Ahuja K, Lio P. An Integrative Approach to Treating Hyperpigmentation in Pregnancy. *Journal of Integrative Dermatology*. Published online February 1, 2024.

Review Article

An Integrative Approach to Treating Hyperpigmentation in Pregnancy

Kripa Ahuja, MS[1], Peter Lio, MD[2]

[1] Eastern Virginia Medical School, [2] Dermatology, Northwestern University

Keywords: hyperpigmentation, melasma, pregnancy, therapy, safety

Journal of Integrative Dermatology

Background

Pregnancy is characterized by a myriad of physiological changes, particularly in the skin. Hyperpigmentation continues to be one of the most troublesome dermatologic symptoms in pregnancy.

Objective

This review aims to discuss the safety and potential teratogenicity of traditional and integrative treatment options for hyperpigmentation in pregnancy.

Methods and Materials

A literature search was conducted on PubMed, Cochrane Library, and MedLine.

Results

Conventional regimens for hyperpigmentation including topical retinoids and hydroquinone are controversial in pregnancy. Topical steroids remain safe, while oral steroids should be avoided. Safe integrative treatments include kojic acid, liposomal aloe vera, topical nicotinamide, turmeric, glycolic acid, and ascorbic acid. Azeleic acid may be used to limited body surface area only, with caution during the first trimester. Licorice root/glabridin and green tea extract are not considered safe in pregnancy.

Conclusion

Safe integrative approaches can be utilized to treat hyperpigmentation during pregnancy. Kojic acid, liposomal aloe vera, topical nicotinamide, turmeric, glycolic acid, and ascorbic acid can be safely used during pregnancy to treat hyperpigmentation.

INTRODUCTION

The skin undergoes a multitude of physiological changes during pregnancy.[1] While many of these changes are poorly understood, a temporary alteration in the interplay of metabolism, immunology, and hormones leads to hyperpigmentation, hair and nail changes, vascular changes, and changes in apocrine and eccrine gland activity.[2] Hyperpigmentation may be the most cosmetically-distressing skin condition among pregnant women.[3]

Pregnancy is a unique state where pharmaceutical treatment presents a special concern because the physiology of pregnancy can affect the pharmacokinetics of medications used.[4] Certain drugs can also cross the placenta and damage the fetus.[4] In the 1960s, thalidomide was given to pregnant women as a morning sickness medication. Unfortunately, the women who took this drug gave birth to children with phocomelia.[4] Following this public health crisis, in 1979, the United States Food and Drug Administration (FDA) developed a system that determines the teratogenic risk of drugs by considering the quality of data from animal and human studies.[4] In this review, we characterize the teratogenicity of common treatments for pregnancy-related pigmentary disorders and discuss integrative regimens.

PIGMENTARY CHANGES

HYPERPIGMENTATION

Up to 90% of women experience hyperpigmentation during pregnancy.[1,2] While this hyperpigmentation is usually mild, areas including the genitals, areolae of the breast, axillae, inner thigh region, and anal region may undergo accentuation of baseline pigmentation.[1-3] Another area that experiences prominent hyperpigmentation is the midline of the abdomen: the linea alba subsequently becomes the linea nigra in pregnancy.[1-3] The linea nigra typically appears during the first trimester, extends from the umbilicus to the symphysis pubis, and is most prominent in patients with more richly-pigmented skin.[1-3] Those with more pigmented skin at baseline are also prone to develop vulvar melanosis, and pigmentary demarcation lines at the posterior leg or upper arms called Voigt or Futcher lines.[1,2] Ephelides, nevi, and recent scars can also undergo additional hyperpigmentation and increase in size during preg-

nancy.[1,2] Most hyperpigmentation in pregnancy appears early, progresses until delivery, and diminishes in the postpartum period.[1-3] However, the aforementioned sites that undergo more pronounced hyperpigmentation typically do not return to their previous color.[1-3]

