study of 1200 pregnant women among whom no statistically significant increased risk of malformation was found to be associated with an increased intake of vitamin A (dietary plus supplements). Because these events are rare, however, cautious interpretation of this study's conclusion is advised as its design and/or statistical power may have been inadequate.

France has thus considered the potential harmful effect of too much vitamin A, especially for women of reproductive age, and has instituted regulatory measures to minimize risks. In addition to decreasing the vitamin A content of animal feed and limiting the vitamin A concentration of supplements to one RDA/unit, measures include the establishment of scientific groups to keep a coordinated watch on the situation. Similar measures should be considered in other countries where vitamin A intakes habitually exceed the RDA.

Summary of discussions

Adequate maternal vitamin A status ensures protection from the adverse consequences of either too much or too little vitamin A for the mother, fetus and newborn. Adequate status is maintained by intakes at the level of the RDA. Where habitual diets are up to three times the RDA, there is no demonstrated benefit in taking a supplement during pregnancy or lactation.

Where habitual vitamin A intakes are low, a pregnant women and her developing fetus are expected to benefit without risk from daily vitamin A intakes of 10 000 IU from diet and/or supplement or 25 000 IU weekly. Lactating women can safely be given a high-dose vitamin A supplement during the infertile postpartum period of 200 000–300 000 IU, which will maintain breast milk concentrations for at least 6 months.

In areas with a high prevalence of iron-deficiency anaemia and VAD, vitamin A supplements will improve the maternal response to iron supplementation but are not a substitute for iron prophylaxis. The benefit to mother, fetus and newborn of supplements to HIV-1-infected mothers who are vitamin A deficient remains to be demonstrated by studies that are in progress.

Limited current evidence suggests that concentrated food sources of vitamin A (e.g. animal liver) are utilized differently than preformed vitamin A supplements of similar retinol equivalence. This finding requires confirmation. Meanwhile, where median intakes of pregnant women exceed the RDA three-fold, countries should be encouraged to monitor and control levels of vitamin A in animal livers. Occasional consumption of cooked liver (e.g. weekly or less frequently in about a 50–70 g serving size) by pregnant women poses no significant teratogenic risk while providing a valuable source of other nutrients such as iron and folic acid.

Teratogenicity of vitamin A in humans

Animal studies have demonstrated that both too little and too much vitamin A during critical periods in embryonic development can have teratogenic consequences. There are limited human data that directly link teratogenicity in women exposed early in pregnancy to high doses of preformed vitamin A, i.e. retinol and retinyl esters. However, teratogenic effects from naturally occurring metabolites of vitamin A, e.g. trans-retinoic acid, 13-cis retinoic acid, and their oxo-derivatives, are well documented from case-studies of women directly exposed to high doses of preformed retinoic acid derivatives within the first six weeks of pregnancy. Extensive epidemiologic studies have produced no evidence for teratogenicity in humans after 6 weeks of pregnancy. Other, as yet unpublished, reports of toxic non-teratogenic developmental effects have not been sufficiently documented to date. A review was presented summarizing what is known about the developmental toxicity of inadequate and excess vitamin A during human pregnancies. A condensed version of the review appears below.

Vitamin A and human developmental toxicity (Dr Edward Lammer)

It is generally accepted that physiological serum concentrations of retinol and its metabolites are non-teratogenic and that retinoic acid plays an essential role in controlling many aspects of normal embryogenesis. In the embryo, retinoic acid (like several isomers) acts as a ligand that binds to a nuclear hormone receptor. This ligand-receptor complex then acts to coordinate expression of many other genes by binding to a regulatory element (DNA sequence) of a target gene, including genes coding for other transcription factors. Experimental evidence indicates that the embryonic concentration of retinoic acid determines at least some of the differential

specificity of genetic regulatory control attributable to retinoic acid. This suggests that tight control over retinoic acid levels in embryonic tissues is of critical importance, and that the teratogenic effects probably result from receptor-mediated processes. Thus, the potential for vitamin A teratogenicity stems from intakes that increase maternal blood levels of retinoic acid isomers, not retinol or retinyl esters. How much of an increase is "too much" is unknown.

Given the global magnitude of VAD, it is surprising that there are so few observations of malformed babies delivered to pregnant women who have symptoms of VAD. Countries in which VAD is endemic do not appear to have a higher prevalence of birth defects than other countries. Only a handful of published case reports of teratogenicity can be found and they describe eye malformations and central nervous system problems. However, no systematic studies of VAD during pregnancy have been reported.

Experimental studies strongly suggest that retinoic acid (all-trans-RA, 13-cis-RA, 4-oxo-all-trans-RA, 4-oxo-13-cis-RA), and not retinol, is the proximate teratogen. Thus, most concern about excessive maternal intake relates to preformed vitamin A supplements that produce elevations in maternal serum retinoic acid levels, rather than to increases in maternal serum retinol or retinyl esters. The potential for human teratogenicity from excess maternal consumption of preformed vitamin A is based on the unequivocal demonstration of human teratogenicity of 13-cis-retinoic acid (isotretinoin) when it is taken during early pregnancy. Daily therapeutic doses result in peak serum concentrations of isotretinoin of >200 ng/ml, compared to endogenous levels of 1–4 ng/ml. Isotretinoin causes a characteristic pattern of spontaneous abortion, premature delivery and malformations that involve central nervous system, cranio-facial and cardiac development. The magnitude of the teratogenic risk is unusually high when isotretinoin is used beyond the 15th day after conception but is not increased if it is stopped within the first 15 days after conception. Additional adverse outcomes of pregnancy, although less severe, have been reported when isotretinoin was used exclusively during the fetal period of development (beginning more than 60 days after conception). Thus, there is no "safe" time during pregnancy when a high dose of vitamin A might be given without putting a fetus at some risk, except during the first 15 days after conception.

