# Skin Changes and Safety Profile of Topical Products During Pregnancy

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*J Clin Aesthet Dermatol.* 2022;15(2):49–57.

**OBJECTIVE:** We sought to know the efficacy and safety profile of topical products for use during pregnancy. **METHODS:** We used PubMed, Embase, and Cochrane Library to review literature on topical products and pregnancy. **RESULTS:** A majority of pregnant women develop skin changes, including physiological or hormonal changes, worsening of preexisting skin conditions, or the appearance of new dermatoses during pregnancy. Most pregnant women are concerned about the availability of treatments options with good safety profiles, especially for skin and hair treatments, to maintain their appearance and health. Although most of the treatments are recommended to be used after delivery, there are some alternatives to prevent and treat skin lesions during pregnancy. **CONCLUSION:** The most current and comprehensive information about the efficacy and safety profile of topical products in pregnancy are necessary. **KEY WORDS:** Skin care, cosmetics, pregnancy, safety

Ninety percent of pregnant women often experience some skin changes, including physiological (hormonal) changes, worsening of preexisting dermatoses, and specific pregnancy dermatoses, which need special care and treatment. All of these conditions are associated with alteration in hormones, vascular, metabolism, and immunologic conditions during pregnancy.[1] One of the prominent physiological changes during pregnancy is the increase of androgens, which induce progression or worsening of acne vulgaris and increasing of hair growth in several body parts.[2] A descriptive study by Urasaki revealed that 91.1 percent of pregnant women developed skin lesions associated with pregnancy and about 67.2 percent of the skin changes has been affecting their confidence and health. Skin pigmentation is the most common problem during pregnancy, followed by vascular changes, stretch mark, and acne vulgaris.[3] Therefore, treatments options with good safety profiles, especially topical products, become an important issue among pregnant women.[4]

In general, there are some concerns regarding the safety profile of the skin care products for pregnant population. Dermatologists are often asked regarding the safety of prescribed topical and systemic drugs during pregnancy. Clinical trials and systematic review regarding the safety profile of topical products in pregnancy are very limited due to ethical issue. Although most of treatments are recommended to be used only after delivery, there are some alternative therapies to prevent and treat skin lesions during pregnancy. Food and Drug Administration of United States of America (US FDA) has classified 5 categories (A, B,C, D, X) in order to describe the drug potency for inducing congenital defects if it is used during pregnancy.[5] These categories can guide the physican and health practitioner in providing safe skin treatment for pregnant women. However, some topical products have not been approved and categorized according to the fetomaternal risk by this worldwide known classification. Safety profile data of topical products are either difficult to be obtained or not listed comprehensively in single reference guideline.[6] Therefore, the latest and comprehensive information about the efficacy and safety profile of topical products during pregnancy are necessary.

## PHYSIOLOGICAL CHANGES AND SKIN PROBLEMS DURING PREGNANCY

During pregnancy, skin problems are mostly caused by elevation of hormones, such as estrogen, progesterone, prolactin, β-HCG, alteration in metabolism of protein, lipid, carbohydrate, and also in adaptive immunity.[4] Due to these physiological changes, cutaneous changes in pregnancy may include pigmentation, hair, nail, glands, connective tissues, and blood vessels (Table 1). Hyperpigmentation is the most common skin lesion, affecting up to 90% of pregnant women, and even higher in darker skin type.[7] Furthermore, melasma is commonly found during pregnancy (up to 70%), as it is often called "the mask of pregnancy".[7,8] These conditions generally improve after delivery, but they often persist and cause treatment challenges.[8]

Other than that, hair changes such as hirsutism are found frequently on the face and sometimes on extremities and back of pregnant women. Furthermore, telogen effluvium is common among this population due to elongation of anagen phase during pregnancy and increased number of hairs in telogen phase within 70 to 80 days post delivery.[7,9,10] This