While the exact pathogenesis of the increased melanogenesis in pregnancy is debated, the cause is attributed to the higher levels of certain hormones, including melanocyte-stimulating hormones such as estrogen, progesterone, and endorphins.[1-3] This theory is supported by some women who experience hyperpigmentation while taking oral contraceptives, and previously occurring hormonal-induced hyperpigmentation can be predictive of the subsequent development of hyperpigmentation in pregnancy.[1-3] Future pregnancies and hormonal contraceptives may cause pregnancy-induced hyperpigmentation to recur.[3] Additionally, subcutaneous implantation of hormonal contraceptives can also lead to hyperpigmentation.[5,6] Longer duration of use and darker skin may increase the risk of hyperpigmentation, possibly due to localized steroid release or a foreign body reaction; however, the exact pathogenesis remains elusive.[5,6]

MELASMA

Melasma, or chloasma, sometimes known as the "mask of pregnancy," often presents as symmetric, irregular but sharply demarcated, blotchy, light to dark-brown coalescing macules and patches of hyperpigmentation.[1-3,7] Various patterns of distributions exist for melasma, but the most common locations affected are the cheeks, chin, nose bridge, forehead, and upper lip.[1-3,7] One-half to two-thirds of pregnant women experience melasma, usually in the second half of pregnancy.[1,2,7]

The pathophysiology of melasma is similar to hyperpigmentation of pregnancy deriving from increased hormones.[1-3,7] However, melasma also has a genetic component, as 50% of patients report a positive family history, and identical twins have been shown to develop melasma.[1,2,7] Sunlight is also involved in melasma, as ultraviolet (UV) radiation induces cellular damage via lipid peroxidation in cellular membranes to generate free radicals, which may stimulate melanocytes to produce excess melanin.[1,2,7] Patients with pre-existing thyroid dysfunction have a fourfold increase in melasma, although this relationship needs to be better understood.[7]

TREATMENT

Conventional treatment of melasma focuses on topical formulations of retinoids, lightening agents such as hydroquinone, and corticosteroids, sometimes used in combination, with mild to moderate success.[1-3,7] Patients are also recommended to consistently use sunscreen to prevent UV damage and avoid irritant cosmetics.[1-3,7] While the combination of these topical agents has proven to be efficacious in some, it is vital to consider the possible impact on pregnancy of these drugs.

Prior to 2015, the FDA classified drugs in categories A, B, C, D, and X to characterize their teratogenicity.[8] Further information regarding each category of drug can be found in Table 1. Since 2015, the FDA has shifted from this categorial system to "The Pregnancy and Lactation Labeling Rule."[9]

While this current category system is more detailed than the older category system, many critics have expressed concern over changing drug labels to reflect the new rules and how drug labels will incorporate new data as it becomes available.[10] Another worry is how physicians will manage the transition from a long-used category system to a novel, more complex system.[11]

TERATOGENICITY OF CONVENTIONAL TREATMENT

While there is a paucity of data investigating the teratogenicity of hydroquinone, in vitro studies have shown that hydroquinone can induce chromosomal abnormalities in eukaryotic cells.[12] In the previous category labeling system, hydroquinone was labeled as a Category C drug by the FDA.[13] The description of Category C drugs states that animal reproduction studies have shown an adverse effect on the fetus with no adequate and well-controlled studies in humans, but potential benefits may warrant the use of the drug in pregnant women despite potential risks.[13] Despite its categorization as a Category C drug, most over-the-counter (OTC) preparations of topical hydroquinone do not come with this imperative warning.[14]

Numerous studies have demonstrated that a high intake of preformed vitamin A is teratogenic, resulting in significant cardiac and craniofacial abnormalities, and the FDA has issued a black-box warning on oral vitamin A products accordingly.[15,16] However, the topical use of vitamin A derivatives such as retinoids in pregnancy is highly debated.[8,15-18] While the exact absorption of topical retinoids is unknown, and animal studies have shown that the teratogenicity of topical retinoids is far less than conventional vitamin A supplements, the use of topical retinoids in pregnancy is generally not recommended.[8,15-18]