A review of evidence of human developmental toxicity from excessive preformed vitamin A intake included case reports and controlled studies. At least six relatively complete case reports of adverse pregnancy outcome associated with daily intake of 25 000 IU, or more, preformed vitamin A have been published. No pattern of anomalies is obvious among these cases, except for an unexpected number of renal/urinary tract anomalies. Other later case reports, published after identification of the retinoic acid (isotretinoin) embryopathy, more closely resemble that phenotype, probably because of reporting bias.

Four case-control studies of vitamin A supplement intake during pregnancy were reviewed. For most, the measure of exposure was ingestion of 10 000 IU or more per day of retinol or retinyl palmitate. Among the studies, the frequency of such "exposure" was 0.14%, 0.3%, 1.3% and 0.5%. In three of these studies, cases were selected for the presence of a malformation that involved a structure that was embryologically derived, at least in part, from cranial neural crest cells (e.g. orofacial clefts, conotruncal cardiac defects, ventricular septal defects). These

malformations were targeted because experimental and human studies of retinoic acid teratogenesis indicated that activities of cranial neural crest cells were adversely affected. The results of these studies do not demonstrate human teratogenicity when exposure is quantified as >10 000 IU preformed vitamin A per day.

Four cohort studies of vitamin A use during pregnancy were summarized. Two were small and not controlled. In the third there was no excess of birth defects among the offspring of women who took a multivitamin that had 6000 IU of preformed vitamin A. The population of the fourth study was a large, prospectively followed cohort of women referred to an (academic) urban medical centre for prenatal diagnostic services. In many studies of supplement users, high vitamin A exposure was defined as more than 10 000 IU of retinol per day. The overall incidence of birth defects was low (1.5%), indicating substantial under-ascertainment of abnormalities. There were 10 malformed outcomes among the higher-dose group. Using least squares regression, the authors showed that the prevalence of cranial neural crest outcomes (n=7) among the maternal intake category of >10 000 IU/day was greater than the prevalence in the lowest exposure category by 1.7% of births, or 1 baby in 57. The authors concluded that "1 of every 57 babies is born with a birth defect attributable to the high vitamin A intake of the mother" among women who take more than 10 000 IU of preformed vitamin A from supplements. The strengths and limitations of this research are discussed in detail.

Because retinoic acid in therapeutic doses is a human teratogen, and because many of the embryological roles of vitamin A are carried out by conversion to retinoic acid, it makes sense that preformed supplemental vitamin A must be teratogenic at some unknown dose that is "too high". The cohort study described above attempted to determine this threshold dose by defining the high dose as >10 000 IU of preformed vitamin A per day. Such a cutoff, if correct, is of public health importance because this dose is so close to the upper range of normal dietary intakes of pro-vitamin and preformed vitamin A, and because women of reproductive age have been advised to take a daily multivitamin supplement to prevent malformations. Recent studies strongly suggest that periconceptional supplements of vitamin A that are close to, but less than 10 000 IU/day, and that are given as a component of a multivitamin, are much more likely to be associated with reduced, rather than increased, risk of malformations.

Although many of the human teratology studies of vitamin A use have methodological limitations, the preponderance of the data does not allow an inference to be made that 10 000 IU/day is a threshold. Human teratogenic effects from supplemental vitamin A intake presumably result from increased maternal blood levels of retinoic acid. However, preliminary results presented at this consultation (U. Wiegand, personal communication) of human pharmacokinetic studies using various supplemental doses of preformed vitamin A from 10 000 to 30 000 IU/day do not show significant increases of maternal serum levels of retinol or retinoic acid. This lack of evidence of any significant change in serum levels after supplementation with commonly available unit doses of preformed vitamin A makes it highly unlikely that such supplements are teratogenic in humans. Further pharmacokinetic research will be valuable in providing information on how data on vitamin A doses can be more biologically modelled to reflect changes in maternal blood levels that can potentially be induced with supplements. This will be useful to epidemiological research.

Mechanism of teratogenic action

Discussion of the background paper highlighted several pertinent issues. There was agreement that the mechanism by which vitamin A exerts teratogenic effects is now understood to be mediated through the influence of high concentrations of some retinoic acid metabolites on gene function at critical periods of organogenesis and embryonic development. This can occur upon exposure to the spike in circulating chylomicra-solubilized retinyl-esters that follows a mother's ingestion of a large dose of preformed vitamin A during the first 6 weeks following conception. Potential teratogenicity of metabolites is related to the area under the blood-level curve and the half-life of the metabolite. Primate and human pharmacokinetic studies show that risk of teratogenicity from high blood levels of vitamin A metabolite, all-trans and 13-cis-retinoic acid, after single-dose supplementation decreases after 5 days. Within this period, circulating chylomicra-solubilized retinyl ester levels are reduced by depositing retinol in reserve tissues, primarily the liver, and metabolite levels return to a physiological range. Retinol in liver reserves—following deesterification—is bound to its carrier protein and subsequently mobilized under tight homeostatic control, further complexed with transthyretin, to maintain circulating levels of the trimolecular complex between 300–800 μg/l over a wide range of liver reserves and usual dietary intakes. As a consequence, materno-fetal transfer of RBP-R is well regulated and concentrations of endogenously generated, potentially teratogenic metabolites remain physiological. As noted earlier, epidemiologic evidence for teratogenicity comes primarily from studies in which preformed teratogenic retinoic acid metabolites were directly ingested.