**FUNDING:** No funding was provided for this article.
**DISCLOSURES:** The authors report no conflicts of interest relevant to the content of this article.
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**TABLE 1**. Physiological changes of the skin, hair, and nails during pregnancy[7]

| |
|---|
| Pigmentation |
| Hyperpigmentation |
| Melasma |
| Hair |
| Hirsutism |
| Telogen effluvium post delivery |
| Androgenetic alopecia post delivery |
| Nail |
| Hyperkeratosis subungual |
| Distal Onycholysis |
| Transverse grooving |
| Fragile nail |
| Gland |
| Increased function of eccrine and sebaceous glands |
| The decreased function of apocrine gland |
| Connective tissue |
| Striae distensae (Striae gravidarum) |
| Vascular |
| Telangiectasia |
| Erythema palmaris |
| Edema non-pitting |
| Varices |
| Hemorrhoid |

condition persists for 1 to 5 months, and up to 15 months in some cases.[7,11] Although complete hair growth eventually occurs, it seldom regains its previous thickness.[12] Aside from that, mild frontoparietal recession during pregnancy, resembling androgenetic alopecia, may happen and will not grow back to normal after delivery.[9,10,13] In addition, homogenous thinning of hair affects some women during late pregnancy due to the inhibition of anagen phase.[7,14]

Nail changes during pregnancy include hyperkeratosis subungual, distal onycholysis, transverse grooving, and fragile nail (Table 1).[7] Erpolat et al. found that 62.4% of healthy pregnant women experience one or two nail lesions. The highest frequency is leukonychia (24.4%), followed by foot nail ingrown (9%) and onychoschizia (9%) which commonly found in third trimester. Other findings may include rapid nail growth (6.7%), hyperkeratosis subungual (4.2%), melanonychia (3.2%), distal onycholysis, and fragile nail (1.9%). The underlying pathogenesis for these lesions is not well understood. However, it is hypothesized that estrogen induce the increase of peripheral blood circulation, which stimulates nail growth and results in the higher risk of matrix dysfunction, slower keratin maturation, and nail fragility.[15]

The activity of eccrine and sebaceous gland increase during pregnancy, except apocrine gland.[7] Elevation of eccrine gland activity is found throughout the body, except palms, and manifest clinically as hyperhidrosis and miliaria. Other than enlargement of Montgomery glands around the areola, the increased activity of sebaseous glands during pregnancy may worsened acne vulgaris. However, some studies reported various results, in which some studies reported the improvement of acne during pregnancy.[16]

Striae distensae (i.e., stretch mark) is the most common connective tissue changes during pregnancy, occurring in 63 to 90% pregnant women during the sixth and seventh months of gestation.[7,8,16] The clinical manifestation is atrophic line with pink or purplish (striae rubra) color on mammary, abdomen, gluteal, and femoral region. The color will fade gradually but not completely, and results in atrophic white lines (striae alba). Several factors associated with this condition, including the increase of hormonal activity, genetics, physical strain on the skin, and weight gain during pregnancy.[7,16]

In terms of vascular change during pregnancy, elevation of estrogen may cause telangiectasis in 67% of pregnant Caucasian women during the second and fifth months of gestation, and resolve within three months after delivery.[7] In addition, high hydrostatic venous pressure, especially on lower extremites can lead to non-pitting edema and varicose. There are increased incidences and enlargement of previous tumor and other vascular lesions, like hemangioma, pyogenic granuloma, purpura, and petechiae during pregnancy.[16]

## SAFETY PROFILE OF TOPICAL PRODUCTS FOR CUTANEOUS CHANGES IN PREGNANCY

**Pigmentation lesions.** Until present, standard therapy for hyperpigmentation and melasma is still hydroquinone. However, high systemic absorption has lead to caution of its use during pregnancy.[17] Accoring to animal study, dosage ≤300 mg/kg/day during organogenesis caused no adverse effects on reproductive system.[18] Although human study showed low risk and no increase in adverse events, it is best to minimize hydroquinone usage in pregnancy with US FDA category C.[5,20] As an alternative, azelaic acid is preferred in pregnancy with US FDA category B.[5] Topical use of this tyrosinase inhibitor leads to 3 to 8 percent systemic absorption.[21] An animal study revealed no harmful effect on fetuses and newborns even when administered in high dosages during pregnancy.[22] Until present, controlled studies of azelaic acid usage in human during pregnancy are still lacking,[23] but no adverse events have been reported in parenteral usage.[24] Therefore, azelaic acid should only be used on small skin surfaces and preferably not in the first trimester.[25]

