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Case Report Open Access

Vitamin A Deficiency and Female Fertility Problems: A Case Report and Mini Review of the Literature

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Abstract

We present a case of a vitamin A deficient woman who, presented to our clinic with secondary infertility to emphasize the importance of a good history and a multidisciplinary input in the management. This is a rare case of established vitamin A deficiency related to secondary infertility. Secondary infertility was quickly solved (30-45 days) after restoration of Vitamin A levels and the woman managed to get pregnant. It also illustrates that, though highly teratogenic, pregnancies on vita A replacement can be normal. Important fact here is that she was being replaced with vitamin A that her body was deficient in rather than supplementing leading to overdose of vitamin A (as in cases of treatment for Acne etc). Therefore, it may mean that for cases of vitamin A deficient women, termination should not be considered, as replacing normal vitamin A levels does not necessarily lead to hypervitaminosis and therefore increased chances of congenital malformations.

Keywords Vitamin A; Infertility

Abbreviations

VAD: vitamin A deficiency

Introduction

It has been over 100 years since essential micronutrient vitamin A was firstly described. Excessive or reduced vitamin A (also known as retinol) is frequent in humans [1-3]. It has long been known that vitamin A is required in rats and mice for testicular functions [1-6]. In the females the data is limited but it seems that placental development ovarian germ cells' normal meiotic prophase and entrance of germ cells into first meiotic division are affected by vitamin A [5,7-16].

Moreover, vitamin A and the other members of the retinoids family (bexarotene, isotretinoin, etretinate, tretinoin, etc.) have been studied for their possibly teratogenic actions during embryogenesis. Several reports of prenatal supplementation have associated high vitamin A dosage with congenital anomalies but the only prospective study, which examined women receiving daily from 10000 to 300000 IU of vitamin A did not draw any definitive conclusion [17]. However, commonest malformations attributed to retinoids involve malformations in the cranial area, central nervous system, heart and thymus gland. Although vitamin A deficiency affects reproductive functions, there are no reported cases in the literature to suggest management of cases with vitamin A deficiency and infertility. We present a case of a vitamin A deficient woman who, presented to our clinic with secondary infertility to emphasize the importance of a good history and a multidisciplinary input in the management.

Case Report

A 28-year old lady, presented in the ophthalmologic department of our hospital, with punctuate staining in the cornea. During evaluation of her opthalmological findings, she was found to suffer from Vitamin B12 and Vitamin A deficiency, attributed to gastrointestinal malabsorption. Therefore, she had been given Vit A supplementation (intramuscular injection of 100000 IU).

She attended infertility clinic with, secondary infertility para 2+0 (two vaginal deliveries, 2006 and 2008), of a duration of 48 months. Her menstrual periods were regular and mid luteal progesterone suggested ovulation. Transvaginal ultrasound revealed a polycystic appearance of her ovaries. (Antral Follicle Count was 40 in total for both ovaries) Her BMI was 19. As per protocol for fertility investigations, tubal testing was organized and she was booked for laparoscopy, due to previous history of chlamydial infection, which was treated.

Due to confidentiality of infertility treatment, case notes in infertility clinic were separate. Hence clinicians treating the patient in fertility clinic were not aware of her treatment with vitamin A and vice-versa.

Laparoscopy could not be done on the day as she has had an unprotected intercourse. Two weeks later, we received information from an ophthalmology colleague, to let us know that this patient is pregnant, worried about the health of the baby and the possibilities of congenital anomalies since she was on vitamin A.

Advice was sought from obstetrician consultants, who suggested waiting and seeing, as this was not an indication for termination of pregnancy (TOP). Vitamin A levels were checked– they were within normal range. It was advised that she continues with the pregnancy. A dating scan followed by detailed USG was done which revealed no

congenital anomaly. Patient is now in the 28th week of an uncomplicated, so far, pregnancy. Detailed anomaly scan has not revealed any problems.

Discussion

Vitamin A deficiency and infertility is a rarely found pathologic entity, especially in the industrialized world. We present a rare case of established vitamin A deficiency related to secondary infertility. Secondary infertility was quickly solved (30-45 days) after restoration of Vitamin A levels and the woman managed to get pregnant.

