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Influence of narrowband ultraviolet B phototherapy on serum folate level in skin of color females: A cross-sectional study

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ABSTRACT

Background: Narrowband ultraviolet B (NB-UVB) (311–312 nm) is widely used for dermatological conditions with a favorable side-effect profile during pregnancy. Recently published data showed that NB-UVB might decrease serum folate level in Fitzpatrick skin phenotype I–III, especially at higher doses; this may predispose newborns to neural tube defects.

Objective: To compare serum folate levels of skin of color females treated with NB-UVB and healthy females of childbearing age, as well as to note whether subsequent complications have been observed, if any.

Methods: Multicenter, cross-sectional study of 30 females (*N* = 30): 15 female patients undergoing NB-UVB phototherapy as well as 15 age-, gender-, and skin phenotype-matched healthy volunteers who were enrolled into the study after excluding factors known to alter serum folate concentration. NB-UVB exposures were performed 2–3 times a week for at least 8–12 weeks (mean cumulative NB-UVB dose ± standard deviation [SD] was 55 ± 79 J/cm^2).

Results: Mean serum folate ± SD in NB-UVB exposed and healthy controls were 10.3 ± 4 and 8.3 ± 3 ng/mL, respectively. This was not a statistically significant difference between the 2 groups (*P* = .14).

Limitations: Small sample size (*N* = 30) and a cross-sectional study type.

Conclusion: Cumulative NB-UVB exposure is not associated with a statistically significant difference in serum folate level (*P* > .05) in skin of color females of childbearing age in comparison to age-, gender-, and skin phenotype-matched healthy females, even with the relatively higher cumulative doses (mean ± SD was 55 ± 79 J/cm^2) that have been shown to reduce serum folate level in lighter skin phenotypes.

Keywords: Fitzpatrick skin phenotype, folate, narrowband ultraviolet B, neural tube defects, phototherapy, ultraviolet A

Introduction

Narrowband (NB) ultraviolet (UV) B (311–312 nm) is used to treat psoriasis, vitiligo, mycosis fungoides, and atopic dermatitis, among other dermatoses,[1] with a favorable side-effect profile compared with systemic alternatives, especially during pregnancy or in women of childbearing age. One serious issue related to phototherapy is the potential to decrease serum folate levels, which is of interest primarily to women of childbearing age, as birth defects, including neural tube defects (NTDs), have been noted to increase in women with folate deficiency.[2,3]

Folate, also known as vitamin B9, is an essential nutrient that facilitates the transfer of 1-carbon groups in DNA synthesis and other biosynthetic reactions.[4] Naturally occurring folate is found primarily in the form of 5-methyltetrahydrofolate in leafy vegetables and other foods.[5] Folic acid is the synthetic, oxidized form of folate found in the majority of supplements.[5] Both folate and folic acid undergo degradation upon exposure to UV.[1] The action spectrum for folic acid photodegradation spans the UVA, UVB, and part of UVC (260–400 nm), with a maximal degradation wavelength of 270 nm.[6] Common wavelengths used in dermatology practice, such as NB-UVB, are within the degradation spectrum.

Furthermore, 2 of 6 studies—Shaheen et al.[7] and El-Saie et al.[8]—on the effect of NB-UVB on serum folate levels demonstrated significant decreases in folate levels in 20 vitiligo patients and 30 psoriasis patients, respectively (Table 1). The 2 studies used higher cumulative doses (76 J/cm^2 and 118 J/cm^2) than 3 of the 4 negative studies (all used <46 J/cm^2 over 9–20 treatments). The remaining study—Ataş et al.[12]—found no decrease in 52 vitiligo patients after comparable cumulative

Highlights

1. Narrowband ultraviolet B (311–312 nm) is widely used for dermatological conditions with favorable side-effect profile even during pregnancy.
2. Higher cumulative doses have been shown to reduce serum folate level in lighter skin phenotypes (I–III), which may predispose newborns to neural tube defects.
3. In our study, cumulative narrowband ultraviolet B exposure is not associated with a statistically significant difference in serum folate level in skin of color females of childbearing age (IV–VI), even with the relatively higher cumulative doses.

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What is known about this subject in regard to women and their families?