Proper use of topical steroids in pregnancy is considered safe, as many studies have demonstrated no increased risk to the fetus with these drugs.[19-21] To contrast, oral steroids should be used with caution in the first trimester of pregnancy, because there may be an association with the fetal development of orofacial clefts.[22] The long-term use of glucocorticosteroids in pregnancy may increase the risk of gestational diabetes, preeclampsia, membrane rupture, and preterm delivery.[22] Additionally, the long-term use of topical steroids on the face should be avoided as major adverse effects can occur including acneiform eruptions, perioral dermatitis, topical steroid withdrawal syndrome, glaucoma, Cushing's Syndrome, and other possible systemic effects.[23,24] Nevertheless, the use of mild to moderate-potency topical steroids is thought to pose no significant harm to the mother or fetus.[19-21]

Another treatment for melasma and hyperpigmentation in pregnancy is laser treatment. Although the efficacy of these treatments varies depending on the specific laser, how it is used, and both patient and operator factors, laser

Table 1. Former FDA categorization of drugs for use in pregnancy[4]

Category	Description
A	Adequate, well-controlled studies in pregnant women have not shown an increased known risk of fetal abnormalities.
B	Animal studies have revealed no evidence of known harm to the fetus; however, there are no adequate and well-controlled studies in pregnant women. Or Animal studies have shown an adverse effect, but adequate and well-controlled studies in pregnant women have failed to demonstrate a known risk to the fetus.
C	Animal studies have shown an adverse effect and there are no adequate and well-controlled studies in pregnant women. Or No animal studies have been conducted and there are no adequate and well-controlled studies in pregnant women.
D	Studies, adequate well-controlled or observational, in pregnant women have demonstrated a known risk to the fetus. However, the benefits of therapy may outweigh the potential risk.
X	Studies, adequate well-controlled or observational, in animals or pregnant women have demonstrated positive evidence of fetal abnormalities. The use of the product is contraindicated in women who are or may become pregnant.

therapy has generally been deemed safe for both the baby and the mother.[25,26]

AN INTEGRATIVE APPROACH

Kojic acid (KA) is a natural metabolite produced by fungi that can inhibit the primary enzyme responsible for melanin synthesis, tyrosinase.[27-29] Kojic acid has significant anti-oxidant properties and protects against UV damage and infectious agents.[27-29] Studies have demonstrated that kojic acid can significantly improve hyperpigmentation and is safe to use in pregnancy.[27-29] In particular, a formulation of kojic acid combined with vitamin E, vitamin A, plant oil, and lactic acid was found to be especially successful.[27] The patients who were treated with this kojic acid formulation wore daily sunscreen, so the application of daily sunscreen may also be recommended with kojic acid use.[27]

Glycolic acid is an alpha-hydroxy acid (AHA), a plant and animal-derived amino acid that successfully treats hyperpigmentation and is safe to use during pregnancy.[29,30]

Liposomal aloe vera is also found to be effective and safe in treating melasma in pregnant patients.[31] Aloe vera is thought to exert its effects by inhibiting tyrosinase.[32] In a double-blinded, randomized clinical trial, two groups of pregnant women with melasma, each containing 90 subjects (n=90) who were in their second trimester or beyond were followed for five weeks.[31] The two groups consisted of an experimental group, treated with topical liposome-encapsulated aloe vera gel leaf extract and a control group, treated with non-liposomal encapsulated aloe vera gel leaf extract.[31] After 5 weeks, there was a statistically significant improvement of 32% in the Melasma Area Severity Index (MASI) score for the liposomal treatment group as compared to a 10% improvement in the control group.[31] No major side effects were noted in the study for either the liposome-encapsulated aloe vera gel extract or the non-liposomal encapsulated aloe vera gel extract.[31] Minor side effects that may occur with topical aloe vera use include redness, burning, and stinging at the site of application.[33] Finally, the liposomal formulation of aloe vera gel is thought to penetrate the skin more effectively since liposomal formulations can hold hydrophilic substances in their inner aqueous phase and hydrophobic substances in the bilayer wall.[31]