It also illustrates that, though potentially teratogenic, pregnancies on vitamin A replacement can be normal. Important fact here is that she was being replaced with vitamin A that her body was deficient in rather than supplementing leading to overdose of vitamin A. One weakness of our study is that we cannot clearly demonstrate that lack of Vitamin A was the true cause of the secondary infertility presented. Moreover, we cannot clarify if lack of Vitamin A alone, or in co-efficiency with lack of Vitamin B12, also demonstrated. The nature of fertility mechanism is complex and does not facilitate clear demonstration in our case. Despite that, the fact that supplementation of Vitamin A lead to quickly achieved pregnancy, shows that ,at least, Vitamin A plays an important role in accomplishing pregnancy either alone or in co-action with other nutritional elements.

A further weakness is that Vitamin A levels before previous spontaneous conceptions were not available, in order to check if they were within normal values then. However, vitamin A levels, two weeks after conception (at positive pregnancy test) were within normal range.

In the past several studies in rats and mice reporting Vitamin A deficiency and defective male spermatogenesis, secretion of testosterone, degeneration of meiotic germ cells abnormal testicular functions have been published [1-5,18]. Interestingly, these can be compensated for by dietary vitamin A supplementation or injection of high doses of retinoic acid, the active metabolite of vitamin A [6,7,19,20].

Fewer studies examined female reproductive system. Warkany and Schraffenberger showed that limited amounts of provitamin A carotenoid given to VAD female rats prior mating – causing therefore a less severe maternal A deficiency- facilitate both fertilization and implantation, though embryonic death during gestation is a frequent finding [21]. When given in adequate amounts, normal reproduction and embryonic development occur [19]. When vitamin A deficiency (VAD) is imposed prior to mating, the most significant finding is that cornified cells are always present in vaginal smears and failure of reproduction happens prior to implantation [22,23]. VAD female rats continue to ovulate and corpus luteum formation is either irregular or at normal intervals; however, degenerated eggs are found and there is no evidence that blastogenesis has taken place. These experimental findings, may explain the course of our patient: when vitamin A was supplemented, pregnancy occurred quickly. Moreover, studies in VAD rats show that placental changes also occur and these may be responsible for female infertility [5,19,21]. Microscopic examination of these placentas revealed that sufficient dietary support with retinyl acetate(RA) prevents these changes [5,7-11]

In our case, no miscarriage or biochemical pregnancy has been reported (in order to think that placental deficiency may be a problem), as this is a viable ongoing pregnancy already reaching 28th week of pregnancy.

A further possible explanation for the secondary infertility in the woman of our study is a defective onset meiotic prophase in ovarian germ cells. From what is already known, the germ cells of the embryos most severely lacking vitamin A fail to enter meiosis, while it seems that RA supplementation and sufficient vitamin A levels support meiotic entry into meiosis I as presented in a number of studies [12, 20-25]. That may be an explanation for our case, as it explains both latter infertility and former normal pregnancies achieved by the lady of our study.

Conclusion

In summary, vitamin A is essential for normal female reproductive function as well as for many embryonic events throughout pregnancy and, finally, to a complete failure of reproduction prior to implantation or abnormal fetal development. More studies need to be organized in order to clarify cell types and molecular pathways that are dependent on Vitamin A. However, if a woman with vitamin A deficiency is seeking pregnancy, it seems a better solution to have its vitamin A levels replenished and then starting active attempts to become pregnant. For cases of vitamin A deficient women, termination should not be considered, as replacing normal vitamin A levels does not necessarily lead to hypervitaminosis and therefore increased chances of congenital malformations.