- Overall, narrowband ultraviolet B (NB-UVB) is a safe treatment option for variable skin conditions during pregnancy and for females of childbearing age.
- Few studies showed a reduction in serum folate level in females who underwent NB-UVB sessions, especially those taking a higher cumulative dose and those with lighter skin phenotype.
- Theoretically, this reduction in serum folate level in pregnant women may predispose newborns to neural tube defects.

What is new from this article as messages for women and their families?

- Our results showed no significant difference in serum folate level in skin of color women exposed to NB-UVB and those who were not exposed.
- Although this is a small study, NB-UVB seems to be a safe treatment option for skin of color pregnant women and women of childbearing age.
- Supplemental folic acid tablets of 1–5 mg daily are advised to all women of childbearing age, regardless of skin phenotype or whether they receive phototherapy or not.

doses (112 J/cm^2) were split across more treatments (80 vs 36). However, reported UV exposure does not entirely reflect the actual dose that penetrates the skin, which may depend on other factors such as skin phenotype.[13] Two of the 6 studies mentioned the skin phenotype of treated patients, which were in the I–III range, while the remaining studies did not mention the skin phenotype of treated patients (Table 1). Moreover, no studies have been done on darker skin phenotypes (IV–VI) to evaluate the effect of NB-UVB on serum folate level.

The prevalence of NTD in Saudi Arabia (4.5–53.5/10,000 births), per the World Bank classification, makes the country a high-prevalence one, with the highest prevalence recorded in Al-Khobar and the lowest in Riyadh.[14] NB-UVB theoretically has the potential to deteriorate the prevalence of NTD in the country further if it is causing photodegradation of serum folate in pregnant females or females of childbearing age.

Materials and methods

The study was conducted in 2 tertiary hospitals in Saudi Arabia: King Fahad Armed Forces Hospital in Jeddah and King Fahd Specialist Hospital in Buraydah.

Written informed consent and Institutional Review Board approval were obtained. Blood samples were obtained from 15 patients undergoing narrowband UVB phototherapy for vitiligo, psoriasis, atopic dermatitis, mycosis fungoides, and lichen planus. Their ages ranged between 16 and 39 years, with a mean ± standard deviation (SD) of 27.7 ± 8.3 years (Table 2). Control samples from 15 age, gender, and Fitzpatrick skin phenotypes matched healthy female volunteers chosen as controls. Their ages ranged between 16 and 40 years, with a mean ± SD of 28.4 ± 6.9 years.

Inclusion criteria for the studied subjects included:

1. Female patients ages 15–40.
2. Skin Fitzpatrick phenotypes IV–VI.
3. Regular NB-UVB sessions for at least 8–12 weeks.
4. Full-body NB-UVB treatment sessions.

Exclusion criteria for the studied subjects included:

1. Current pregnancy or nursing.
2. Personal or family history of NTD.
3. Any form of dieting or excessive alcohol use.
4. Hemolytic anemia, bariatric surgeries, or dialysis.
5. Use of vitamins or other supplements, including folic acid.
6. Any form of UV therapy within 8–12 weeks prior to the study, including tanning beds.
7. Medications known to impair folate metabolism, such as methotrexate, trimethoprim/sulfamethoxazole, dapsone, and anticonvulsants.

A narrowband UVB phototherapy unit was used that was fitted with 8 standard fluorescent tubes emitting dominant peak wavelengths of 311 nm. For each patient, the initial dose was given based on skin phenotype or a fixed dosing schedule, starting with 200–400 mJ/cm^2 and increasing by 10–20% per week of the previous well-tolerated dose. The aim was to reach and maintain minimally perceptive nonpainful erythema lasting less than 24–48 hours. Patients received 2–3 treatments per week for at least 8–12 weeks.

For the analysis of data, we used the Student's *t* test for *P*-value calculation by analyzing 2 independent variables with the treated-group serum folate as an independent variable and the healthy control serum folate as another independent variable, using Microsoft Excel Office 365 (Version 16.28).

Results

The characteristics of the 15 patients included in the current study are summarized in Table 2, with mean age ± SD of 27.7 ± 8.3 (range, 16–39) compared with the control group mean ± SD of 28.4 ± 6.9 (range, 16–40), and there was an equal female distribution of similar skin Fitzpatrick phenotypes of IV–VI in both groups.

Cumulative dose ± SD was 55 ± 79 J/cm^2 given to 15 patients over a mean ± SD of 42 ± 37 treatment sessions (range, 13–127).

