

Vitamin A and causes of maternal mortality: association and biological plausibility

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Abstract

Objective: To review the association between major causes of maternal mortality and vitamin A, trying to determine if these associations are causal in nature, and to highlight possible biological pathways that may explain vitamin A effects.

Design: Literature review, observational studies and clinical trials. The strength of association was determined by applying Bradford Hill criteria of causality.

Results: In a vitamin A deficient population, vitamin A is essential for adequate treatment of anaemia. While vitamin A does not seem to be capable of preventing uterine atony, obstetric or surgical trauma, which are important causes of haemorrhage, it might be capable of preventing or decreasing coagulopathy. Possible effects on the placenta as regards implantation, site and size are not clear. As regards pregnancy-related infections, vitamin A supplementation can improve wound healing by decreasing fibrosis and increasing transforming growth factor- β (TFG- β). It can increase resistance to infection by increasing mucosal integrity, increasing surface immunoglobulin A (sIgA) and enhancing adequate neutrophil function. If infection occurs, vitamin A can act as an immune enhancer, increasing the adequacy of natural killer (NK) cells and increasing antibody production. β -carotene in its provitamin form can act as an antioxidant by decreasing endothelial cell damage (the pathognomonic feature of pre-eclampsia) and promote the vasodilator effect of nitric oxide that might bring about a better outcome of toxemia in pregnancy. It is unlikely that vitamin A or β -carotene has an effect on obstructed labour.

Conclusions: Plausible biomedical pathways can only be constructed for obstetric haemorrhage, anaemia in pregnancy, hypertension in pregnancy and pregnancy-related infections. A 40% reduction in the maternal mortality ratio, as observed in Nepal, is unlikely to be solely explained through the aforementioned pathways.

Keywords
Vitamin A
Maternal mortality
Biological plausibility

Over the last decade, the role of vitamin A in decreasing the mortality and morbidity of infectious diseases in children has been established. Now, its importance to women of reproductive age has become a focus of interest. The results of a randomized controlled trial of vitamin A and β -carotene supplementation to women aged 15–45 years in Nepal suggest that this supplementation resulted in a significant reduction in maternal mortality (vitamin A, 40% reduction; β -carotene, 50% reduction¹). Maternal mortality is a major public health problem in developing countries, and decreasing its burden is vital. Of the estimated 585 000 maternal deaths that occur every year approximately 25% are caused by haemorrhage, 15% by infections, 13% by abortion complications, 12% by complications of hypertensive disease in pregnancy, pre-eclampsia or eclampsia and 8% by obstructed labour². Anaemic women are at higher risk of death if these complications occur.

Only if the effect of vitamin A supplementation can be explained through biomedical pathways can we assume

that the observed massive reduction in maternal mortality ratios can be attributed to the vitamin A supplementation. This review focuses on the biomedical relationship between vitamin A and the major causes of maternal mortality.

Vitamin A and β -carotene are not the same

The term 'retinoids' introduced in 1976 includes carotenoids, the natural forms of vitamin A as synthetic analogues, retinol, the vitamin A alcohol (which is derived from animal sources), retinal and retinoic acid, which are the main vitamin A active metabolites. When taken orally, the body can absorb vitamin A much better than β -carotene. The bioavailability and conversion of β -carotene to vitamin A itself is very variable, being dependent on the dietary content of fat, bile salt concentration and the level of other vitamins in the body. β -carotene does not combine with specific carrier proteins and does not require receptors to perform its provitamin actions. Vitamin A, however,

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requires a specific carrier serum protein (retinol-binding protein, RBP) and specific cellular receptors to perform its actions. Clinical and subclinical infection as well as malnutrition affect RBP and receptor levels. Unlike β -carotene, vitamin A is highly toxic when taken in high doses and there is concern about its teratogenicity, although the level that could produce this in humans is still ill defined³. High doses of vitamin A are toxic because the body lacks efficient mechanisms to excrete or destroy excessive loads of it – this could cause catastrophic effects, particularly on cell membranes and possibly on the genome⁴.