Threshold levels for teratogenicity

There are no available data showing to what extent circulating levels of potentially teratogenic retinoic acid metabolites become elevated, and for how long they remain elevated, when single doses of 100 000– 200 000 IU (30 000–60 000 μg RE) retinyl ester are given, i.e. when there could be exposure to spikes of potential teratogens. These dosage levels are commonly used to supplement young children and non-pregnant lactating mothers. It is not clear whether the potential teratogenicity of metabolites is correlated better with the area under the blood-level curve or with peak blood levels. Research is needed, therefore, to determine the pharmacokinetics of metabolites of vitamin A following high doses of retinyl esters given to women who enter pregnancy with *elevated*, as well as low, vitamin A stores. It is possible to conduct such research in women of reproductive age while they are protected from becoming pregnant.

For obvious ethical reasons, prospective studies of maternal dosage levels associated with teratogenicity cannot be undertaken in humans. The closest approximation is non-human primate studies. Participants were apprised of ongoing studies in which retinyl palmitate clearly had teratogenic effects—60% abnormal fetuses—at an exposure level of 80 000 IU/kg (24 000 μg RE/kg). The threshold in monkeys replete with vitamin A—8% of fetuses showed minor defects—was close to 20 000 IU/kg (6000 μg RE/kg). The teratogenic dose in primates, therefore, is 20–30 times the human RDA per day during pregnancy (800 μg RE), or the equivalent of 50 000–80 000 IU/day (15 000–24 000 μg RE/day) for pregnant women.

Nevertheless, participants cautioned that exposure to a daily dose might be less toxic than a single high dose because of metabolic adaptation. Neither teratogenicity nor toxicity is observed in species exposed to high-dose supplements of beta-carotene.

Unpublished and published research was presented regarding systemic concentrations of vitamin A and its metabolites in female volunteers who received daily oral doses of vitamin A for three weeks. Systemic concentrations of vitamin A metabolites (retinoic acid and 13-cis retinoic acid) following doses of 10 000 and 30 000 IU were compared with the concentrations in women not receiving vitamin A supplements during the first trimester of pregnancy. Systemic concentrations after 10 000 IU were not significantly different from those before intake and were well within the physiological concentrations in pregnant women who were not supplemented during the first trimester and who gave birth to healthy babies. Even after doses of 30 000 IU, concentrations in serum were only slightly elevated, and just beyond the range of physiological concentrations (2).

The recently reported study by Rothman et al. (3) was extensively discussed because it has raised concern internationally. Results suggested that there is an increased risk of birth defects (1 in 57, but with a wide range down to 1 in 300 births) among women consuming more than 15 000 IU (4500 μg RE) vitamin A daily in their total diet, or above 10 000 IU (3000 μg RE) from a supplement alone. The period of ingestion associated with birth defects was obtained retrospectively and was described as between 2 weeks before and 7 weeks after conception. No birth defects were seen in mothers with similar levels of ingestion after 7 weeks of pregnancy.

These doses are low enough for there to be concern about the potential teratogenicity of doses within currently recommended ranges. The legitimate criticisms of the Rothman et al. study raised in published letters to the editors of *New England Journal of Medicine* and *The Lancet* – about poor quantitative measurement of ingested vitamin A, inappropriate assignment of birth defects associated with vitamin A, and bias in the sampled population – do not explain away the results of the study. Indeed, some of these criticisms would tend to mask results thereby implying that in reality the relationship is even greater than reported. The Rothman et al. study, therefore, needs to be examined within a broader context.

In view of the dose-response metabolite data, reviewed earlier, the consultation pointed out that the production of retinoic acid metabolites necessary to produce the level of teratogenicity reported does not occur at vitamin A dosage levels of 10 000–15 000 IU (3000–4500 μg RE), but only at levels above 30 000 IU (9000 μg RE). Hence, a three-fold higher intake than that suggested by the Rothman et al. study did not raise systemic concentrations of vitamin A metabolites sufficiently to cause a teratogenic effect. This raises the question of whether the doses that caused the teratogenicity in the Rothman et al. study were in fact much higher (e.g. extrapolation from the study's actual findings to a 100 000 IU [30 000 μg RE] threshold leaves large opportunity for error). Participants in the consultation therefore questioned the reliability of the evidence from the Rothman et al. study regarding increased teratogenic risk from regular intake of a 10 000 IU (3000 μg RE) supplement during pregnancy since even a two-to-three-fold higher intake did not raise potentially teratogenic metabolite levels in the blood.

Participants also pointed out that, in vitamin A replete women, added dosing results in more retinoic acid production. In contrast to much of the developing world where inadequate vitamin A intake is prevalent, the women in the study by Rothman et al. were from a population where VAD rarely occurs and, therefore, they were likely to be replete in vitamin A stores. Newly ingested vitamin A is unlikely to endure in the circulation when the liver stores are depleted, but circulating elevated esters may persist when the liver is replete. No added benefit is expected from vitamin A supplementation in replete situations, so there is no rationale for such supplementation whether or not there is a risk.

Evidence from regional registries of birth defects

An additional point that was noted was the lack of consistency of the conclusions of Rothman et al. with findings from other regional registries of birth defects in Europe and the USA. In Europe, a registry was started in 1996 by the European Network of Teratology Information Services (ENTIS) in Rome. In the USA, registries are maintained at the Centers for Disease Control and Prevention in Atlanta, Georgia, and in California. These registries have recorded no increase in birth defects that could be attributed to excess intakes by pregnant women of preformed vitamin A, i.e. regular intakes of retinol or retinyl palmitate above 10 000 IU (3000 μg RE) from multivitamin and/or single vitamin A supplements.

In response to the controversy stimulated by the Rothman et al. article, ENTIS conducted an analysis of pregnancy outcomes observed prospectively among a cohort of women counseled in recent years by the 11 participating teratology information services that used vitamin A supplements in excess of 10 000 IU (3000 μg RE) or more before 70 days of gestation. The study cohort was compared to two convenience control cohorts, one made up of women exposed to vitamin A supplements beyond 70 days gestation and the other made up of women with non-teratogenic drug exposures. Detailed exposure information was collected directly during the risk assessment consultation. A structured survey questionnaire on pregnancy outcomes, addressed to attending doctors or women with infants who had cranio-facial defects, was administered by mail or by telephone 2–8 weeks after expected delivery dates.

