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A study of maternal vitamin A status and its relationship with intrauterine growth restriction

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OBJECTIVE(S) : To determine the prevalence of vitamin A deficiency in mothers of intrauterine growth restriction (IUGR) neonates and to evaluate the relationship of vitamin A levels with birth weight.

METHOD(S) : In a case control-cross sectional study, 50 mothers at term with small for gestional age neonates and 50 mothers at term with appropriate for gestational age neonates were studied to determine the prevalence of clinical and biochemical status of vitamin A deficiency. Serum vitamin A level was then correlated with birth weight in each of the two groups separatelty, and also jointly only in all the mothers in the two groups who had body mass index (BMI) of more than 18 kg/m^2 and hemoglobin level of more than 10 g /dL. Student t test and chi square test were used as applicable to find out the significance between two observed values, and regression analysis was used to determine the correlation between two continuous variables.

RESULTS: Clinical signs and symptoms of vitamin A deficiency (night blindness, conjunctival xerosis, Bitot's spots, corneal xerosis) and low levels of serum vitamin A were commonly seen almost twice often in mothers who delivered IUGR newborns. At least 24% mothers delivering IUGR babies and 10% mothers delivering appropriate for gestational age babies had one or the other clinical sign of hypovitaminosis A. Clinical signs of vitamin A deficiency correlated well with serum vitamin A levels. Severe deficiency of vitamin A (serum vitamin A < 10 mg/dL) was observed in 4% mothers who delivered IUGR babies, while it was not observed in mothers of appropriate for gestational age babies. There was no correlation between serum vitamin A levels and birth weight when other factors such as malnutrition and anemia were associated, but increasing serum vitamin A levels were associated with higher birth weight when mothers had BMI of more than 18 kg/m^2 and hemoglobin level of more than 10 g/dL.

CONCLUSION(S): Vitamin A deficiency during pregnancy may be a very important factor for growth hindrance of the fetus. In malnourished mothers, besides vitamin A many other factors also have an influence on intrauterine growth restriction but vitamin A deficiency appears to be a key factor in mothers who are otherwise not severely malnourished.

Key words : vitamin A, intrauterine growth restriction

Introduction

Intrauterine growth restriction (IUGR) has always been a worldwide dilemma and global challenge for epidemiologists, nutritionists, clinicians, and custodians of fetal health. A bird's eye view of the world literature reveals that modern day researchers have been troubled by the etiological spectra of the condition and volumes have been contributed to unravel the mystery surrounding the etiology of IUGR which is multi-factorial. Nearly 50 individual factors have been evaluated for their role in fetal growth with statistical significance for several of them [1]. They are having direct and indirect causal influences and have been broadly categorized into sociodemogrphic, nutritional, anthropometric, physical factorys, obstetric factors, and factors related to heavy

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physical activity during pregnancy [2-4]. Most important factors leading to high prevalence of IUGR in developing countries are nutritional (macronutrient and/or micronutrient) deficiencies. Amongst macronutrients, energy and protein consumption have been postulated to play a major role [1]. Amongst micronutrients, iron, zinc, folic acid, vitamin D, vitamin A, and magnesium are presumed to play an important role. As already stated, the role of some of these has been confirmed by various studies while the role of others is yet to be confirmed. Although it has been emphatically established that folate supplementation and to some extent magnesium and zinc supplementation also tend to decrease incidence of low birth weight (LBW) other nutrient supplementations are yet to establish a clear cut role in prevention of IUGR [1].

Recently, researchers have shown a very positive influence of vitamin A on plasma progresterone and estrogen levels during pregnancy [5]. Since progesterone is responsible for healthy fetoplacental function, it is postulated that besides its confirmed role in cellular differentiation and morphogenesis, vitamin A may also have an indirect role in fetal growth and maturity [5,6]. A pioneer study conducted by Burns et al [7] revealed that women with low and very low vitamin A levels before third trimester were more likely to deliver LBW infants than those with higher levels. In fact not many studies are yet available to make an impact on the observations made by Burns et al [7], particularly from the developing world including India. Various studies have however revealed a very high prevalence (11-30%) of vitamin A deficiency in pregnant women [7-10]. Whether this translates into LBW and IUGR or not is yet to be established.

The present study was therefore performed to determine the prevalence of hypovitaminosis A in mothers delivering at term small for gestational age (SGA) babies vis-a-vis in mothers delivering at term appropriate for gestational age (AGA) babies. We also tried to determine whether maternal hypovitaminosis A had any causal relationship with IUGR or both were part of the same overall etiological syndrome resulting in simultaneous but unrelated occurrence of both the conditions.