The antioxidant effect of vitamin A is largely attributed to β -carotene and other carotenoids. Therefore, while β -carotene can perform all the actions of vitamin A, the reverse is not true.

Methods

This paper has used extensive reviews of published literature. Two databases were used: Medline, 1966 to September 1999; and BIDS, 1981 to September 1999. We searched titles, abstracts and meshes for different terms (a thesaurus search for vitamin A and β carotene and a word search for vitamin A, β carotene, retin*, caroteno*) and a thesaurus and word search (search terms: sepsis, infection, abortion, haemorrhage, hypertension, pre-eclampsia, eclampsia, obstructed labour and anaemia) for conditions associated with the main causes of maternal mortality. Papers were retrieved and any relevant references and review articles were followed up. Unless otherwise specified, only studies which adequately described their study population, the intervention or exposure investigated and the method of determining the outcomes were included. Specific *in vitro* and animal experiments were included in the review. The published literature associating vitamin A and the causes of maternal mortality is extremely limited, therefore we also drew material from unpublished reports by WHO, UNICEF and proceedings of meetings.

Results

Vitamin A and obstetric postpartum or post-abortion haemorrhage

We found no studies linking vitamin A directly to obstetric haemorrhage. Obstetric haemorrhage can be the result of: insufficient uterine contraction following delivery (uterine atony); retained products of conception (usually placental parts); trauma (whether obstetric or surgical); and dysfunction of the blood-clotting system. Despite a comprehensive review we were unable to identify a biological pathway linking vitamin A/ β -carotene deficiency to uterine atony (the leading cause of postpartum haemorrhage).

Abnormalities of the placenta (size, site, vessels and depth of its implantation in the uterine wall) can all lead to

haemorrhage. Placental development depends on a complex and not completely understood interaction between foetal and maternal cells. Highly specific receptors for RBP (essential for the action of retinol) are expressed in the human placenta⁵. The level of RBP in the placenta is higher than in any other tissue of the body, including the retina⁶. Placental β -carotene level is almost twice as great as those found in the liver⁷. The presence of these high and specific levels of both vitamin A and its precursors suggest that vitamin A is essential for the placenta, or foetus, or both. It is conceivable that vitamin A deficiency could lead to problems of implantation and placental development, which in turn could lead to problems of placental separation and postpartum or post-abortion haemorrhage, or placenta praevia and placental abruption. Indeed, Sharma *et al.*⁸ reported significantly lower levels in serum vitamin A and β -carotene when comparing cases with abruptio placentae to controls. However, vitamin A deficiency may be the cause or effect of the abruption as a decrease in vitamin A can be part of an acute phase response and decreased β -carotene may be the result of increased consumption as an antioxidant to combat the oxidative stress of placental abruption.

Other causes of obstetric haemorrhage include coagulopathy. Normal coagulation depends on the adequate function of platelets, healthy endothelium and harmony between coagulation factors. Vitamin A seems to have no effect on platelet aggregation and adhesion^{9,10}.

Endothelium injury is the starting point that triggers abnormal aggregation of the coagulation factors and leads to coagulopathy. Vitamin A appears to increase the integrity and vitality of endothelial cells¹¹ and so could possibly prevent endothelial injury. After endothelium injury, coagulation factors start to accumulate, forming abnormal small clots that initiate a vicious cycle of disseminated intravascular coagulopathy. The increased consumption of coagulation factors leads to its exhaustion and profound haemorrhage. Vitamin A supplementation may have an effect on the clotting system through increasing thrombomodulin^{12,13}, decreasing antithrombin III¹⁴ and increasing tissue plasminogen activator^{15,16}. This, together with the endothelial protective effect, suggests that vitamin A may be capable of preventing coagulopathy from the beginning or decrease its severity if it occurred.