In all NB-UVB treated patients and controls, serum folate levels were within the normal range, and no statistically significant

Table 1.

Literature review of NB-UVB effect on serum folate

Study	Skin types[a]	Disease	*N*	Sessions	Cumulative dose in mJ/cm^2 (SD)	Serum folate level (ng/mL)[b]			
						Pre	Post	% Change	*P* < .05
Shaheen et al.[7]	I–III	Vitiligo	20	36	75,950 (3670)	8.1 (2.6)	5.9 (1.5)	–27	Y
Rose et al.[9]	I–III	Psoriasis	35	18–20	<46,000	6.34 (3.6)	6.35 (3.26)	0.2	N
Cicarma et al.[10]		Mixed	16	9–15	6900 (4500)	6.7 (1.8)	6.9 (2.1)	3.0	N
El-Saie et al.[8]		Psoriasis	30	36	118,160 (22,770)	8.64 (4.08)	6.32 (2.29)	–26.9	Y
Magina et al.[11]		Psoriasis	20	18	21,900 (6100)	6.64 (2.75)	6.38 (2.31)	–3.9	NR
Ataş et al.[12]		Vitiligo	52	80	112,000	9.8 (2.9)	9.8 (2.5)	0	N

N, no; NB-UVB, narrowband ultraviolet B; NR, not reported; Post, after narrowband ultraviolet B; Pre, before narrowband ultraviolet B; SD, standard deviation; Y, yes.

[a] Classified by Fitzpatrick scale.

[b] Serum folate >4 ng/mL is sufficient, <2 ng/mL is deficient.[1]

Table 2.

Patients' characteristics on NB-UVB

Number	Age	Sex	Skin phenotype[a]	Frequency	Diagnosis	Sessions	CD mJ/cm²	Serum folate level (ng/mL)[b]
1	20	F	IV	3/wk	Psoriasis	18	12,885	7.28
2	17	F	V	3/wk	Mycosis fungoides	127	63,276	5.2
3	27	F	IV	3/wk	Vitiligo	16	8478	9.81
4	35	F	V	3/wk	Atopic dermatitis	105	309,799	7.89
5	17	F	IV	2/wk	Vitiligo	80	118,489	9.7
6	30	F	VI	2/wk	Vitiligo	44	25,196	8
7	18	F	IV	2/wk	Vitiligo	31	14,219	10.1
8	38	F	VI	2/wk	Lichen planus	88	119,256	7.41
9	27	F	V	3/wk	Psoriasis	16	15,950	16.4
10	32	F	IV	3/wk	Psoriasis	14	11,780	10.7
11	33	F	IV	2/wk	Lichen planus	13	8800	14.6
12	39	F	VI	3/wk	Vitiligo	17	16,800	11
13	16	F	IV	3/wk	Vitiligo	19	25,200	19
14	29	F	V	3/wk	Mycosis fungoides	36	59,900	14
15	38	F	VI	3/wk	Psoriasis	18	15,740	5

CD, cumulative dose; F, female; NB-UVB, narrowband ultraviolet B; wk, weeks.

[a] Classified by Fitzpatrick scale.

[b] Serum folate >4 ng/mL is sufficient, <2 ng/mL is deficient.[15]

Table 3.

Clinical characteristics and serum folate level of the NB-UVB exposed versus healthy control subjects

Category	Age	Sex	Skin type[a]	Diagnosis	Cumulative dose (mJ/cm²)[b]	Serum folate level[b] (ng/mL)[c]
NB-UVB exposed (N = 15)	27 ± 8 (16–39)	F	IV: 7 V: 4 VI: 4	Vitiligo: 6 Psoriasis: 4 Mycosis fungoides: 2 Lichen planus: 2 Atopic dermatitis: 1	55,051 ± 79,767 (8478–309,799)	10.3 ± 4 (5–19)
NB-UVB nonexposed (N = 15)	28 ± 7 (16–40)	F	IV: 8 V: 4 VI: 3	Healthy		8.3 ± 3.2 (4.1–14.4)

F, female; NB-UVB, narrowband ultraviolet B; SD, standard deviation.

[a] Classified by Fitzpatrick scale.

[b] Values = mean ± SD (range).

[c] Serum folate >4 ng/mL is sufficient, <2 ng/mL is deficient.[15]

difference was found between the groups ($P > .05$). See Table 3 and Figure 1.