Other topical products commonly used in hyperpigmentation disorders such as arbutin and kojic acid, have low systemic absorption, no reported fetomaternal risk in animal and no data available on human reproductive system.[27-29] These drugs have not been approved and classified by the US FDA. As a glycosylated hydroquinone, arbutin has lower toxicity than its main metabolite and considered safe to be used in pregnancy.[4] However, no recommendation available yet regarding the use of these two drugs in pregnancy and further studies are required. Retinoic acid is often used to treat melasma, as tretinoin in combination with hydroquinone and topical corticosteroid.[19] Even though, it has low systemic absorption (1–2%),[30] some congenital malformations have been reported in animal and human studies.[20,31] However, a multicenter prospective study revealed no evidence of an increase in anomalies consistent with retinoic acid embryopathy.[32] US FDA classified retinoic acid with category C.[5] Until more data are available, it is recommended to avoid using retinoic acid during pregnancy.[20]

Alpha hydroxy acid (AHA) has been used in hyperpigmentation with good efficacy. The vehicle used for formulation plays an important role in its absorption.[33] Glycerin has a strong affinity for AHA, but cannot substantially penetrate the stratum corneum and results in lower absorption. In contrast, propylene glycol in the vehicle can enhance the penetration of AHA by modifying the permeability of the stratum corneum.[34] In animal study, no teratogenic effects reported with the daily dose of 250 mg/kg, but no controlled human study is available yet.[35] With category B in US FDA,5 it is considered safe to use AHA in concentration up to 10% with pH > 3.5.[36] Photoprotection remains the most important aspect in

**TABLE 2.** Summary of safety profile of topical products used in pigmentation disorders during pregnancy.

| TOPICAL PRODUCTS | SYSTEMIC ABSORPTION | ANIMAL STUDY | HUMAN STUDY | US FDA[5] | RECOMMENDATIONS IN PREGNANCY |
|---|---|---|---|---|---|
| Hydroquinone | 45.3 ± 11.2% from 24-hour application of 2% cream[17] | ≤300 mg/kg/day during organogenesis caused no adverse effects on reproduction[18] | A single study with 68 pregnant women using hydroquinone showed no increase in adverse events[19] | C | Low risk, but more data are needed. It is best to minimize exposure because of the amounts absorbed into the systemic circulation.[20] |
| Azelaic Acid | 15% gel has absorption (8%) higher than the 20% cream (3%).[21] | No harmful effect on fetuses and newborn animals, even when administered in high dosages during pregnancy.[22] | Systematic studies on its use in humans are lacking.[23] However, parenteral infusion resulted in no adverse effects.[24] | B | Preferred in pregnancy[23] but should only be used for strict indications on small skin surfaces, preferably not in the first trimester.[25] |
| Arbutin | Topical 2% only has 0.27 ± 0.13% dermal absorption26 and α-arbutin will undergo partial hydrolysis into hydroquinone in the skin.[27] Systemic distribution is estimated to be very minimal. | No data available on reproductive system.[27] | No data available on reproductive system.[27] | - | No recommendation available yet. However, low systemic absorption and lower toxicity compared to hydroquinone lead to an assumption that arbutin can be safely used in pregnancy.[4] |
| Kojic Acid | Topical 1% has percutaneous absorption of 17% with very low systemic absorption (0.03 – 0.06 mg/kg).[28] | In mice study, kojic acid was reported to have no maternal risks or fetal damage.[29] | No data available on reproductive system.[29] | - | Still not recommended and further studies are required. |
| Retinoic Acid | Less than 1% after single application of tretinoin gel 0.1% or less than 2% using cream preparation.[30] | An increasing incidence of severe microphthalmia, anophthalmia, and iridial colobomata at dose 1.25 mg/kg. Slightly higher threshold doses produced exencephaly (2.5 mg/kg) and marked craniofacial defects (7.5 mg/kg) representative of the holoprosencephaly–aprosencephaly spectrum.[31] | Five reports of congenital malformations in newborns whose mother were using tretinoin during the first trimester.[20] A multicentre prospective study revealed women exposed to topical retinoids during the first trimester of pregnancy do not seem at higher risk for major birth defects in neonates, above the baseline rate of 1% to 3%. No evidence of an increase in anomalies consistent with retinoic acid embryopathy was found.[32] | - | Until more data are available, the safest course is to avoid the use of retinoic acid during pregnancy, especially in the first trimester. But if inadvertent exposure does occur during early pregnancy, the fetal risk, if any, appears to be very low.[20] |
| AHA | The vehicle used for formulation plays an important role in absorption.[33] Glycerin based has lower AHA absorption, but propylene glycol enhance its penetration.[34] | No teratogenic effects with the daily dose of 250 mg/kg[35] | Controlled study in human is not yet available[35] | B | Considered safe to use in concentration up to 10% with pH more than 3.5[36] |
| Photoprotection Physical[37] | No absorption | No report | No report on teratogenicity | - | Considered safe in pregnancy |
| Chemical[38] | Benzophenone-3 has 1-2% absorption and was found in urine excretion (3.7%). | No report on teratogenicity | - | Considered safe in pregnancy | Preferred in pregnancy[23] but should only be used for strict indications on small skin surfaces, preferably not in the first trimester.[25] |