References

1. Mora JO, Gueri M, Mora OL (1998) Vitamin A deficiency in Latin America and the Caribbean: an overview. Rev Panam Salud Publica 4: 178-186.
2. Gerster H (1997) Vitamin A--functions, dietary requirements and safety in humans. Int J Vitam Nutr Res 67: 71-90.
3. Hercberg S, Preziosi P, Galan P, Devanlay M, Keller H, et al. (1994) Vitamin status of a healthy French population: dietary intakes and biochemical markers. Int J Vitam Nutr Res 64: 220-232.
4. Wolbach SB and Howe PR (1925) Tissue changes following deprivation of fat-soluble A vitamin. Journ Exp Med 42: 753-777.
5. Howell JM, Thompson JN, Pitt GA (1964) Histology of the Lesions Produced in the Reproductive Tract of Animals Fed a Diet Deficient in Vitamin A Alcohol but Containing Vitamin A Acid. II. The Female Rat. J. Reprod Fertil 7: 251-258.
6. Appling DR, Chytil F (1981) Evidence of a role for retinoic acid (vitamin A-acid) in the maintenance of testosterone production in male rats. Endocrinology 108: 2120-2124.
7. White JC, Shankar VN, Highland M, Epstein ML, DeLuca HF, et al. (1998) Defects in embryonic hindbrain development and fetal resorption resulting from vitamin A deficiency in the rat are prevented by feeding pharmacological levels of all-trans-retinoic acid. Proc Natl Acad Sci USA 95: 13459-13464.
8. White JC, Highland M, Clagett-Dame M (2000) Abnormal development of the sinuatrial venous valve and posterior hindbrain may contribute to late fetal resorption of vitamin A-deficient rat embryos. Teratology 62: 374-384.
9. White JC, Highland M, Kaiser M, Clagett-Dame M (2000) Vitamin A deficiency results in the dose-dependent acquisition of anterior character and shortening of the caudal hindbrain of the rat embryo. Dev Biol 220: 263-284.
10. Kaiser ME, Merrill RA, Stein AC, Breburda E, Clagett-Dame M (2003) Vitamin A deficiency in the late gastrula stage rat embryo results in a one to two vertebral anteriorization that extends throughout the axial skeleton. Dev Biol 257: 14-29.

11. See AW, Kaiser ME, White JC, Clagett-Dame M (2008) A nutritional model of late embryonic vitamin A deficiency produces defects in organogenesis at a high penetrance and reveals new roles for the vitamin in skeletal development. Dev Biol 316: 171-190.
12. Noback CR, Takahashi YI (1978) Micromorphology of the placenta of rats reared on marginal vitamin-A-deficient diet. Acta Anat (Basel) 102: 195-202.
13. Li H, Clagett-Dame M (2009) Vitamin A deficiency blocks the initiation of meiosis of germ cells in the developing rat ovary in vivo. Biol Reprod 81: 996-1001.
14. Bowles J, Knight D, Smith C, Wilhelm D, Richman J, et al. (2006) Retinoid signaling determines germ cell fate in mice. Science 312: 596-600.
15. Zhao X, Sirbu IO, Mic FA, Molotkova N, Molotkov A, et al. (2009) Retinoic acid promotes limb induction through effects on body axis extension but is unnecessary for limb patterning. Curr Biol 19: 1050-1057.
16. MacLean G, Li H, Metzger D, Chambon P, Petkovich M (2007) Apoptotic extinction of germ cells in testes of Cyp26b1 knockout mice. Endocrinology 148: 4560-4567.
17. Mastroiacovo P, Mazzone T, Addis A, Elephant E, Carlier P, et al. (1999) High vitamin A intake in early pregnancy and major malformations: a multicenter prospective controlled study. Teratology 59: 7-11.
18. Morales C, Griswold MD (1987) Retinol-induced stage synchronization in seminiferous tubules of the rat. Endocrinology 121: 432-434.
19. Thompson JN, Howell JM, Pitt GA (1964) Vitamin A and Reproduction in Rats. Proc R Soc Lond B Biol Sci 159: 510-535.
20. Kumar S, Chatzi C, Brade T, Cunningham TJ, Zhao X, et al. (2011) Sex-specific timing of meiotic initiation is regulated by Cyp26b1 independent of retinoic acid signalling. Nat Commun 2: 151.
21. Warkany J, Schraffenberger E (1946) Congenital malformations induced in rats by maternal vitamin A deficiency; defects of the eye. Arch Ophthal 35: 150-169.
22. Evans HM, Bishop KS (1922) On an invariable and characteristic disturbance of reproductive function in animals reared on a diet poor in fat soluble vitamine A. Anat Rec 23: 17-18.
23. Mason KE, Ellison ET (1935) Changes in the vaginal epithelium of the rat after vitamin A-deficiency. J Nutr 9: 735-755.
24. Clagett-Dame M1, DeLuca HF (2002) The role of vitamin A in mammalian reproduction and embryonic development. Annu Rev Nutr 22: 347-381.
25. Li H, MacLean G, Cameron D, Clagett-Dame M, Petkovich M (2009) Cyp26b1 expression in murine Sertoli cells is required to maintain male germ cells in an undifferentiated state during embryogenesis. PLoS One 4: e7501.