Nicotinamide, also known as niacinamide, is the amide form of vitamin B3.[34] Topical nicotinamide has been proven to be worthwhile in treating melasma and hyperpigmentation by suppressing the transfer of melanosomes from melanocytes to keratinocytes.[34] While nicotinamide can cross the placenta and concentrate in fetal blood, there are no reports of adverse effects due to nicotinamide in fetuses.[34] While the effects of high doses of nicotinamide and long-term systemic use of topical nicotinamide remain unknown, topical nicotinamide appears safe to use in the hyperpigmentation of pregnancy.[34]

Turmeric, a popular spice used in many cultures, contains curcumin which promotes skin lightening, mediates oxidative damage, and suppresses inflammation cutaneously.[35-37] The topical application of turmeric is safe in pregnancy; numerous studies have demonstrated the systemic use of turmeric via the possible role of curcumin in managing pregnancy complications, including gestational diabetes, preeclampsia, and fetal intrauterine growth restriction.[38,39]

Topical ascorbic acid (vitamin C) is an acidic anti-oxidant found in high concentrations in citrus fruit that serves many crucial biological functions such as the synthesis of bile acids, catecholamines, and neurotransmitters, wound healing, tyrosine degradation, iron absorption, and immune system function.[40] Topical ascorbic acid has shown to improve hyperpigmentation and melasma,[40] and most importantly, is safe to use in pregnancy as it may have a role in preventing preeclampsia.[41] Furthermore, vitamin C deficiencies during pregnancy have been associated with impairments in neonatal neurological development.[42]

Azelaic acid is a dicarboxylic acid derived from the fungus *Pityrosporum ovale* and is found in rye, wheat, and barley.[40] Azelaic acid disrupts DNA synthesis, mitigates free-radical damage, and competitively inhibits tyrosinase.[40] Azelaic acid preferentially targets abnormal and highly active melanocytes with minor effects on uninvolved skin, making it an excellent agent for treating melasma and hy-

perpigmentation.[40] The FDA had previously categorized azelaic acid in category B, meaning that animal reproduction studies have failed to demonstrate a risk to the fetus, and there are no adequate and well-controlled studies in pregnant women.[29,43] Thus, while azelaic acid use in pregnancy does not pose an immediate risk to the fetus, azelaic acid should only be used on limited areas and preferably not in the first trimester to minimize any possible harm to the baby.[29]

Green tea has been historically marketed for its antioxidant and anti-inflammatory properties,[40] but caution should be taken with this compound in pregnancy.[44,45] Green tea extracts have proven to help treat melasma and pigmentary disorders by inhibiting UV-induced erythema and protecting DNA from UV radiation.[40] However, in rat studies, rat mothers fed green tea extract developed lower body weights and birthed fetuses with lower birth weights.[44] Additionally, analysis of neuronal tissues from rat mothers fed green tea extract showed various degrees of degeneration in a dose-dependent manner,[44] while analysis of adipose tissue demonstrated greater degrees of inflammation.[45] Thus, though the benefits of green tea are many, care should be taken when using this product topically in a gestational state.

Licorice root contains the isoflavone compound glabridin, a type of phenol, which has been shown to scavenge reactive oxygen species, inhibit UV-B-induced pigmentation, inhibit tyrosinase, and mediate inflammation.[40] In vitro, glabridin has been shown to have a skin-lightening effect 16 times greater than hydroquinone.[40] Despite its efficacy, licorice root consumption is not recommended in pregnancy due to severe detrimental effects on the fetus, including delays in cognition, development, and memory.[46,47] The application of topical licorice root extract has not been studied in expecting mothers due to the teratogenicity of oral licorice; pregnant women are safer avoiding this topical compound.