Among women exposed to 10 000 IU or above before 70 days of gestation, 10 out of 302 women (3.3%) delivered babies with birth defects compared to 6 out of 113 women (5.3%) who were exposed to the same amount after 70 days. However, only one case was attributable to cranial nerve crest origin and this occurred in the group where exposure was at a level of 100 000 IU (30 000 μg RE) *after* 70 days gestation. There was no statistical difference in the occurrence of birth defects between exposed and control groups. In addition, there was no evidence of a relationship between increased vitamin A exposure and spontaneous and induced abortion. It is noteworthy that there was a lack of any indication from the European registry of congenital anomalies attributable to exposure to vitamin A in excess of 10 000 IU (3000 μg RE). However, the sample size in this study is insufficient to validate or discard confidently the results from the study by Rothman et al.

Summary of discussions

Little information is available on safe levels of vitamin A in humans exposed at weekly or monthly intervals at different periods of gestation. Participants saw no reason to question the safety of the current recommended exposure for women of reproductive age of 10 000 IU (3000 μg RE) daily throughout pregnancy. Participants also agreed that, after the first trimester, exposure to levels in excess of 10 000 IU of preformed vitamin A or retinoic acid is less risky. However, caution is advisable because some preliminary data in humans suggest mild abnormalities in CNS-related performance (e.g. speech and language, and verbal IQ tests) from exposure to 13-cis retinoic acid during the fetal period of development. These observations, which need verifying, would extend the period for possible toxic exposures into the second trimester of pregnancy.

The effects of supplement exposure could differ between well nourished and poorly nourished women, and according to whether exposure is from a concentrated supplement or a food source. Participants noted recent data that indicate less risk of elevated circulating metabolites from concentrated food sources of vitamin A, such as animal liver, than from supplements (4). These findings—which need to be confirmed—reinforce the current recommendation for safely improving the vitamin A status of pregnant women from dietary food sources, including animal liver, where this is programmatically feasible.

On the basis of available data, participants concluded that there is no teratogenic risk from preformed vitamin A supplement of 10 000 IU (3000 μg RE) given to pregnant women who habitually consume less than the RDA. However, there is no justification for daily supplements at a level above 8000 IU (2400 μg RE) for pregnant women who habitually consume vitamin A at the level of the RDA (800 μg RE) or above. A weekly supplement of 25 000 IU (7500 μg RE) given to women who regularly under-consume vitamin A is unlikely to produce peak levels of blood metabolites above their physiological ranges or to exceed tissue storage potential. On the contrary, the potential benefits derived from correcting maternal deficits outweigh the risks.

Determinants of the return of fertility

From a programmatic perspective, the benefits that vitamin-A-deficient women and their nursing infants can obtain from periodic exposure to high-dose preformed vitamin A supplement must occur within a "safe period" during which there is contact with the health system. Such contact varies with the health service infrastructure. It is important, therefore, to identify the determinants of postpartum infertility and the practical indicators available in the field for identifying the risk of the return of fertility. The relevant issues are summarized below.

Physiological determinants of the return of fertility postpartum and the duration of lactational infertility in developing countries (Dr Kathy I. Kennedy and Dr Alan S. McNeilly)

Lactational infertility depends on the neuroendocrine stimulus of suckling. Suckling affects ovarian activity by suppressing the normal pattern of release of the gonadotropin-releasing

hormone (GnRH) in the hypothalamus and by increasing the sensitivity of the hypothalamus and pituitary to the negative effects of estradiol. As suckling declines, there is a progressive escape from this inhibition, a gradual return to pulsatile secretion of GnRH/luteinizing hormone (LH), and eventually a return to the positive effects of estradiol that are necessary to generate the pre-ovulatory LH surge. The pattern of suckling plays a crucial role in maintaining the disruption of the release of GnRH and the consequent suppression of fertility.

The onset of the first postpartum menses is a clear indication that ovarian activity has occurred, that fertility is returning, and that a family planning method should be used if pregnancy is to be avoided. During lactational amenorrhoea there is, by definition, no menstruation. Bleeding of any sort is due to a withdrawal of steroid support to the uterine endometrium after a period of exposure to increased steroid. Thus any bleeding during lactation is indicative of ovarian activity or, more accurately, the end of a period of steroid secretion by the ovary. In the absence of ovulation there is no corpus luteum, no progesterone secretion, and hence no progesterone withdrawal to precipitate the normal menstrual bleeding, although bleeding of shorter than normal duration may occur after withdrawal of estradiol. If the first ovulation precedes the first menstruation during breast-feeding, it is usually associated with abnormal function of the resulting corpus luteum, which secretes progesterone in levels that are too low to support a pregnancy.

The Bellagio Consensus was achieved in 1988 on the basis of data about the return of fertility in 13 prospective studies in eight countries. The consensus states that "...the maximum birth spacing effect of breastfeeding is achieved when a mother 'fully' or nearly fully breastfeeds and remains amenorrhoeic ... When these two conditions are fulfilled, breastfeeding provides more than 98% protection from pregnancy in the first six months." Prospective clinical trials have been carried out to test the indicators identified in reaching the Bellagio Consensus, and the consensus has been operationalized as the lactational amenorrhea method (LAM) of family planning. These trials involved women who were actively using LAM to avoid pregnancy. The studies found that the rate of pregnancy at the end of six months postpartum in amenorrhoeic, fully breast-feeding women was indeed less than 2%.

