Vitamin A in the Treatment of Menorrhagia

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SUMMARY

Hypovitaminosis A was found to be an important cause of menorrhagia, and a statistically significant difference between the fasting serum vitamin A values of healthy controls and patients with menorrhagia was noted. Vitamin A is a co-factor of 3β-dehydrogenase in steroidogenesis and deficiencies of this vitamin may result in impaired enzyme activity. The level of endogenous 17β-oestradiol appears to be elevated with vitamin A therapy, and menorrhagia was alleviated in more than 92% of patients.

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Little is known of the effect of vitamin A (retinol) deficiency on the reproductive system of women. In animals, vitamin A deficiency causes lowered adrenal steroid production, which returns to normal 4 hours after administration of the vitamin.[1] Deficient enzymatic conversion of the Δ^5-3β-hydroxysteroids into the corresponding Δ^4-3-oxosteroids occurs *in vivo* and *in vitro*, even if the vitamin A deficiency is mild.[2,3] Vitamin A is a co-factor of Δ^5-isomerase 3β-hydroxydehydrogenase[4] and desmolase[5] and deficiency of this vitamin impairs enzyme activity and hormone production in the ovaries, testes and adrenals of animals.[2] Vitamin A is important in the development and maturation of the ovarian follicle and deficiency results in 'suspension of the menstrual cycle' and decreased oestrogen synthesis in animals.[6]

The purpose of this investigation was to determine whether vitamin A deficiency causes menorrhagia in women and whether administration of this vitamin alleviates the disorder.

SUBJECTS AND METHODS

A group of 191 normal, healthy, adult White women who attended a gynaecological clinic for contraceptive advice, cervical cytology, or minor problems, were selected as controls. Their ages ranged between 13 and 55 years and none were taking oral contraceptives or Depo-Provera. A total of 71 patients with menorrhagia, but without demonstrable organic lesions, was selected for the study of serum vitamin A levels. Menorrhagia was defined as either excessive daily bleeding during menstruation, or a prolonged flow beyond the patient's norm, or both.

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After standard initial gynaecological assessment and an overnight fast (14 hours), a 40-ml sample of blood was drawn from each patient and from each control subject, at any phase in the cycle; 20 ml of the sample, suitably screened from light, was used for duplicate vitamin A assays and the remaining 20 ml was used to determine the blood count, protein-bound iodine and vitamin E. The blood samples were assayed at the South African Institute for Medical Research and serum vitamin A values were determined by a spectrophotometric method.[7] On their second visit to the clinic the patients were prescribed retinol (25 000 IU) twice daily for 15 days, and instructed to return at monthly intervals.

In order to define more precisely the role of vitamin A deficiency, the records of 103 patients who presented a wider spectrum of the causes of menorrhagia (not just dysfunctional bleeding) were combined with those of the original group.

The effects of vitamin A on 17β-oestradiol levels were determined by means of radio-immunoassay.[8] Because decreased oestrogen synthesis occurs in vitamin A-deficient animals, 6 subjects (aged 16 - 31 years) with amenorrhoea were selected to ascertain the effect of vitamin A (60 000 IU/d for 35 days) on their 17β-oestradiol levels. Subjects with amenorrhoea were chosen because of a possibility of fluctuating oestradiol values in menorrhagia.

Further studies of the hormonal effects of vitamin A were undertaken in subjects who were taking 100 000 IU vitamin A per day for 15 days. Patients with amenorrhoea and oligomenorrhoea were studied, and an example of the effects of this therapy is shown in Table III. The 17β-oestradiol, growth hormone (GH) and thyroid-stimulating hormone (TSH) assays were performed at the Natal Medical School. CEA-IRE-SORIN kits were used to assay 17β-oestradiol and GH, and Byk-Mallinckrodt kits for TSH.

RESULTS

The mean serum vitamin A level of the 191 control subjects was 166,16 IU/100 ml (SD 43,34) and of the 71 patients with menorrhagia 67,00 IU/100 ml (SD 41,14). The difference is statistically significant at the $P<0,01$ level.