Bakuchiol is a meroterpene phenol and retinol alternative that has received recent attention in dermatology and may be considered for the treatment of hyperpigmentation in pregnancy.[48,49] Bakuchiol is thought to improve hyperpigmentation via the inhibition of melanogenesis.[48,49] While there is no explicit data advising against the use of bakuchiol in pregnancy, there are also no large-scale trials evaluating bakuchiol's teratogenicity. Thus, bakuchiol should be used with caution.

CONCLUSION

Of many changes experienced during pregnancy, hyperpigmentation may be the most cosmetically-distressing skin condition among pregnant women. Conventional regimens for hyperpigmentation including topical retinoids and hydroquinone are controversial in pregnancy. Topical steroids remain safe, while oral steroids should be avoided. Kojic acid, liposomal aloe vera, topical nicotinamide, turmeric, glycolic acid, and ascorbic acid can be safely used during pregnancy to treat hyperpigmentation (Table 2). Licorice root/glabridin and green tea extract should generally be avoided in pregnancy. Azelaic acid should be used on limited areas only, and preferably not during the first trimester.

CORRESPONDING AUTHOR

Peter Lio, MD
363 W Erie Street, Suite 350
Chicago, IL 60654
Phone: (312) 995-1955
Fax: (312) 995-1956
peterlio@gmail.com

FUNDING SOURCES

No funding sources were secured for this study.

DISCLOSURES

Dr. Lio reports research grants/funding from the National Eczema Association, AOBiome, Regeneron/Sanofi Genzyme, and AbbVie; is on the speaker's bureau for Regeneron/Sanofi Genzyme, Pfizer, Eli Lilly, LEO, Galderma, and L'Oréal; reports consulting/advisory boards for Almirall, ASLAN Pharmaceuticals, Dermavant, Regeneron/Sanofi Genzyme, Pfizer, LEO Pharmaceuticals, AbbVie, Eli Lilly, Micreos, L'Oréal, Pierre-Fabre, Johnson & Johnson, Level Ex, Unilever, Menlo Therapeutics, Theraplex, IntraDerm, Exeltis, AOBiome, Realm Therapeutics, Altus Labs (stock options), Galderma, Amyris, Bodewell and My-Or Diagnostics.

KA reports no conflict of interest.

Submitted: July 19, 2023 PST, Accepted: January 23, 2024 PST

Table 2. Summary of integrative treatment for hyperpigmentation in pregnancy

Agent	Method of Action	Teratogenicity
Kojic Acid	Inhibits tyrosinase, anti-oxidant	No known harm to fetus, low absorption
Aloe vera gel leaf extract	Inhibits tyrosinase	No known harm to fetus
Nicotinamide	Suppresses transfer of melanosomes	Can concentrate in fetal blood. Topically safe
Turmeric	Anti-oxidant, anti-inflammatory	No known harm to fetus
Topical Vitamin C	Anti-oxidant, wound healing, increases immunity, neurotransmitter, catecholamine, bile acid synthesis, tyrosine degradation, iron absorption	No known harm to fetus, deficiencies associated with impairments in neurological development
Licorice root/ glabridin	Anti-oxidant, inhibits tyrosinase, anti-inflammatory	Harmful neurocognitive effects on fetus
Azelaic Acid	Disrupts DNA synthesis, anti-oxidant, inhibits tyrosinase	Animal studies have revealed no known evidence of harm to the fetus; however, there are no adequate and well-controlled studies in pregnant women. Preferred to use only on small surfaces and preferably not in first trimester
Green Tea extract	Protects DNA from UV radiation	Harmful effects to fetus in rat studies