Methods

In this cross-sectional study the study group consisted of 50 randomly selected mothers who delivered at term SGA babies (birth weight less than 2.5 kg and gestational age 37-41 weeks). The control group comprised of 50 randomly selected appropriately matched mothers (for age, socioeconomic status, place of residence, religion, and parity) who delivered at term AGA babies (birth weight more than 2.5 kg and gestational age 37-41 weeks). Lubchnenco's charts were used to determine weight for a particular gestational age and babies weighing less than 10th percentile were considered as SGA and IUGR. Mothers suffering from pregnancy induced hypertension, eclampsia, antepartum hemorrhage and insulin dependent diabetes mellitus, and mothers of babies having congenital malformations, perinatal asphyxia, respiratory distress syndrome, and meconium aspiration were excluded from the study as these are well established determinants of IUGR and may be having an impact on vitamin A status of mothers.

The purpose of interrogation and investigation was explained to every mother and an informed consent was obtained. Approval of ethics committee of the institution was also obtained. The details of mother's socioeconomic profile and daily dietary intake were noted in the predesigned performa. The postpartum weight and height of all the mothers were measured and body mass index (BMI) was calculated. Vitamin A status of mothers was assessed within 24 hours of the delivery by history of night blindness, clinical examination, and biochemical estimation. Clinical examination included detailed ophthalmic examination in day light, specially searching for conjunctival xerosis, Bitot's spots, and corneal xerosis, ulceration, and scarring. Biochemical estimation of serum vitamin A was performed using ultraviolet absorption spectrophotometry [8]. Hemoglobin of all the mothers was estimated using the Sahli's method.

Apgar score, birth weight, gestational age (by modified Perkin's criteria), head circumference, chest circumference, and length of every baby were recorded in the performa, and Ponderal index was also calculated. Data for each variable were obtained separately for mothers of SGA and AGA neonates and results were statistically analyzed using student t test, chi square test and regression analysis.

Results

Mean age of mothers in the study group was 20.98 ± 2.55 years, similar to 21.68 ± 2.64 years in the control group. Sixty-six percent mothers in the study group and 42% in the control group were from tribal belts of Udaipur and Banswara. Sixty-two percent mothers of SGA babies were from lower castes (SC, ST, and backward class) as compared to 52/% mothers of AGA babies. Number of women belonging to Hindu and Muslim religions were comparable in the two groups. Mean education of mothers in the study and control group was 3.44 ± 4.7 years and 5.56 ± 4.42 years respectively, the difference being statistically significant (P=0.011) (Table 1). Fifty percent women in the study group and 54% in the control group were second and third gravidas. Mean height of mothers was 148.8±4.0 cm and 155.4±3.0 cm in study group and control group respectively, and the difference was statistically significant ($P<0.001$). Mean prepregnancy weight of mothers in the study and the control group was 40.9 ± 3.3 kg and 46.9 ± 4.6 kg respectively. The difference was statistically significant (P<0.001). Mean BMI of mothers in study and control group was 18.6 ± 1.2 and 19.9 ± 1.9 respectively and the difference was statistically significant (P<0.002) (Table 2). Evaluation for clinical features of hypovitaminosis A revealed that history of night blindness was present in 10% mothers in the study group as compared to 4% mothers in the control group. Clinical signs of vitamin A deficiency were present in 36% mothers in the study group as compared to 10% mothers in the control group (Table 3). However, 80% mothers in the study group as compared to 42% in the control group were having serum vitamin A levels less than 20 mg/dL. Out of the five mothers in the study group who had Bitot's spots in the eyes, one was having severe (serum vitamin A < 10 mg/dL) and four were having borderline (10-20 mg/dL) vitamin A deficiency. One mother from the study group who had corneal xerosis also had very low levels of serum vitamin A (Table 4).

Table 1. Age, religion, caste and education.

	Study group (n=50)	Control group (n=50)
Age (years)	20.98±2.55	26.68 ±2.64
Hindu	44 (88)	43 (86)
Muslim	6 (12)	7 (14)
Scheduled caste	4 (8)	1 `(2)
Scheduled tribe	8 (16)	6 (12)
Other backward classes	19 (38)	19 (38)
Others castes	19 (38)	24 (48)
Education (years)	3.44 ± 4.7 [a]	5.56 ± 4.42 [a]

Figures in brackets represent percentages. [a] P = 0.011

Table 2. Anthroprometry.