management of melasma.[4] During pregnancy, physical sunscreen is the safest option because titanium oxide and zinc oxide are inorganic, not absorbable, have lower skin irritation potency.[37] In addition, chemical type sunscreens such as benzophenone-3, have systemic absorption and can be found in urine excretion.[38] Although no teratogenic effect reported, it is recommended to use with caution during pregnancy.

**Acne vulgaris.** Topical retinoid as a derivative of vitamin A has been used to treat acne vulgaris for more than 30 years. Adapalene and tretinoin are classified as category C, but tazarotene is classified as category X by US FDA due to the report regarding retinoid embryopathy associated with topical usage, although the role was still controversial.[25,31,45] However, two prospective studies of tretinoin usage during first trimester on pregnant women reported neither congenital malformation nor evidence of retinoid embryopathy.[41,42] The use of topical retinoid during pregnancy should be avoided due to its questionable risk-benefit ratio until further large scale study is available.

Erythromycin and clindamycin are two most common prescribed topical antibiotics for inflammatory acne. They are classified as category B by US FDA and no teratogenic effects has been reported. Therefore, these two topical antibiotics are the most preferred in pregnancy.[23] Their combination with benzoyl peroxide (BPO) can reduce the resistance level of bacteria and increase the efficacy of treatment. Although it is absorbed 5% systemically with topical use, BPO undergo complete metabolism into benzoic acid and rapid excretion in the kidney. Therefore, it has very low risk in causing congenital malformation and considered safe for pregnant women even though US FDA classified as category C.[5,48] Recently, dapsone has just approved by US FDA with pregnancy risk category C. Although no reported teratogenic effect in animal, it is recommended to use with caution due to the risk of hemolytic anemia in G6PD deficiency patient.[51-53] Other than hyperpigmentation, azelaic acid is safely used in the treatment of acne vulgaris among pregnant women due to its antimicrobioal, comedolytic, and mild anti-inflammatory effects.[39,48]

Keratolytics are widely used in acne vulgaris treatment. Topical salicylic acid and glycolic acid are the most commonly used ingredient for OTC skin care products to treat acne, as it acts as keratolytic agent and has various systemic absorptions. Animal studies reported embryo malformation is associated with systemic administration of salicylic acid and high dose glycolic acid.[54,56] However, most studies did not reveal increased risk of the congenital malrofmation in salicylic acid topical use and it is recommended to limit duration, area of application and avoid occlusion.[39,55] Currently, there is no available study about the use of topical glycolic acid during pregnancy. US FDA has not classified glycolic acid in any category, but it is considered safe to be used during pregnancy due to its minimal absorption.[48]