Table I shows the effects of vitamin A acetate therapy on 40 patients with menorrhagia and a comparison has been made with Sutherland's Amfac therapy.[9] In the group who received vitamin A, menstruation returned to normal in 23 (57,5%) for a period of at least 3 months. Material improvement, defined as a substantially diminished menstrual period or a reduction in the duration of the menses (or both), was obtained in 14 (35%). Failure of treatment occurred in 3 (7,5%). The over-all result with vitamin A therapy shows that 37 (92,5%) of the 40 patients who returned for follow-up were cured or alleviated. Of the 71 original patients with menorrhagia, 12 were lost to follow-up and 18 who returned to the clinic were seen by other

TABLE I. PATIENTS WITH MENORRHAGIA RECEIVING VITAMIN A AND AMFAC THERAPY

	Vitamin A (60 000 IU/d for 35 d)	Amfac glanules (mammalian liver extract 6/d for 3 mo.)
Total number	**52**	**50**
Lost to follow-up	**12**	**4**
Total traced	**40**	**46**
Complete cure	**23 (57,50%)**	**28 (60,87%)**
Material improvement	**14 (35,00%)**	**4 (8,70%)**
	37 (92,50%)	**32 (69,57%)**
Failure	**3 (7,50%)**	**14 (30,43%)**
	40 (100,00%)	**46 (100,00%)**

doctors who, unaware of the trial in progress, used conventional hormonal and surgical treatment.

Table II details the causes of menorrhagia in 174 patients. Vitamin A deficiency appeared to be the major aetiological factor in 43,68% of these women. The aetiology was unknown in 17,24%. A number of patients (11,49%) had previously been subjected to sterilization. Pyridoxine (vitamin B_6) deficiency was found in 9,77% and was diagnosed clinically[10,11] and subsequently biochemically.[12] Eight patients with both vitamin B_6 and vitamin A deficiency were classified as vitamin A-deficient. In the remaining patients (10,92%) local uterine lesions (due to fibroids, polyps, IUCDs or cancer) were demonstrated. Lastly, 6,90% of patients exhibited excessive endometrial bleeding while on, or subsequent to stopping, oral contraceptives. The vitamin A levels (Table II) were classified as being mildly deficient 100 - 115 IU (13,79%); moderately deficient 50 - 100 IU (38,51%); and markedly deficient 0 - 50 IU (15,52%). A total of 118 patients (67,82%) could therefore be regarded as having suboptimal vitamin A levels (<115 IU).

In the 6 selected amenorrhoeic patients the 17β-oestradiol increased from a mean of 78 pg/ml (range 52 - 125) to 308 pg/ml (range 176 - 440) over periods varying from 8 to 59 days (average 36 days).

Table III shows a marked rise in 17β-oestradiol levels in a 19-year-old White patient with oligomenorrhoea after vitamin A therapy. This therapy also increased GH and TSH and lowered thyroxine levels. These changes are characteristic of those observed in White and Asiatic patients.

DISCUSSION

The mean serum vitamin A values of the control group (166 IU) were comparable to the fasting levels found both in Danish[13] and in English women (150 IU for both). The serum values of the latter were for days 18 - 21 of the menstrual cycle[14] (conversion 1,0 IU $\equiv$ 0,3 μg). The low mean serum vitamin A values in menorrhagia (67 IU) are readily explained when the causes of hypovitaminosis A are known.[15] The causative factors most frequently observed were deficient diet, malabsorption, recent infections, overexposure to sunlight[16] and excessive intake of alcohol.[17]