Authropometry	Study group (n=50)	Control group (n=50)	P value
Height (cm)	148.8 ± 4.0	155.4 ± 3.0	<0.001
Weight (kg)	40.9 ± 3.3	46.9 ± 4.6	<0.001
Midarm circumference (cm)	20.0±1.3	22.3 ± 1.6	<0.001
Body mass index	18.6± 1.2	19.5 ± 1.9	<0.05

Table 3. Signs and symptoms of vitamin A deficiency.

Signs and symptoms	Study group (n=50)	Control group (n=50)
Night blindness	5 (10)	2 (4)
Conjunctival xerosis	12 (24)	5 (10)
Bilot's spots	5 (10)	— —
Corneal xerosis	1 (2)	— —

Figures in brackets represent percentages.

Table 4. Serum vitamin A levels.

Vitamin A (mg/dL)	Sutdy group (n=50)	Control group (n=50)
< 10	2 (4)	- -
10-20	38 (76)	21 (42)
> 20	10 (20)	29 (58)
Mean ± SD	16.7±3.6 (mg/dL)	21.0±3.7 (mg/dL)

Figures in brackets represent percentages.

On a detailed dietary analysis, it was revealed that 50% of mothers in the study group and 76% in the control group were receiving vitamin A rich diet seasonally and 46% mothers in the study group and 4% in the control group were taking low vitamin A diet.

All babies in both the groups, were born at term (37 to 41 weeks gestation). Of the IUGR babies 22% were weighing less than 2 kg and 78% weighed between 2 and 2.5 kg. Of the IUGR babies 72% were asymmetrical while 28% were symmetrical indicating that they were affected during last trimester of their intrauterine stay. In the control group all the babies were weighing more than 2.5 kg.

Discussion

For a long while vitamin A deficiency was known to be prevalent only in children but recent studies have shown that it is also very common during pregnancy [8-10]. In the present study clinically overt vitamin A deficiency was observed in at least 24% mothers in the study group and 10% in the control group. Recent data reported from Nepal by Katz et al [8] and from India by Dixit [9] reveal that 12-20% of all pregnant women have a history of night blindness. In the present study, 80% mothers in the study group who delivered IUGR babies and 42% monthers in the control group had serum vitamin A levels less than 20 mg/dL indicating borderline hypovitaminosis A (Table 4). Out of the five mothers in the study group who were having Bitot's spots in the eyes, one had severe (serum vitamin A< 10 mg/

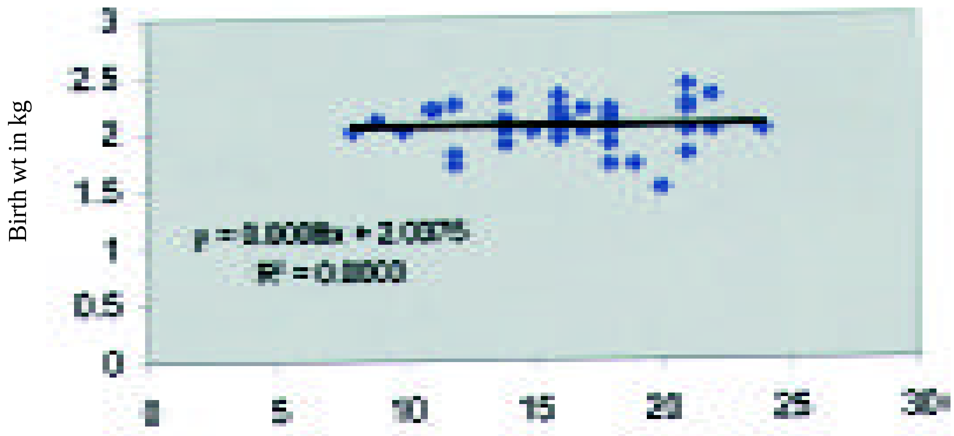
dL) and four borderline (10-20 mg/dL) vitamin A deficiency. One mother from the study group who was having corneal xerosis also had very low level of serum vitamin A. Pioneer studies from other parts of the country conducted by Vinutha et al [10] however report a low (29.6%) but still significant prevalence of biochemical hypovitaminosis A during the last trimester of pregnancy. Burns et al [7] also observed that 29.6% of pregnant women had low and 11.1% very low serum vitamin A levels during last trimester of pregnancy. Although the studies by Vinutha et al [10] and Burns et al [7] were conducted in almost similar epidemiologic settings like ours, the higher prevalence in our study seems to be because of years of deprivation coupled by continuing drought situations in the last 10 years in Rajasthan. Further, it was also observed that the mothers in the study group who had higher prevalence of hypovitaminosis A and delivered term SGA babies were also significantly malnourished when compared to the control group mothers.