REFERENCES

1. Wong RC, Ellis CN. Physiologic skin changes in pregnancy. *J Am Acad Dermatol*. 1984;10(6):929-940. doi:10.1016/s0190-9622(84)80305-9

2. Tyler KH. Physiological Skin Changes During Pregnancy. *Clin Obstet Gynecol*. 2015;58(1):119-124. doi:10.1097/grf.0000000000000077

3. Tunzi M, Gray GR. Common skin conditions during pregnancy. *Am Fam Physician*. 2007;75(2):211-218.

4. Sachdeva P, Patel BG, Patel BK. Drug use in pregnancy; a point to ponder! *Indian J Pharm Sci*. 2009;71(1):1-7. doi:10.4103/0250-474x.51941

5. Alvarez F, Brache V, Faundes A, Jorge A, Sousa MH. Local side effects observed among long-term users of norplant contraceptive implants. *Contraception*. 2003;68(2):111-115. doi:10.1016/s0010-7824(03)00144-6

6. Ramdhan RC, Simonds E, Wilson C, Loukas M, Oskouian RJ, Tubbs RS. Complications of Subcutaneous Contraception: A Review. *Cureus*. 2018;31. doi:10.7759/cureus.2132

7. Basit H, Godse KV, Al Aboud AM. Melasma. In: *StatPearls*. StatPearls Publishing; 2022. Accessed November 21, 2022. http://www.ncbi.nlm.nih.gov/books/NBK459271/

8. Tsamantioti ES, Hashmi MF. Teratogenic Medications. In: *StatPearls*. StatPearls Publishing; 2022. Accessed November 22, 2022. http://www.ncbi.nlm.nih.gov/books/NBK553086/

9. Research C for DE and. Pregnancy and Lactation Labeling (Drugs) Final Rule. *FDA*. Published online March 5, 2021. Accessed November 22, 2022. https://www.fda.gov/drugs/labeling-information-drug-products/pregnancy-and-lactation-labeling-drugs-final-rule

10. Blattner CM, Danesh M, Safaee M, Murase JE. Understanding the new FDA pregnancy and lactation labeling rules. *Int J Womens Dermatol*. 2016;2(1):5-7. doi:10.1016/j.ijwd.2015.12.005

11. Pernia S, DeMaagd G. The New Pregnancy and Lactation Labeling Rule. *P T Peer-Rev J Formul Manag*. 2016;41(11):713-715.

12. Devillers J, Boule P, Vasseur P, et al. Environmental and health risks of hydroquinone. *Ecotoxicol Environ Saf*. 1990;19(3):327-354. doi:10.1016/0147-6513(90)90035-4

13. Hydroquinone topical Use During Pregnancy. *Drugs.com*. Accessed November 22, 2022. https://www.drugs.com/pregnancy/hydroquinone-topical.html

14. Bio LL, Cies JJ. Lack of pregnancy warnings on over-the-counter dermatologic products containing potentially harmful hydroquinone. *J Perinatol*. 2017;37(7):778-781. doi:10.1038/jp.2017.35

15. Rothman KJ, Moore LL, Singer MR, Nguyen USDT, Mannino S, Milunsky A. Teratogenicity of High Vitamin A Intake. *N Engl J Med*. 1995;333(21):1369-1373. doi:10.1056/nejm199511233332101

16. Williams AL, Pace ND, DeSesso JM. Teratogen update: Topical use and third-generation retinoids. *Birth Defects Res*. 2020;112(15):1105-1114. doi:10.1002/bdr2.1745

17. Veraldi S, Rossi LC, Barbareschi M. Are topical retinoids teratogenic? *G Ital Dermatol E Venereol Organo Uff Soc Ital Dermatol E Sifilogr*. 2016;151(6):700-705.

18. Rothman KF, Pochi PE. Use of oral and topical agents for acne in pregnancy. *J Am Acad Dermatol*. 1988;19(3):431-442. doi:10.1016/s0190-9622(88)70195-4

19. Alabdulrazzaq F, Koren G. Topical corticosteroid use during pregnancy. *Can Fam Physician Med Fam Can*. 2012;58(6):643-644.