A prospective study of over 4000 women in seven countries was conducted by WHO to study infant feeding practices and the return of menses. It was not a study of women using LAM, but it found that the rate of pregnancy was less than 1% at the end of six months among breast-feeding women who perceived that they were still amenorrhoeic, regardless of how much or how little food supplement they were giving to their infants.

Thus, it was determined at a follow-up meeting in 1995, that "the Bellagio Consensus clearly has been upheld" by subsequent prospective research.

A large array of factors secondary to the breast-feeding stimulus have been assumed to affect the duration of lactational infertility. Among the many potential factors are characteristics of the infant, such as general health (including gestational age at delivery, size/weight and nutritional status) and the intensity of suckling. Potential maternal factors include age, parity, ethnicity, employment and psychological, environmental and socioeconomic factors. Maternal

nutritional status is associated with lactational infertility, but probably acts by mediating the stimulus of suckling.

Data from the DHS in 47 countries are available on the percentage of women still breast-feeding at increasing times postpartum. Such data help in making informed decisions about the risk of pregnancy in developing countries. Summary data by region presented in Table 2 illustrate the wide ranges encountered among countries even within the same region.

Table 2. Ranges of percentage of women still breast-feeding, amenorrhoeic, abstaining and insusceptible to pregnancy, by region and time since delivery

	Breast-feeding	Amenorrhoeic	Abstaining	Insusceptible
	2–3 months postpartum			
Sub-Saharan Africa	87–100	73–93	12–93	84–99
Asia/Near East/ North Africa	81–99	57–81	10–75	62–91
Latin America	61–96	46–90	22–55	53–93
	4–5 months postpartum			
Sub-Saharan Africa	86–100	67–90	13–82	75–95
Asia/Near East/ North Africa	76–100	40–63	1–38	42–68
Latin America	45–95	19–82	8–35	32–85
	6–7 months postpartum			
Sub-Saharan Africa	75–99	53–82	7–75	70–88
Asia/Near East/North Africa	69-99	22-62	35453	25-65
Latin America	35-95	8-67	35726	15-73

The data summarized in Table 3 show the positive relationship between the breast-feeding stimulus and the duration of lactational amenorrhoea that has been observed prospectively in clinical studies. The longest durations of both breast-feeding and lactational amenorrhoea are generally observed in sub-Saharan Africa. In no sub-Saharan African country studied was the median duration of breast-feeding less than 17 months, or the median duration of lactational amenorrhoea less than 8 months. Only in Latin America were median durations of breast-feeding observed to be less than one year. However, there are likely to be subgroups of women with short durations of both lactation and infertility, as well as subgroups with long durations, in all countries.

The level of breast-feeding stimulation required to induce lactational infertility appears to vary widely. A practical measure of a woman's natural capacity to respond to the breast-feeding stimulus is the duration of her previous lactational amenorrhoea, which obviously excludes women breast-feeding their first child.

Clinical studies of lactational infertility, as well as the DHS data, suggest that strategies for vitamin A supplementation should vary from region to region and country to country, just as the duration of lactational amenorrhoea or postpartum insusceptibility varies. Within a regional

or country strategy, advice to individual women to use contraception before or when their LAM protection expires may be an appropriate adjunct to vitamin A supplementation.

Table 3. Ranges of median durations of breast-feeding, amenorrhoea, abstinence and insusceptibility to pregnancy by region

	Breast-feeding	Amenorrhoeic	Abstaining	Insusceptible
Sub-Saharan Africa	17–28 months	8–17 months	1–19 months	13–22 months
Asia/Near East/ North Africa	12–36+ months	4–10 months	1–4 months	4–11 months
Latin America	4–18 months	3–12 months	2–5 months	3–13 months

HRP-sponsored multicentre study

Participants in the consultation reviewed the unpublished results of a seven-country multicentre study carried out in Australia, China, Chile, Guatemala, India, Nigeria and Sweden using a standardized protocol to examine the duration of lactational amenorrhoea in relation to breast-feeding practices. Highly significant centre effects were seen in the duration of lactational amenorrhoea. In addition to the centre differences, 10 factors were significantly related to the duration of amenorrhoea: seven of these were infant feeding characteristics, and the remaining three were parity, body mass index and frequency of infant illness. A strong correlation was found in all centres between the length of amenorrhoea when breast-feeding the previous child and the duration of lactational amenorrhoea in the study.

Among the cohort of women with previous breast-feeding experience, median durations of amenorrhoea ranged from 122 days in India to 282 days in China. Cumulative pregnancy rates during breast-feeding and lactational amenorrhoea (woman's perception) from all centres were 0.1% (95% CI = 0.0-0.3) at day 112 (3.5 months) postpartum, and 0.8% (95% CI = 0.2-1.4) at day 182 (6 months).

DHS data on risk of conception

Data from DHS surveys in 27 countries were evaluated from a different perspective to address the question of risk of subsequent conception following a birth under different feeding regimes. Three approaches to data analysis were used, namely:

- the duration of "closed birth intervals" assuming a pregnancy duration of 9 months;
- construction of tables for the probability of conception according to breast-feeding status;
- susceptibility to conception.

Each approach has limitations, but the inaccuracies were thought to give a conservative bias. Consideration of the data from these viewpoints indicated that the "best case" scenario of exclusive and full breast-feeding showed an approximately 2% conception *susceptibility* as early as two months postpartum. Participants emphasized that susceptibility was not equivalent to probability of conception, i.e. many physiological and social factors can decrease the likelihood

of conception following the first postpartum ovulation. For example, up to 80% of first postpartum ovulations do not result in a viable pregnancy even if conception occurs, and cultural factors sometimes dictate extended periods of postpartum sexual abstinence.