Vitamin A and infection in pregnancy or the post-abortion or postpartum period

Pregnancy-related infection (PRI) may result from colonization of retained products of conception (usually a part of the placenta), pre-existing infection or from unsterile invasive procedures. PRI has rarely been associated with vitamin A deficiency. In the Vanderbilt cooperative study of infant and maternal nutrition of 1945, women who experienced puerperal infection were found to have lower vitamin A levels starting from the second trimester and continuing through the postpartum examination¹⁷.

Bacteriuria (suggestive of urinary tract infection) was observed in 80% of pregnant women presenting with clinical vitamin A deficiency¹⁸. Cases with vaginal candidiasis showed a significant decrease in β -carotene concentration in exfoliated vaginal epithelial cells when compared to controls¹⁹. Pregnant women with night blindness were also twice as likely to have clinical genitourinary tract infections (lower abdominal pain, painful micturition or vaginal discharge) than controls without night blindness²⁰. The relationship between infection and decreased vitamin A levels is, however, not that simple. Night-blind women in the study mentioned above were also more likely to be anaemic, undernourished, of lower cast and illiterate which could explain an element of the association²⁰.

The decreased vitamin A levels found in infection might be due to decreased absorption of dietary vitamin A (due to diarrhoea or the activity of intestinal pathogen)²¹, decreased RBP production²² or increased loss of vitamin A in urine^{23,24}. In acute phase reaction, there is a transient decrease in the production of small molecular weight proteins, including RBP, and an increase in the permeability of renal epithelial cells. Decreased vitamin A might also be due to increased uptake of retinol by certain tissues²⁵.

PRI could be reduced through three main pathways: promotion of wound healing; increased resistance to infection; and immune enhancement if infection occurs. Vitamin A increases the production of TGF- β , which is involved in the promotion of wound healing²⁶ and decreases fibrosis through suppression of the fibroblasts. These two actions may increase the integrity of the mucosal surfaces of genitourinary tracts and promote better healing of episiotomy and perineal laceration, thereby decreasing the chance of infection. Vitamin A augments natural resistance through increasing the naturally present antibodies, IgA, and promoting the function of neutrophils. Neutrophils are an important part of the first line of defence against infection as they engulf bacteria, viruses, parasites and virally infected cells. An alteration in all the components of neutrophil function has been demonstrated in vitamin A-deficient rats²⁷.

The progress of infection depends on three factors: (i) the virulence and dose of the pathogen; (ii) host immunity; and (iii) the usage of appropriate antimicrobial agents. It is unlikely that either vitamin A deficiency or supplementation could alter the pathogen but the expected effect will be brought about through enhancing different components of the immune system.

Vitamin A helps the control of viral infection. Retinoids regulate cell growth and differentiation as well as apoptosis (programmed cell death seen in viral infection and tumour cells)²⁸. Both the number and the activity of NK cells (which are involved in antiviral and antitumour immunity) are decreased in vitamin A deficiency²⁹. Supplementation of vitamin A results in an increase of NK cells in children with acquired immunodeficiency syndrome

(AIDS)³⁰. The methodology of this study could not be evaluated as it is published only as a meeting abstract.

The successful production of antibodies to compete with the bacteria depends on three types of cells: (i) antigen-presenting cells (APC), which present the bacterial antigen to the immune-specific cells (lymphocytes); (ii) B lymphocytes, which are responsible for antibody production; and (iii) T lymphocytes, which regulate the immune response. Retinol is required for growth and activation of B lymphocytes in humans^{31,32}. Transretinoic acid augments the production of two types of antibodies: IgM (antibody of the first immune response) and IgG (antibody of the secondary immune response)³³. Retinol seems to be required for the activation of T lymphocytes³⁴. In vitamin A deficiency, antibody response is impaired for both T-cell-dependent antigen³⁵ and T-cell-independent antigen³⁶.

Vitamin A may decrease the incidence and severity of RPI by promoting wound healing, increasing resistance to infection and immune enhancement if infection occurs.