After a mean of 42 sessions, serum folate levels ± SD had been in the normal range for all 15 patients 10 ± 4 ng/mL (range, 5–19 ng/mL), compared with that of the control group of 15 healthy females, which was 8 ± 3 ng/mL (range, 4.1–14.4 ng/mL), with no statistically significant difference found between the groups ($P = .14$).

Discussion

Our study addressed whether NB-UVB exposure is associated with a decrease in serum folate level of females of childbearing age with darker skin phenotype of IV–VI (Middle eastern skin phenotype [Table 4]) in comparison to age-, gender-, and skin phenotype-matched healthy females and found that there was no statistically significant difference between the treated and healthy controls ($P > .05$).

One possible explanation is the protective role of melanin in preventing the photolysis of folic acid.[13] Theoretically, the skin of darker-colored individuals living in high-UV areas near the equator should have lower folate levels due to photodegradation. However, the "vitamin D–folate hypothesis" proposes that the original purpose for increased pigmentation in high-UV environments was driven by a need to protect folate from photodegradation.[17] Vice versa, folate has a role in melanogenesis by regulating the production and stabilization of tetrahydrobiopterin, a required cofactor for tyrosine hydroxylase, an enzyme involved in the initial steps of melanogenesis.[18] These may explain why our patients did not have abnormally low serum folate levels even after receiving a high cumulative dose of NB-UVB.

Our findings are in conflict with Shaheen et al.[7] and El-Saie et al.,[8] which demonstrated significant decreases in serum folate levels after 1 course of 36 treatments of NB-UVB with cumulative doses of 76 and 118 J/cm², respectively. Skin phenotype was I–III in the study group for Shaheen et al.[7] and not specified in that published by El-Saie et al.[8] On the other hand, our findings converge with the previous findings of Rose et al.,[9] Cicarma et al.,[10] and Ataş et al.,[12] in which NB-UVB exposure did not lead to a significant decrease in serum folate level. To our knowledge, our findings show for the first time that NB-UVB exposure in darker skin phenotype patients (IV–VI) did not show a significant difference in serum folate level in comparison to the control group, even with a high cumulative dose (mean ± SD = 55 ± 79 J/cm²), which have been shown to decrease the serum folate level in lighter Fitzpatrick skin phenotype (I–III).[7,8]

In vitro photodegradation of folate has been demonstrated consistently, with the action spectrum spanning UVA, UVB, and part of the UVC range (260–400 nm) with a peak at 270 nm.[1] However, within in vivo studies showing decreased folate levels following sun exposure, the decrease was noted to be limited to those taking folic acid supplements.[19,20]

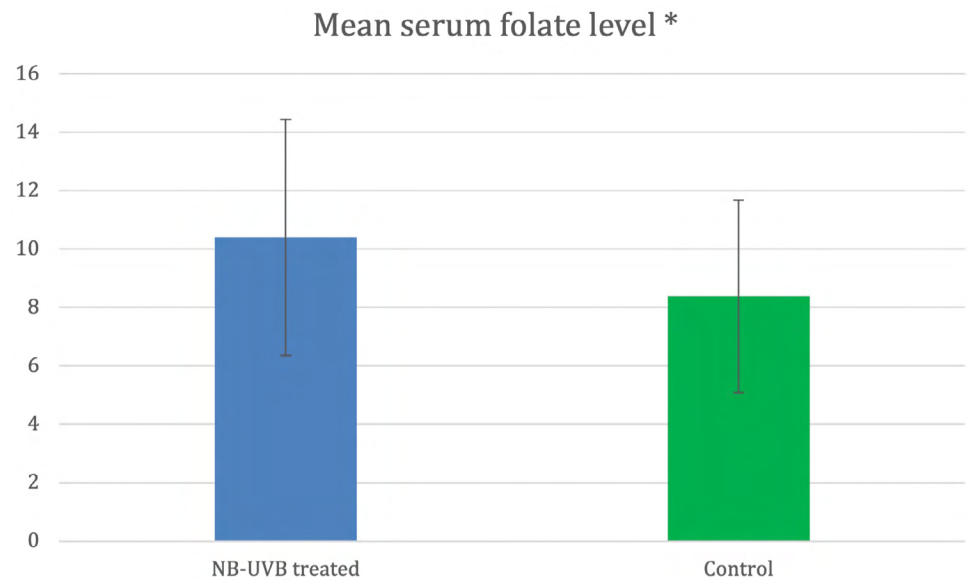

Fig. 1. Serum folate level of NB-UVB treated and control subjects. NB-UVB, narrowband ultraviolet B.

