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/cm²).

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/cm²) 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.1 Folic acid is the synthetic, oxidized form of folate found in the majority of supplements.1 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.5 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.—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/cm² and 118 J/cm²) than 3 of the 4 negative studies (all used <46 J/cm² over 9–20 treatments). The remaining study—Ataş et al.—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.
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/cm²) 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.11 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 further if it is causing photodegradation of serum folate and those who were not exposed.
• Theoretical, this reduction in serum folate level in pregnant women may predispose newborns to neural tube defects.

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.

Exclusion 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.

Table 1.

| Study          | Skin types  | Disease     | N   | Sessions | Cumulative dose in mJ/cm² (SD) | 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. 8   | 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-Saei et al. 11| Mixed      | Psoriasis   | 30  | 36       | 118,160 (22,770)           | 8.64 (4.08) | 6.32 (2.29) | −26.9    | Y       |
| Magina et al. 12| I–III       | Psoriasis   | 20  | 18       | 21,300 (6100)              | 6.64 (2.75) | 6.38 (2.31) | −3.9     | NR      |
| Abo et al. 13   | I–III       | 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.

Classified by Fitzpatrick scale.

Serum folate >4 ng/mL is sufficient, <2 ng/mL is deficient.
A 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 melamin 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.14 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
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 folic acid 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 (\(P > 0.05\)).

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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**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 |

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

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