Vitamin A and hypertensive disorders of pregnancy

Many observational studies found a significant decrease in vitamin A and β -carotene in pre-eclamptic women when compared with normal pregnant women. This decrease was found both in serum^{37–40} as well as amniotic fluid⁴¹. The constant association between decreased retinol and β -carotene levels with pre-eclampsia, however, does not prove a causal relationship. Decreased retinol might be a part of an acute phase reaction. Many studies found decreased serum proteins in toxemia of pregnancy^{37,42,43} and retinol is carried on proteins, thus its decrease could be secondary to decreased protein levels. Other studies correlated pre-eclampsia and eclampsia with increased oxygen free radicals⁴⁴ and decreased antioxidant activity^{45–50}. Thus, the decreased β -carotene might be due to increased consumption as it is an antioxidant. These observational studies are supported by an *in vitro* study that showed that β -carotene levels present in normal pregnant women significantly inhibited peroxide-induced vasoconstriction in a dose-dependent manner. Lower levels of β -carotene, like those present in pre-eclampsia, were not able to achieve the same effect⁵¹. A recent nested case–control study from Nepal compared 109 pregnant women with impending night blindness (xerophthalmia, XP) (cases) and without XP (controls). Plasma levels of retinol (but not β -carotene) were significantly decreased ($P < 0.001$) while rates of pre-eclampsia/eclampsia were significantly increased in patients with imminent XP²⁰. The effect on pre-eclampsia/eclampsia was not observed after XP had developed.

Endothelial cell dysfunction is the common pathway in the pathogenesis of pre-eclampsia. β -carotene is a recognized antioxidant and free radical scavenger, and this beneficial effect is related to its provitamin activity. β -carotene and other carotenoids are much more effective antioxidants than vitamin A. Nitric oxide is a potent

vasodilator substance that is believed to play a major role in increasing placental perfusion⁵². Oxidation of low density lipoprotein (LDL) decreases the release of nitric oxide. β -carotene is carried on LDL and protects it against oxidation and thus promotes nitric oxide vasodilatation. This effect has been demonstrated in animals⁵³, *in vitro*⁵⁴ and in humans⁵⁵. A randomized, double-blind placebo-controlled trial of vitamins E and C (stronger antioxidants than β -carotene) supplementation in women at increased risk of pre-eclampsia showed a marked reduction in pre-eclampsia in the intervention group (adjusted odds ratio 0.39 [0.17–0.90])⁵⁶.

The underlying pathology in pre-eclampsia appears to be insufficient placental implantation. This is thought to lead to a relatively hypoxic maternal–foetal interface, an increased turnover of trophoblast tissue, higher xanthine and hypoxanthine concentrations and higher levels of circulating cytokines and an increased production of uric acid and free radicals⁵⁷. It is unlikely that β -carotene or other antioxidants can totally correct these multiple abnormalities. In established severe cases it is unlikely to restore normality except by delivery. We do not believe that β -carotene alone can restore normality in established pre-eclampsia but it may contribute to a more favourable outcome. As of September 1999, it remains biologically plausible that β -carotene, by decreasing endothelial cell damage and promoting vasodilatation, could have the potential to decrease the incidence and severity of pre-eclampsia.

Vitamin A and obstructed labour

Conceptually obstructed labour can be caused by problems of the passenger (foetus), the passages (bony pelvis, cervix and vagina) and the forces (uterine contraction). Despite the best of intentions and imaginative effort, it was not possible to identify any studies linking obstructed or prolonged labour and vitamin A deficiency.