Table 4.

Fitzpatrick skin phenotype scale[16]

Skin type	Skin color	Characteristics
I	White, very fair, red or blond hair, blue eyes, freckles	Always burns, never tans
II	White; fair; red or blond hair; blue, hazel, or green eyes	Usually burns, tans with difficulty
III	Cream-white, fair with any eye or hair color	Sometimes mild burn, gradually tans
IV	Brown, typical Mediterranean white skin	Rarely burns, tans with ease
V	Dark brown, Middle Eastern skin types	Very rarely burns, tans very easily
VI	Black	Never burns, tans very easily

Recent studies regarding the effect of NB-UVB on serum folate show some evidence of a dose-dependent effect. Two studies[7,8] that administered a cumulative dose of >40 J/cm^2 and an average dose of >2 J/cm^2 per treatment demonstrated 19–27% decreases in serum folate levels. However, lower cumulative or treatment doses did not show a significant reduction in serum folate level.[9,10,11] Most importantly, the risk of NTD increase with relative decreases in maternal folate levels, even if the patient is not deficient by definition.[21]

Because neural tube closure completes approximately 4 weeks after conception,[22] even before many women realize they are pregnant, both the US Preventive Services Task Force[23] and American College of Obstetricians and Gynecologists[22] for all women of childbearing age recommend a range of folate intake of 0.4–0.8 mg/d. Due to the lack of consistency across in vivo studies, as well as the lack of a direct link between phototherapy and NTD, there is no evidence to warrant higher levels of supplementation for phototherapy patients than the recommended doses for women of childbearing age in the general population.

Interestingly, a higher daily dose of folic acid supplementation (5 mg) was associated with a higher risk reduction of NTD than the lower recommended folic acid supplementation (0.4–0.8 mg daily) of 85% and 36–46%, respectively.[21]

At present, only women who have previously had an NTD pregnancy are advised to take the 5-mg dose daily.[21] No known or suspected adverse effects of folic acid at the 5-mg daily dose have been reported, and it has no absolute contraindications, although antiepileptic medication should be checked, and vitamin B12 deficiency should be ruled out.[21]

Conclusion

Taken together, our findings and the findings of previous studies point toward the conclusion that NB-UVB exposure with low to moderate cumulative doses did not show a statistically significant difference in serum folate levels, especially among patients with darker skin phenotypes, although supplemental folic acid tablets of 1–5 mg daily are advised for all women of childbearing age whether they receive phototherapy or not.

Our study has few main limitations. First, it is a small sample size with a short NB-UVB treatment duration that may not represent the target patients. Second, it is a cross-sectional study type lacking pre-NB-UVB serum folate level of patients. Lastly, a few patients had fewer than 20 NB-UVB treatment sessions.

In the present article, we investigated the effect of NB-UVB on the serum folate level in skin of color patients compared with nonexposed matched healthy individuals and found that there is no statistically significant difference between the 2 groups ($P > .05$).

We are keeping in mind that our results are preliminary, and due to the limitation of small sample size and short duration of NB-UVB exposure, future larger studies with larger sample sizes are needed.

Author Contributions

- MMA: Conceptualization, Methodology, Formal analysis, Investigation, Writing - Original Draft.
- MAB: Methodology, Writing - Review & Editing, Supervision.

Conflicts of interest

None.

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None.

Study approval

The author(s) confirm that any aspect of the work covered in this manuscript that has involved human patients has been conducted with the ethical approval of all relevant bodies.

Patient consent

Informed, written consent was received from all patients and confirmed to the journal prepublication, stating that the patients gave consent for their photos and case history to be published.