**Anti aging.** Anti-aging products usually contain various antioxidants, such as vitamin C, vitamin E, lipoic acid, and ubiquinone, which act by suppressing oxidation process in the cell, neutralizing reactive oxygen species (ROS)¸ and restoring the homeostasis.[57] Vitamin C (ascorbic acid) acts as antioxidant on peroxide free radical and hydroxyl group. It inhibits metalloproteinase-1 (MMP-1) to control oxidative stress. In addition, vitamin C stimulates the collagen synthesis and possesses the capability for skin lightening due to the inhibition of oxidative process during melanin synthesis.[58,59] Vitamin E or α-tochoperol acts by capturing free radical to form α-tochoperoxyl, which directly inhibits the peroxidation of lipid.[69] Once it is bounded with ubiquinole, it will revert to active Vitamin E as antioxidant and ubiquinone produced in the fatty layers of cell membrane. Ubiquinone can stop chain reaction of free radical. Since it is synthesized endogenously, the use of this antioxidant during pregnancy should not bring any harms to fetus and pregnant women.[59,60]

Lipoic acid is the antioxidant, known as superficial chemical peeling agent. It works together with ascorbic acid to protect biological membrane from oxidation. Lipoic acid stimulates fibroblast; reducing skin aging, and actin damage.[61] The effective concentration of lipoic acid ranges between 0.5 – 5% as this dose range is not associated with toxic effect to human body. Therefore, its use during pregnancy is considered safe.[62]

There are some traditional antioxidants derived from plants, such as ferulic acid (abundantly found in flaxseed, corn, bran) and resveratrol polyphenol (found in some plants species especially grapes). Ferulic acid is a strong antioxidant, which can prevent erythema due to UVB radiation, and act synergically with vitamin C to give photoprotection effect. Resveratrol has antioxidant effect on free radical through hydrogen molecule in its phenol component. Topical cosmetic products containing both of these antioxidants are considered safe for pregnant women. However, oral resveratrol might affect the fetus.[4]

**Striae distensae.** The available treatments for stretch mark are laser therapy, carboxytherapy, emollient cream with abundant nutrient content, and active substance to induce to collagen synthesis and reepithelialization. The ruptures of collagen and elastin fibers cause striae distensae due to dehydration or excessive strain. The use of emollient and humectant can treat or prevent the injury due to the tear in the epidermal strain as presented in striae. Some moisturizer ingredients, which are safe to be used during pregnancy, include AHA, ammonium lactate, organic silica, phospholipid, cholesterol, fatty acid, propylene glycol, glycerin, and sorbitol.[4] In addition, vitamin E can be used too as emollient since its antioxidant activity can prevent transepidermal water loss (TEWL).[63]

There are some cosmetic products, which used as additional treatment for stretch mark, such as hyaluronic acid, panthenol, allantoin, elastin, and collagen. Hyaluronic acid is glycosaminoglycan polysaccharides, which forming the connective tissue and intracellular space in mammals. It maintains the flexibility and elasticity of epithelial tissue and cartilages by retaining water bound in the tissue. The use of hyaluronic acid during pregnancy is considered safe and can be used liberally. However, hyaluronic acid with low molecular density is more favourable as it is produced through fragmentation of polymer or nanotechnology process to facilitate better absorption to dermal layer. Panthenol is considered safe since it is one of the elements in the skin.[4] On the other hand, topical use of combination cream containing hydroxyprolisilane C, rosehip oil, *Centella asiatica* triterpenes and vitamin E has been reported to prevent the development and reduce the intensity of striae with no harmful fetomaternal effects associated.[64] However further studies are necessary to confirm this promising treatment option in pregnancy.

Some researchers recommend the use of topical tretinoin 0.1% at night time post delivery to stimulate mitosis, epidermal cell regeneration, and synthesis of dermal collagen.