Country experience

Bangladesh provided an example for situational analysis and evaluation of the length of the postpartum non-conception period under real community conditions. In Bangladesh, with a population of 120 million, infant mortality is about 78 per 1000 live births, low birth weight occurs at a rate of 40%, contraceptive use rates are 46% among married women (median age at marriage is 18.3 years), mean duration of breast-feeding is 28.6 months and postpartum amenorrhoea averages nearly 12 months. A review of experience from longitudinally collected data on fertility return from the Matlab study area confirmed a reduced risk of the return of fertility among fully breast-feeding women. For breast-feeding women, the overall risk of conception was 4 per 10 000 at 6 months postpartum. However, among women who abruptly stopped breast-feeding, most because their infants died, the cumulative probability of conception was 30 per 10 000. Hence, the return to fertility was much faster when breast-feeding was abruptly interrupted in the early postpartum lactational period. This confirms in a practical setting the experimental findings reviewed in the background paper.

Summary of discussions

Participants agreed that the available data indicate that suckling is the stimulus that drives the mechanism that postpones the recovery of fertility. Breast-milk substitutes or supplements affect the return of fertility to the extent that they decrease the suckling stimulus. Among women in affluent societies, "supplementation" is often a substitute for breast-feeding and the overall amount of suckling is decreased, leading to an earlier return of fertility. Less affluent women may eventually supplement breast-feeding; however, they may or may not concurrently reduce suckling.

The importance of exclusive breast-feeding (i.e. nothing else but breast-feeding) and full breast-feeding (i.e. minor amounts of low-caloric additions) in extending the time to fertility return is confirmed on a population basis across a wide variety of communities. Although the three indicators associated by the Bellagio Consensus with less than 2% risk of pregnancy—amenorrhoea, the first 6 months postpartum, and full or nearly full breast-feeding—are reliable guidelines for populations, there is no field-applicable *certain* indicator of infertility on an individual basis. However, individual risk will be low if the breast-feeding woman is in compliance with the Bellagio guidelines. These guidelines provide, therefore, simple indicators that could be used by field-workers in areas of endemic VAD to screen women of reproductive age who are eligible to receive a high-dose vitamin A supplement but who are in contact with the health services only beyond 2–3 months postpartum.

For women who are not breast-feeding there are limited data on which to base an estimate of the infertile postpartum period. Although it often takes 5–10 weeks for normal fertility to

return, the first ovulation can occur within 27 days of delivery. The cycle of such an early ovulation will occasionally have normal characteristics.

Policy and programme implications

Participants identified four scenarios for giving vitamin A supplements, through public health programmes, primarily to improve the vitamin A status of the infant before six months of age in order to realize the benefit of protection against morbidity and mortality beyond six months. The scenarios, each of which have implications for safe dosage and frequency of administration, were:

1. Maternal supplementation during pregnancy for mothers whose habitual intakes are above the RDA or below the RDA, from 1–60 days following conception, and after 60 days following conception.
2. Supplementation for mothers in the first six months postpartum.
3. Direct supplementation of infants before six months of age.
4. Supplementation both for mothers during the "safe" infertile postpartum period and for infants under six months of age.

Working groups were formed to discuss each of the scenarios and to reach consensus on safe doses and timing—so that policy and programmes could be drawn up without waiting for additional research—and to identify research required before current guidelines should be altered. The consensus views on recommendations and research needs for each of the scenarios were as follows.

Recommendations on doses and timing

1. Maternal supplementation during pregnancy

(Either during the first 60 days following conception when there is a teratogenic risk or after the first 60 days following conception, for women whose habitual intakes are above the RDA or below the RDA)

For fertile women, independent of their vitamin A status, 10 000 IU (3000 μg RE) is the maximum daily supplement to be recommended at any time during pregnancy.

Where VAD is endemic among children under school age and maternal diets are low in vitamin A, health benefits are expected for the mother and her developing fetus, with little risk of detriment to either, from:

- either a **daily supplement** not exceeding 10 000 IU vitamin A (3000 μg RE) at any time during pregnancy;
- or a **weekly supplement** not exceeding 25 000 IU vitamin A (8500 μg RE). In this regard:
- a single dose > 25 000 IU is not advisable, particularly between day 15 and day 60 following conception (day 0);
- beyond 60 days after conception, the advisability of providing a single dose of > 25 000 IU is uncertain; any risk for non-teratogenic developmental toxicity is likely

to diminish as pregnancy advances. In the case of a pregnant woman who may be reached only once during pregnancy, health workers should balance possible benefits from an improved vitamin A status against potential risks of adverse consequences from receiving a supplement.

Where habitual vitamin A intakes exceed at least three times the RDA (about 8000 IU or 2400 μg RE), there is no demonstrated benefit from taking a supplement. On the contrary, the potential risk of adverse effects increases with higher intakes—above 10 000 IU—if supplements are routinely ingested.

2. Supplementation for mothers in the first six months postpartum

(Single high-dose supplement above 25 000 IU, and usually at a level of 200 000 IU, during the safe period of postpartum infertility for mothers in vitamin-A-deficient areas)

At the population level

Mothers who are not breast-feeding will benefit from a high-dose supplement given safely during the first 28 days (4 weeks or 1 month) postpartum. Although the risk of conception beyond this point is poorly documented, normal fertility does not usually return for 5–10 weeks. Beyond 6 weeks, therefore, non-lactating mothers should be given no more than 10 000 IU daily. Direct supplementation of the non-breast-fed infant < 6 months of age, who is not given a fortified breast-milk substitute, with as much as 50 000 IU (15 000 μg RE) is the recommended safe intervention to meet the infant's need for vitamin A.