References

1. Zhang M, Goyert G, Lim HW. Folate and phototherapy: what should we inform our patients? J Am Acad Dermatol 2017;77(5):958–64.
2. Czeizel AE, Dudás I. Prevention of the first occurrence of neural-tube defects by periconceptional vitamin supplementation. N Engl J Med 1992;327(26):1832–5.
3. Hernández-Díaz S, Werler MM, Walker AM, Mitchell AA. Folic acid antagonists during pregnancy and the risk of birth defects. N Engl J Med 2000;343(22):1608–14.
4. Lucock M. Folic acid: nutritional biochemistry, molecular biology, and role in disease processes. Mol Genet Metab 2000;71(1–2): 121–38.
5. Pietrzik K, Bailey L, Shane B. Folic acid and L-5-methyltetrahydrofolate: comparison of clinical pharmacokinetics and pharmacodynamics. Clin Pharmacokinet 2010;49(8):535–48.
6. Juzeniene A, Thu Tam TT, Iani V, Moan J. The action spectrum for folic acid photodegradation in aqueous solutions. J Photochem Photobiol B 2013;126:11–6.
7. Shaheen M, Fattah NA, El-Borhamy M. Analysis of serum folate levels after narrow band UVB exposure. Egypt Dermatol Online J 2006;2:1–7.
8. El-Saie LT, Rabie AR, Kamel MI, Seddeik AK, Elsaie ML. Effect of narrowband ultraviolet B phototherapy on serum folic acid levels in patients with psoriasis. Lasers Med Sci 2011;26(4):481–5.
9. Rose RF, Batchelor RJ, Turner D, Goulden V. Narrowband ultraviolet B phototherapy does not influence serum and red cell folate levels in patients with psoriasis. J Am Acad Dermatol 2009;61(2):259–62.
10. Cicarma E, Mørk C, Porojnicu AC, et al. Influence of narrowband UVB phototherapy on vitamin D and folate status. Exp Dermatol 2010;19(8):e67–72.
11. Magina S, Cruz MJ, Azevedo F, Moura D, Moura E, Vieira-Coelho MA. Narrowband ultraviolet B treatment for psoriasis increases serum vitamin A levels. Br J Dermatol 2012;167(4):958–60.
12. Ataş H, Cemil BÇ, Gönül M, Basturk E, Cicek E. Serum levels of homocysteine, folate and vitamin B12 in patients with vitiligo before and after treatment with narrow band ultraviolet B phototherapy and in a group of controls. J Photochem Photobiol B 2015;148:174–80.
13. Brenner M, Hearing VJ. The protective role of melanin against UV damage in human skin. Photochem Photobiol 2008;84(3):539–49.
14. Zaganjor I, Sekkarie A, Tsang BL, Saie LT, Rabie AR, Kamel MI, Seddeik al. Describing the prevalence of neural tube defects worldwide: a systematic literature review. PLoS One 2016;11(4):e0151586.
15. Antony A. Megaloblastic anemias. In: Hoffman R, Edward B, Silberstein L, Heslop H, Weitz J, Anastasi J, editors. Hematology: basic principles and practice. 7th ed. Amsterdam: Elsevier; 2018.p.514–45.
16. Elmets CA, Lim HW, Stoff B, et al. Joint American Academy of Dermatology-National Psoriasis Foundation guidelines of care for the management and treatment of psoriasis with phototherapy. J Am Acad Dermatol 2019;81(3):775–804.
17. Jones P, Lucock M, Veysey M, Beckett E. The vitamin D–folate hypothesis as an evolutionary model for skin pigmentation: an update and integration of current ideas. Nutrients 2018;10(5):554.
18. Slominski A, Zmijewski MA, Pawelek J. L-tyrosine and L-dihydroxyphenylalanine as hormone-like regulators of melanocyte functions. Pigment Cell Melanoma Res 2012;25:14–27.
19. Fukuwatari T, Fujita M, Shibata K. Effects of UVA irradiation on the concentration of folate in human blood. Biosci Biotechnol Biochem 2009;73(2):322–7.
20. Borradale D, Isenring E, Hacker E, Kimlin MG. Exposure to solar ultraviolet radiation is associated with a decreased folate status in women of childbearing age. J Photochem Photobiol B 2014;131:90–5.
21. Wald NJ, Law MR, Morris JK, Wald DS. Quantifying the effect of folic acid. Lancet 2001;358(9298):2069–73.
22. Cheschier N; ACOG Committee on Practice Bulletins-Obstetrics. ACOG practice bulletin. Neural tube defects. Number 44, July 2003. (Replaces committee opinion number 252, March 2001). Int J Gynaecol Obstet 2003;83:123–33.
23. US Preventive Services Task Force. Folic acid for the prevention of neural tube defects: US Preventive Services Task Force recommendation statement. Ann Intern Med 2009;150(9):626–31.