The data from the present study certainly support the theory that pregnant mothers like children are another high risk group showing higher prevalence of hypovitaminosis A. But because of severe technical limitations we are unable to put up a plausible explanation for this higher prevalence of vitamin A deficiency during pregnancy. However, scarcity along with poor access to appropriate diet fueled by myths and misconceptions, and inappropriate cultural practices certainly favor the theory of poor nutrient availability to pregnant women.

The role of vitamin A in vision is well established via its 11-cis and all trans retinal forms. Since the last three decades it is well elucidated that vitamin A also plays an important role in cellular differentiation and morphogenesis. Both deficiency and excess of vitamin A adversely affect embryogenesis [6]. Vitamin A is also said to influence synthesis and secretion of various growth factors [11]. Panth et al [5] studied the effect of vitamin A supplementation on plasma progesterone and estrogen levels during pregnancy and concluded that there was a significant increase in progesterone levels without any effect on estradiol levels. It is well known that progesterone is responsible for healthy fetoplacental function. This makes a persuasive case that poor placental function in the presence of hypovitaminosis A can cause IUGR.

We observed that mothers of SGA babies had a higher prevalence of biochemical and clinical hypovitaminosis A as compared to mothers of AGA neonates. Although the aforementioned review of the literature makes sufficient grounds for a role of vitamin A deficiency in development of IUGR the exact players in the genesis of SGA babies in the present study could not be identified because of technical limitations. Since the mothers of SGA babies were also significantly malnourished like mothers of AGA babies, it is also possible that there may have been etiologies other than hypovitaminosis A for IUGR in the present study. The mean hemoglobin level of mothers in the study group (7.95 ± 1.2 g/dL) was significantly lower as compared to the mean hemoglobin level of mothers in the control group (10.3 ± 1.45) ($P<0.001$). Therefore, it is certain that anemia also played an important role along with hypovitaminosis A in the genesis of IUGR.

Malnutrition as a syndrome is an important cause of IUGR and since hypovitaminosis A is usually a part and parcel of malnutrition syndrome which also includes deficiency of other nutrients it is very difficult to pinpoint the contribution of vitamin A deficiency in the etiology of IUGR. In the present study when an attempt was made to determine the relationship between maternal serum vitamin A levels and birth weights of neonates, no significant correlation was observed in any of the groups (Figures 1 and 2). Since all these mothers also had malnutrition and concurrent anemia it was concluded that these two factors may be having a confounding bias/ role in determining the birth weights of neonates in both the groups. To remove this bias we further made an attempt to study the trends between maternal serum vitamin A levels and birth weight of neonates in the two groups whose mothers had hemoglobin levels of more then 10 g/dL and a BMI of more then 18 kg/m^2, since majority of the otherwise normal mothers in India have mean hemoglobin level of 10 g/dL and a BMI of 18-20 kg/m^2. Interestingly, this analysis revealed that increasing maternal serum vitamin A levels corelated well with the increasing birth weight of the neonates (R^2 -0.3262, R=0.5711) in mothers who had hemoglobin levels more than 10 g/dL and a BMI of more then 18 (Figure 3). Since the major cause of vitamin A deficiency in any high risk group is malnutrition, it is practically impossible to evaluate the individual and specific contribution of vitamin A in genesis of IUGR purely by clinical studies. But the aforementioned analysis certainly puts a strong case for the role of vitamin A in determining birth weight and therefore possibly in IUGR. In malnourished mothers, vitamin A may not be the sole or even the key factor but it may certainly be influencing fetal growth. As it is obvious by a review of literature in the aforementioned discussion that vitamin A may influence fetal growth directly by inducing growth factors or indirectly by increasing plasma progesterone levels which may then have an impact on fetal growth and maturity. A study by Semba et al [12] in Malawi also concluded that maternal vitamin A deficiency was independently related to both linear and ponderal growth after adjustments for effects of BMI, gender, and HIV status in mothers who are HIV positive. In fact, another study from West Java by Suharno et al [13], besides concluding that vitamin A supplementation decreases the incidence of LBW babies, also observed that