Mothers who are breast-feeding will benefit from a high-dose supplement given up to 60 days (8 weeks or 2 months) postpartum, as will their nursing infants—through higher levels of vitamin A in breast milk. The risk of pregnancy is related to menstrual status of the breast-feeding mother. If she has resumed menstruation she is regarded as fertile. If she is amenorrhoeic, the risk of pregnancy rises after 60 days, in some circumstances reaching 1%–2% by 6 months postpartum. In some very high-risk areas (e.g. where there is a high prevalence of clinical symptoms of VAD in mothers) where a high percentage of contact with the health system occurs within 8–12 weeks, the risk of extending the period for giving a high-dose supplement from week 8 to week 12 (estimated 2.8% conceptions) might be offset by important benefits to the mother (relief of symptoms) and the nursing infant (increased breast-milk vitamin A consumption and consequent increased likelihood of decreased risk of mortality).

For individuals

Mothers who are not breast-feeding, provide a supplement within 28 days of delivery; otherwise give a supplement directly to the infant.

Mothers who are breast-feeding:

- if using reliable contraception, give supplement anytime;
- if practising postpartum abstinence, give supplement anytime;
- if amenorrhoeic, give supplement up to 6 months postpartum;

- if not amenorrhoeic, give supplement to mother at time of next menstruation (an indication that conception has not occurred) or give supplement to child.

3. Direct supplementation of infants before six months of age

(In areas of endemic vitamin A deficiency)

Firm evidence of benefits to **breast-feeding infants** of direct supplementation before six months of age is insufficient. Studies are in progress to clarify the benefits/risks of single supplementation at 50 000 IU (15 000 μg RE) at birth or thereafter, or multiple supplementation at 25 000 IU (7500 μg RE).

Infants who are **not breast-fed** and who are not given fortified breast-milk substitutes should receive a 50 000 IU supplement, preferably by about 2 months of age—otherwise at any time within the first 6 months of life. As an alternative, two doses of 25 000 IU can be given with an interval of a month or more in-between.

4. Supplementation both for mothers during the "safe" infertile postpartum period and for infants under six months of age

There is currently insufficient information to make firm programmatic recommendations regarding risks and benefits to infants on the basis of this supplementation strategy. A WHO-sponsored trial is being conducted in three countries to clarify this issue and results should be available within the next year.

Research needs

1. Direct supplementation of infants

Comparative study of effects of a single 50 000 IU dose given before 6 weeks versus multiple doses (25 000 or 50 000 IU) given in accord with vaccination schedules at approximately 6, 10 and 14 weeks.

Outcomes to be evaluated:

- mortality/morbidity reduction and vitamin A status.

2. Direct supplementation of mother up to 8 weeks postpartum (possibly longer where infertility is assured)

   Effect of high-dose maternal supplementation (200 000–300 000 IU) on reduction in infant mortality/morbidity up to three years of age, and on maternal vitamin A status.

   Outcomes to be evaluated:

   - acute effects in mother, i.e. serum and milk retinol and retinol metabolites;
   - long-term effects on mortality/morbidity and vitamin A status in infancy up to three years of age, and in mothers;
   - effects of partial weaning/cessation of breast-feeding on mortality, morbidity and vitamin A status and return of fertility.

3. Direct supplementation of both mother and infant (the consultation noted that WHO-sponsored studies are in progress in three countries using the following protocol)

Effect of 200 000 IU vitamin A supplement to mother before 8 weeks postpartum and 25 000 IU to the infant in accordance with vaccination schedules at approximately 6, 10 and 14 weeks.

Outcomes to be evaluated:

- mortality/morbidity of infants up to three years of age, and vitamin A status of both infant/young children and mothers.

4. Risk/benefit analysis:
   - benefit of 200 000 IU vitamin A supplement given to mother at birth on reduction in mortality at birth, at 2 months and at 4 months (followed until three years of age where possible) versus supplementation of infants only after 6 months;
   - benefit to the mother in terms of reduction of incidence of diarrhoea and night blindness.
5. Pharmacokinetic studies using preformed vitamin A and retinoic acid metabolites given to non-pregnant women residing both where there is a history of VAD and where intakes are known to be adequate, using:
   - daily doses of 10 000 IU;
   - weekly doses of 25 000 IU.
6. Developmental psychological studies of children who were exposed *in utero* to doses of preformed vitamin A ≥25 000 IU, and those exposed to weekly doses of vitamin A (25 000 IU) via breast milk. (While acknowledging that such research is methodologically challenging, the results are needed before routine *daily* dosages >10 000 IU or *weekly* doses >25 000 IU can be recommended at any time during pregnancy.) Ongoing human studies of the behavioural teratogenesis of 13-cis-retinoic acid will provide guidance in selecting an efficient and specific battery of testing tools for use in such research.
7. In countries with adequate vitamin A status, development of systems for monitoring vitamin A content of foods with high concentrations (animal livers) and associated risks of human hypervitaminosis and of teratogenicity in pregnant women.
8. Exploratory research to develop a new type of supplement that has advantageous absorption characteristics such as those reported for foods like liver, i.e. delayed absorption with reduced levels of teratogenic retinoid metabolites.
9. Studies on maternal factors that optimize transfer of vitamin A to breast milk (e.g. effect of other nutrient deficits or disease and mammary gland concentrations of vitamin A relative to circulating levels).
10. Level and duration of elevated retinoic acid metabolites in breast milk following high-dose maternal supplementation.

Contact points with the health services

Country-specific information on the contacts of mothers and infants with the health services, and the coverage of these services, is important for selecting appropriate supplementation programmes. Data available from WHO's Maternal and Newborn Health/Safe Motherhood Programme have been used as the basis of the summary global estimates contained in Table 4

for the percentages of antenatal care contacts, place of birth, and level of training of birth attendants.