20. Chi CC, Wang SH, Kirtschig G. Safety of Topical Corticosteroids in Pregnancy. *JAMA Dermatol*. 2016;152(8):934. doi:10.1001/jamadermatol.2016.1009

21. Andersson NW, Skov L, Andersen JT. Evaluation of Topical Corticosteroid Use in Pregnancy and Risk of Newborns Being Small for Gestational Age and Having Low Birth Weight. *JAMA Dermatol*. 2021;157(7):788. doi:10.1001/jamadermatol.2021.1090

22. Stefaniak AA, Pereira MP, Zeidler C, Ständer S. Pruritus in Pregnancy. *Am J Clin Dermatol*. 2022;23(2):231-246. doi:10.1007/s40257-021-00668-7

23. Coondoo A, Phiske M, Verma S, Lahiri K. Side-effects of topical steroids: A long overdue revisit. *Indian Dermatol Online J*. 2014;5(4):416. doi:10.4103/2229-5178.142483

24. Dhar S, Seth J, Parikh D. Systemic side-effects of topical corticosteroids. *Indian J Dermatol*. 2014;59(5):460. doi:10.4103/0019-5154.139874

25. Allameh F, Javadi A, Dadkhahfar S, et al. A Systematic Review of Elective Laser Therapy during Pregnancy. *J Lasers Med Sci*. 2021;12(1):e50. doi:10.34172/jlms.2021.50

26. Wilkerson EC, Van Acker MM, Bloom BS, Goldberg DJ. Utilization of Laser Therapy During Pregnancy: A Systematic Review of the Maternal and Fetal Effects Reported From 1960 to 2017. *Dermatol Surg*. 2019;45(6):818-828. doi:10.1097/dss.0000000000001912

27. Berardesca E, Rigoni C, Cantù A, et al. Effectiveness of a new cosmetic treatment for melasma. *J Cosmet Dermatol*. 2020;19(7):1684-1690. doi:10.1111/jocd.13203

28. Saeedi M, Eslamifar M, Khezri K. Kojic acid applications in cosmetic and pharmaceutical preparations. *Biomed Pharmacother*. 2019;110:582-593. doi:10.1016/j.biopha.2018.12.006

29. Putra IB, Jusuf NK, Dewi NK. Skin Changes and Safety Profile of Topical Products During Pregnancy. *J Clin Aesthetic Dermatol*. 2022;15(2):49-57.

30. Bozzo P, Chua-Gocheco A, Einarson A. Safety of skin care products during pregnancy. *Can Fam Physician Med Fam Can*. 2011;57(6):665-667.

31. Ghafarzadeh M, Eatemadi A. Clinical efficacy of liposome-encapsulated*Aloe vera*on melasma treatment during pregnancy. *J Cosmet Laser Ther*. 2017;19(3):181-187. doi:10.1080/14764172.2017.1279329

32. Austin E, Nguyen JK, Jagdeo J. Topical Treatments for Melasma: A Systematic Review of Randomized Controlled Trials. *J Drugs Dermatol JDD*. 2019;18(11):S1545961619P-S1545961156X.

33. Surjushe A, Vasani R, Saple D. Aloe vera: A short review. *Indian J Dermatol*. 2008;53(4):163. doi:10.4103/0019-5154.44785

34. Rolfe HM. A review of nicotinamide: treatment of skin diseases and potential side effects. *J Cosmet Dermatol*. 2014;13(4):324-328. doi:10.1111/jocd.12119

35. Sawant O, Khan T. Management of periorbital hyperpigmentation: An overview of nature-based agents and alternative approaches. *Dermatol Ther*. 2020;33(4). doi:10.1111/dth.13717