TABLE II. CAUSES OF MENORRHAGIA IN 174 PATIENTS

	Serum vitamin A levels (IU/100 ml)						
Causes of menorrhagia	0 - 50	50 - 100	100 - 115	115 - 150	>150	Total	%
Vitamin A deficiency	**24**	**48**	**4**	**—**	**—**	**76**	**43,68**
After sterilization	**—**	**6**	**3**	**5**	**6**	**20**	**11,49**
Vitamin B_6 deficiency	**—**	**—**	**2**	**6**	**9**	**17**	**9,77**
Oral contraceptives	**1**	**8**	**—**	**—**	**3**	**12**	**6,90**
IUCD	**—**	**1**	**3**	**3**	**2**	**9**	**5,17**
Fibroids/polyps	**1**	**3**	**—**	**1**	**1**	**6**	**3,45**
Cancer	**1**	**1**	**2**	**—**	**—**	**4**	**2,30**
Unknown	**—**	**—**	**10**	**9**	**11**	**30**	**17,24**
Number	**27**	**67**	**24**	**24**	**32**	**174**	
% of total	**15,52**	**38,51**	**13,79**	**13,79**	**18,39**	**—**	**100,00**

TABLE III. HORMONAL EFFECTS OF VITAMIN A (100 000 IU/DAY FOR 15 DAYS) IN A 19-YEAR-OLD PATIENT

Hormone	Pretreatment level	Day 8	Day 15	Normal levels and unit of measurement	
17β-oestradiol (E_2)	**160**	**388**	**420**	**Follicular phase**	**20 - 70 pg/ml**
				Luteal phase	**200 - 400 pg/ml**
				Pre-ovulatory phase	**250 - 500 pg/ml**
Growth (GH)	**2,5**	**17,0**	**4,8**	**Normal**	**1 - 10 ng/ml**
Thyroid-stimulating (TSH)	**2,2**	**6,0**	**5,8**	**Normal**	**1 - 3 μIU/ml**
				Borderline	**3 - 7 μIU/ml**
				Hypothyroid	**7 μIU/ml**
Thyroxine (T_4)	**8,2**	**6,6**	**6,1**	**Normal**	**3,5 - 12,5 μg/100 ml**

There is a divergence of opinion as to whether serum vitamin A levels accurately reflect hepatic vitamin A reserves. A discrepancy may appear when fluctuations in serum vitamin A levels in various stress situations are overlooked.[18] Physical and emotional stress will raise urinary catecholamines[19] and injections of adrenaline increase serum vitamin A levels by 30 - 300%.[20] This indicates the importance of taking blood samples under resting and fasting conditions.

Raised serum vitamin A levels in women using oral contraceptives were confirmed.[14] However, substantially reduced serum vitamin A values were observed in women 2 - 3 months after the discontinuation of long-term oral contraceptives or medroxyprogesterone. The depletion rate of hepatic vitamin A reserves in animals given oral contraceptives was 3 times greater than that in controls.[21] This could be a reason for menstrual disorders which occur after oral contraceptives have been stopped.

Table I shows vitamin A therapy to be 22,9% more effective than a mammalian liver extract.

Table II shows that 67,8% of patients with menorrhagia have serum vitamin A values lower than 115 IU. As hepatic reserves of vitamin A are only assured when plasma levels are greater than 90 IU[22] an investigation of vitamin A levels in patients with menorrhagia is indicated.

The rise in 17β-oestradiol following vitamin A therapy (Table III) is significant, since graphs of the menstrual cycle indicate an association in the peaks of 17β-oestradiol and vitamin A.[23,24] Should vitamin A fail to raise oestradiol levels or alleviate menorrhagia, then checks for hypoproteinaemia, vitamin E (which improves vitamin A storage and utilization)[15] and zinc (required to mobilize hepatic vitamin A)[25] are indicated.

The lysosomal fraction of the cell is the source of the fibrinolytic enzymes[26] which increase in menorrhagia,[27] thus stabilization of the lysosomal membranes with vitamin A may be the mechanism controlling menorrhagia. Alternatively, the rise in 17β-oestradiol levels after administration of vitamin A could simulate the effects of exogenous oestrogens, with resultant control of menorrhagia.

Following the initial results, the use of vitamin A in the treatment of menorrhagia has been standard practice for the past 4 years. No signs of toxicity have been observed with the dosages described, and vitamin A offers a rational and safe basis for the alleviation of menorrhagia. The precise molecular function of vitamin A in human reproductive physiology has still to be determined.

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