Table 4. Global estimate of the percentage of births receiving antenatal care, the place of birth, and the level of training of home birth attendants

	Births in millions	Antenatal care (%)	Place of birth		
			Institution (%)	Home (%)	
				Trained birth attendant	Untrained birth attendant
World	141	64	44	16	40
More developed	15	98	95	4	1
Less developed	126	59	37	18	45
Asia	83	57	33	23	44
Africa	31	59	34	21	45
Latin America	12	72	66	10	24

Additional information on delivery by a medical professional (physician or nurse), contacts with infants under 2 months of age, and contacts with mother/infant within 8 weeks of delivery was provided by DHS surveys from 27 countries. The data are summarized by region in Table 5.

Table 5. Estimates from 27 countries, by region, of contacts with the health services from birth and up to 8 weeks

Region	Health professional (%)			Age < 2 months at vaccination	Contact ≤ 8 weeks after birth
	Physician	Nurse	Total	(%)	(%)
Africa (14 countries)	6.2 (0.3–14.1)	34.3 (10.0–56.4)	40.5	33.0 (19.2–59.9)	59.1 (23.0–79.8)
Latin America (6 countries)	42.0 (10.5–70.9)	17.2 (3.2–31.9)	59.2	25.7 (13.9–40.0)	75.8 (52.3–94.7)
South-East Asia (Indonesia)	5.1	30.1	35.2	7.9	39.7
Europe (Turkey)	33.7	42.2	75.9	13.1	78.8
Eastern Mediterranean (4 countries)	25.5 (5.9–50.3)	16.3 (7.2–37.0)	41.8	17.8 (2.8–43.2)	55.5 (31.9–88.1)
Western Pacific (Philippines)	26.0	26.8	52.8	17.2	59.0

Generic scenarios for populations where supplementation programmes are needed

Although limited, contact data are useful in developing generic scenarios to assist in programme planning. The scenarios in Table 6 are suggested only as a guide. Country-specific situation analysis is required before country-specific programme decisions can be made.

Table 6. Suggested situation analysis guideline for selecting appropriate country-specific vitamin A supplementation programmes

	Case scenario number*					
	1	2	3	4	5	6
	Breast-fed infants					non-breast-fed infants
Adolescent girls	weekly/ monthly	–	–	–	–	–
1st antenatal care visit (mother)	daily/ weekly	–	–	daily/ weekly	–	–
Delivery kit (mother)	200 000 IU at delivery	–	200 000 IU at delivery	–	–	–
1st postpartum contact	–	–	–	200 000 IU at <60 days post-partum to lactating mother	–	50 000 IU to infant
BCG contact within 2 months	–	200 000 IU to mother	–	–	25 000 IU to infant	–
Child DPT 1 & 3rd contact	25 000 IU	25 000 IU	25 000 IU	25 000 IU	25 000 IU	25 000 IU (alternative to single larger dose)
Routine supplement to child ≥ 6 months at 4–6 monthly intervals	100 000 IU at 6–12 months, 200 000 IU afterwards	100 000 IU at 6–12 months, 200 000 IU afterwards	100 000 IU at 6–12 months, 200 000 IU afterwards	100 000 IU at 6–12 months, 200 000 IU afterwards	100 000 IU at 6–12 months, 200 000 IU afterwards	start at 12 months at 200 000 IU
Measles immunization contact (if no routine supplement)	25 000 IU	25 000 IU	25 000 IU	25 000 IU	100 000 IU	100 000 IU

*Description of case scenarios for areas with endemic vitamin A deficiency:

1. "Ideal" situation, i.e. the highest recommended supplementation schedule (starts early with a woman of reproductive age, continues through pregnancy, and extends through infancy and the child's vulnerable years).

2. Breast-feeding and supplementation linked to vaccination schedule.
3. Preferred over case 2 if safe delivery kits are available because of probable wider coverage.
4. Good alternative because it covers the mother during early pregnancy as well as the child's early years.
5. Targeted exclusively at immunization and infant. Although this misses the mother, this is the situation in many developing countries.
6. A difficult situation in which the infant should be supplemented at the earliest contact and should receive doses linked with vaccination schedule as well.

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Vitamin A is essential for normal maintenance and functioning of body tissues, and for growth and development. This is also the case during pregnancy, when the fetus makes demands on the mother's vitamin A stores, and during the postpartum period when the newborn is growing rapidly and, in most cultures, depends on breast milk to obtain adequate amounts of the vitamin. Although the increased requirement during pregnancy is relatively small, in many countries where vitamin A deficiency (VAD) is endemic, women often experience deficiency symptoms such as night blindness that continue during the early period of lactation.
Beyond 4 to 6 months postpartum breast milk from deficient mothers is likely to contain insufficient vitamin A to build —or even maintain—vitamin A stores in nursing infants.

Providing a diet adequate in vitamin A—neither too little nor too much—is the safest solution to meeting needs during pregnancy and lactation. However, this is not easily accomplished in situations of poverty and where food with appropriate vitamin A content is in short supply and/or expensive. In such situations the recommended approach is to provide a vitamin A supplement during pregnancy at a dosage and frequency that will safely meet the needs of growing maternal and fetal tissue and will potentially build maternal body stores in anticipation of lactation. However, using high-dose vitamin A supplements to build maternal stores during pregnancy creates a dilemma because of the vitamin's potential teratogenicity during the early stages of pregnancy.

WHO has received requests for programmatic guidance on the safe use of vitamin A supplements by women of reproductive age. New data have become available concerning the return of menses relative to breast-feeding practices and country-specific contacts with the health system. To review these data and other information, WHO convened a consultation to consider both the safe dosage of vitamin A during pregnancy and the first six months postpartum, and the relevant policy and programme implications. This document, which will be of particular interest for managers of national VAD prevention and control programmes, presents the recommendations of participating experts in nutrition, teratology, reproductive physiology and population-based surveys, who have experience in both basic research and its public health applications.

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