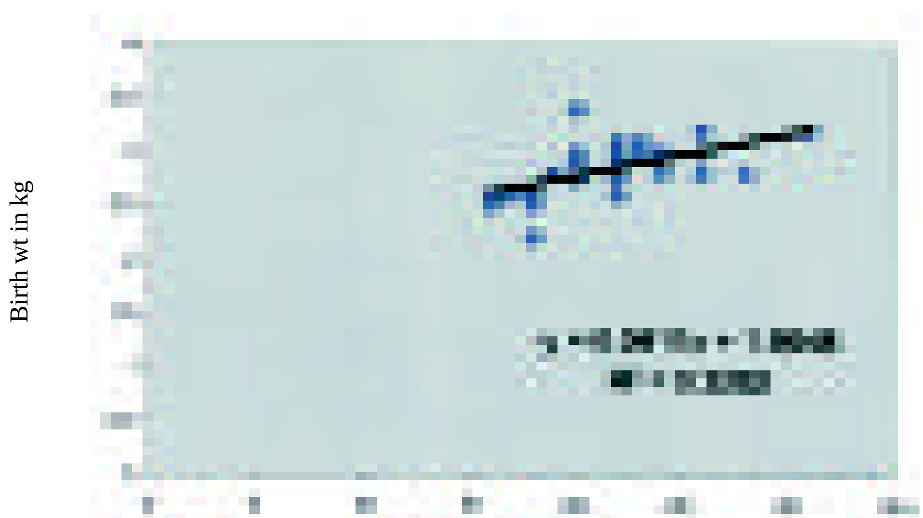


Serum vitamin A level (?g/dL)

Figure 1. Co-relation between serum Vitamin A levels and birth weight in the control group

Serum vitamin A level (?g/dL)

Figure 2. Co-relation between serum Vitamin A levels and birth weight in the control group



Serum vitamin A level (?g/dL)

Figure 3. Corelation between serum Vitamin in A levels and birth weight in mothers (both control & study) having BMI > 18 kg.m³ and Hb level > 10g/dL

97% of anemic mothers who were administered iron with vitamin A became nonanemic as compared to only 68% mothers in whom only iron was supplemented and in only 35% mothers in whom only vitamin A was supplemented.

Conclusion

Vitamin A deficiency is highly prevalent in pregnant women and a persuasive case can be made for a significant role of vitamin A in determining birth weight, and possibly for direct and indirect influences in the pathogenesis of IUGR. Deficiency or abnormal levels of other nutrients in malnourished mothers may however complicate the situation and other factors may also play a significant role in the pathogenesis of IUGR. However more extensive research is needed to elucidate the need for recommending vitamin A supplementation to all pregnant and lactating mothers in areas associated with maternal malnutrition.

References

1. Kramer MS. Determinants of low birth weight: methodological assessment and meta-analysis. *Bull World Health Organ 1987;65:663-737.*
2. Arora NK, Singh M, Paul VK et al. Etiology of fetal growth retardation in hospital born infants. *Indian J Med Res 1987;85:395-400.*
3. Mondal B. Risk factors for low birth weight in Nepali infants. *Indian J Pediatr 2000;67:477-82.*
4. Deswal BS, Singh JV, Kumar D. A study of risk factors for low birth weight. *Ind J Community Med 1999;24:127-31.*
5. Panth M, Raman L, Ravinder P et al. Effect of vitamin A supplementation on plasma progesterone and estradiol levels during pregnancy. *Int J Vitam Nutr Res 1991;61:17-9.*
6. Azais-Braesco V, Pascal G. Vitamin A in pregnancy: requirements and safety limits. *Am J Clin Nutr 2000;71:S 1322 -33*
7. Burns DN, Fitzgerald G, Semba R et al. Vitamin A deficiency and other nutritional indices during pregnancy in human immunodeficiency virus infection: prevalence, clinical correlates, and outcome. Women and Infants Transmission Study Group. *Clin Infect Dis 1999:328-34.*
8. Katz J, Khatry SK, West KP et al. Night blindness is prevalent during pregnancy and lactation in rural Nepal. *J Nutr 1995;125:2122-7.*
9. Dixit DT. Night blindness in third trimester of pregnancy. *Ind J Med Res 1966;54:791-5.*
10. Vinutha B, Mehta MN, Shanbag P. Vitamin A status of pregnant women and effect of postpartum vitamin A supplementation. *Ind Pediatr 2000;37:1188-93.*
11. Blaner WS, Olson JA. Retinol and retinoic acid metabolism. In: Sporn MB, Roberts AB, Goodman DS (eds). *The retinoids: biology, chemistry and medicine*. New York, Raven Press. *1994:229-55.*
12. Semba RD, Miotti P, Chphangwi JD et al. Maternal vitamin A deficiency and child growth failure during human immunodeficiency virus infection. *J Aquir Immune Defic Syndr Hum Retrovirol 1997;219-22.*
13. Suharno D, West CE, Muhilal A et al. Supplementation with vitamin A and iron for nutritional anemia in pregnant women in West Java, Indonesia. *Lancet. 1993;342:1325-8.*