A hypothetical pathway may be related to the central nervous system (CNS) of the foetus. Vitamin A is involved in CNS development and impaired CNS development is known to decrease the frequency of malposition in labour. However, no data was found to support this hypothesis. Increase in size of the foetus or macrosomia is a known cause of obstructed labour, but there is no data reporting abnormal decreased weight with increased vitamin A supplementation. Decreased size is associated with malpresentation and obstructed labour. Low cord vitamin A has been constantly associated with decreased birth weight^{58–63}. Maternal serum of low birth weight newborns did not significantly differ from mothers of normal birth weight newborns^{64,65}. Birth weight was not altered by daily vitamin A supplementation during pregnancy for more than 12 weeks⁶⁶. It is to be noted that these studies used different case definitions and did not differentiate between prematurity and intrauterine growth restriction. Thus, no conclusive evidence can be

drawn from them. From available information the determining factor seems to be the availability of vitamin A for utilization by the growing foetus rather than the maternal serum level of vitamin A.

A further pathway could be related to uncoordinated or insufficient myometrial activity (forces) and vitamin A deficiency. Yet, no evidence was found for this pathway or for any effect of vitamin A deficiency on the soft and bony tissues of the pelvic passage.

Vitamin A and anaemia during or after pregnancy

Very severe anaemia (haemoglobin of less than 4 g dl⁻¹) can lead to heart failure and death especially during a metabolically stressful condition such as delivery. Anaemia increases the likelihood of mortality in cases of haemorrhage. However, anaemia associated with vitamin A deficiency may be more important than generally perceived – vitamin A deficiency affects water metabolism with resulting haemoconcentration and haemoglobin levels may be normal when ‘total body haemoglobin’ is low.

Anaemia in pregnancy is largely attributed to iron deficiency, malaria and hookworm infections. Vitamin A increases the integrity of the epithelial cells of the intestinal tract with resultant better absorption of iron. A recent study suggested that vitamin A can increase the absorption of iron in fortified food by two-fold and β -carotene by three-fold and that it prevents the inhibitory effect of phytates on iron absorption in humans⁶⁷. The results of this study need to be interpreted with caution as the method of food processing used may have affected iron absorption rates. Vitamin A supplementation to pregnant, poorly nourished women results in an increase in circulating iron and transferrin and facilitates the delivery of iron to bone marrow^{68,69}. Vitamin A is necessary for the adequate formation of red blood cells. Impaired red blood cell formation has been demonstrated in the form of poikilocytosis and anisocytosis (abnormal size, shape and staining characters) when 10 male volunteers were fed with a vitamin A-deficient diet for 188 days⁷⁰. *In vitro* studies indicate that retinoids influence the growth and differentiation of various precursors of red blood cells⁷¹.

Randomized controlled trials in India⁶⁶ and Indonesia⁶⁹ showed that the combination of vitamin A and iron supplementation resulted in a significant and important reduction of the prevalence of anaemia in pregnancy when compared with vitamin A or iron supplementation alone.

Vitamin A is necessary for haemopoiesis and iron metabolism. It is likely that vitamin A supplementation can reduce anaemia prevalence in vitamin A-deficient pregnant women.

Conclusions

This paper addressed the relationship between vitamin A and the main causes of maternal mortality. Plausible

biomedical pathways could be constructed for obstetric haemorrhage, anaemia in pregnancy, hypertension in pregnancy and pregnancy-related infections. While the evidence presented in this review does not permit estimating the effect of vitamin A/ β -carotene supplementation on maternal mortality, it is the impression of the authors that a 40% reduction in maternal mortality ratio as observed in Nepal cannot be solely explained through the above described pathways. If vitamin A does reduce the risk of maternal mortality it is likely to do so through multiple pathways. Some of them will include alterations in placentation (inappropriate placentation can be expected to be associated with an increased risk of hypertension in pregnancy, post-abortion haemorrhage and obstetric haemorrhage). If this were the case, vitamin A supplementation during the period of placentation (first trimester) rather than in the second and third trimester may be the explanation of the reduced maternal mortality observed in the Nepal study. This would have important implications for programme planning, as vitamin A supplementation during the conventional antenatal period may not reproduce the beneficial effects of the Nepal study.

Politicians and health planners may be well advised to await the results of further trials before implementing large-scale supplementation programmes. Reducing maternal mortality may require more than vitamin A supplementation in the antenatal clinic.

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