36. Park SY, Jin ML, Kim YH, Kim Y, Lee SJ. Aromatic-turmerone inhibits α-MSH and IBMX-induced melanogenesis by inactivating CREB and MITF signaling pathways. *Arch Dermatol Res*. 2011;303(10):737-744. doi:10.1007/s00403-011-1155-7

37. Vaughn AR, Branum A, Sivamani RK. Effects of Turmeric (Curcuma longa) on Skin Health: A Systematic Review of the Clinical Evidence: Effects of Curcuma longa on Skin Health. *Phytother Res*. 2016;30(8):1243-1264. doi:10.1002/ptr.5640

38. Ghaneifar Z, Yousefi Z, Tajik F, et al. The potential therapeutic effects of curcumin on pregnancy complications: Novel insights into reproductive medicine. *IUBMB Life*. 2020;72(12):2572-2583. doi:10.1002/iub.2399

39. Tossetta G, Fantone S, Giannubilo SR, Marzioni D. The Multifaced Actions of Curcumin in Pregnancy Outcome. *Antioxidants*. 2021;10(1):126. doi:10.3390/antiox10010126

40. Hollinger JC, Angra K, Halder RM. Are Natural Ingredients Effective in the Management of Hyperpigmentation? *A Systematic Review J Clin Aesthetic Dermatol*. 2018;11(2):28-37.

41. Rumbold A, Ota E, Nagata C, Shahrook S, Crowther CA. Vitamin C supplementation in pregnancy. Cochrane Pregnancy and Childbirth Group, ed. *Cochrane Database Syst Rev*. 2015;2016(3). doi:10.1002/14651858.cd004072.pub3

42. Coker SJ, Smith-Díaz CC, Dyson RM, Vissers MCM, Berry MJ. The Epigenetic Role of Vitamin C in Neurodevelopment. *Int J Mol Sci*. 2022;23(3):1208. doi:10.3390/ijms23031208

43. Helbock TLO of MJ. How does the FDA Classify Teratogenic Drugs? The Law Office of Melinda J. Helbock, A.P.C. Published August 26, 2013. Accessed November 22, 2022. https://helbocklaw.com/fda-classify-teratogenic-drugs/

44. El-Borm HT, Abd El-Gaber AS. Effect of prenatal exposure of green tea extract on the developing central nervous system of rat fetuses; histological, immune-histochemical and ultrastructural studies. *Saudi J Biol Sci*. 2021;28(8):4704-4716. doi:10.1016/j.sjbs.2021.04.084

45. Hachul ACL, Boldarine VT, Neto NIP, et al. Maternal consumption of green tea extract during pregnancy and lactation alters offspring's metabolism in rats. Peterson JM, ed. *PLoS ONE*. 2018;13(7):e0199969. doi:10.1371/journal.pone.0199969

46. Nazari S, Rameshrad M, Hosseinzadeh H. Toxicological Effects of Glycyrrhiza glabra (Licorice): A Review: Toxicology of Licorice. *Phytother Res*. 2017;31(11):1635-1650. doi:10.1002/ptr.5893

47. Räikkönen K, Martikainen S, Pesonen AK, et al. Maternal Licorice Consumption During Pregnancy and Pubertal, Cognitive, and Psychiatric Outcomes in Children. *Am J Epidemiol*. 2017;185(5):317-328. doi:10.1093/aje/kww172

48. Puyana C, Chandan N, Tsoukas M. Applications of bakuchiol in dermatology: Systematic review of the literature. *J Cosmet Dermatol*. 2022;21(12):6636-6643. doi:10.1111/jocd.15420

49. Goldberg DJ, Mraz-Robinson D, Granger C. Efficacy and safety of a 3-in-1 antiaging night facial serum containing melatonin, bakuchiol, and ascorbyl tetraisopalmitate through clinical and histological analysis. *J Cosmet Dermatol*. 2020;19(4):884-890. doi:10.1111/jocd.13329