**TABLE 3.** Summary of safety profile of topical products used in acne vulgaris during pregnancy

| TOPICAL PRODUCTS | SYSTEMIC ABSORPTION | ANIMAL STUDY | HUMAN STUDY | UNITED STATES FOOD AND DRUG ADMINISTRATION[5] | RECOMMENDATIONS IN PREGNANCY |
|---|---|---|---|---|---|
| Tretinoin | 1 – 2 % in normal skin,[23] Facial application of 2 g tretinoin 0.05% cream, the rate of transdermal absorption is 2 – 6%.40 No appreciable increase of the endogenous plasma retinoid concentrations (2–5 µg/L) were observed after treatment.[25] | There is an increase risk of congenital malformation, with higher dose poses higher risk.[31] | Five case reports have raised the suspicion that birth defects cannot be ruled out after topical use of tretinoin.[25] Two prospective studies during first trimester on 96 and 106 pregnant women, which reported neither congenital malformation nor evidence of retinoid embryopathy.[41,42] | C | Topical use of all topical retinoids should be strictly avoided during pregnancy. In the case of inadvertent exposure, termination of pregnancy is not necessary, but consultation and fetal investigation should take place.[25] |
| Adapalene | Trace amounts[23] | No teratogenicity from animal studies after high dose dermal application.[43] | A case report of adapalene usage until the thirteenth week of pregnancy revealed incidence of anophthalmia and agenesis of the chiasma opticum and led to termination of pregnancy. However, it is concluded not related to adapalene.[44] | C | |
| Tazarotene | Up to 5 – 6% in normal skin[23,25] | Teratogenic effects and post-implantation fetal loss have been observed in rats and rabbits at doses producing 0.7 and 13 times, respectively, the systemic exposure for topical treatment of 20% of body surface area.[45] | Healthy children were reported after treatment during pregnancy; however, details on the duration of therapy and the dose were not presented.[45] | X | |
| Erythromycin | No data[23] | No teratogenic effect[23] | Surveillance study on clindamycin either oral or topical in pregnant women during third trimester reported that there was no increase of congenital marformation risk. However, there was a report about pseudomembranous colitis after topical clindamycin application.[47] | B | Considered safe in pregnancy and use with caution in patient with history of gastrointestinal disturbance.[47] |

**TABLE 3 (continued).** Summary of safety profile of topical products used in acne vulgaris during pregnancy

| TOPICAL PRODUCTS | SYSTEMIC ABSORPTION | ANIMAL STUDY | HUMAN STUDY | UNITED STATES FOOD AND DRUG ADMINISTRATION[5] | RECOMMENDATIONS IN PREGNANCY |
|---|---|---|---|---|---|
| Clindamycin | 4 – 5 %[23] | No teratogenic effect[23] | Surveillance study on clindamycin either oral or topical in pregnant women during third trimester reported that there was no increase of congenital marformation risk. However, there was a report about pseudomembranous colitis after topical clindamycin application[47] | B | Considered safe in pregnancy and use with caution in patient with history of gastrointestinal disturbance.[47] |
| Benzoyl peroxide (BPO) | There is only 5% of the compound, which can be systemically absorbed and undergone complete metabolism into benzoic acid, also known as food additive substance.[23,25] It undergoes rapid excretion in the kidney without any estimated systemic toxicities and it has low risk in causing congenital malformation.[48] | Rodent teratogen studies have apparently not been conducted.[4] | There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether BPO crosses the human placenta. Considering the dose and route, it is unlikely the maternal systemic concentration will reach a clinically relevant level.[49] | C | Although it is classified as category C by US FDA, BPO generally is still considered to be safe during pregnancy.[48] |
| Dapsone | Twice-daily application to 22.5% body surface area for 2 weeks resulted in a steady-state exposure 126 times lower than that achieved with a single 100 mg oral dose. The half-life of topical dapsone is 48 hours versus 20.6 hours for oral dapsone.[50] | There was no teratogenic effect with high dose usage.[51] | Controlled study on human is not available yet. Until present, the use of topical dapsone did not increase the risk of congenital malformation. There was very minimal risk of maternal hemolytic anemia in patient with glucose-6-phosphatase dehydrogenase (G6PD) deficiency.[52,53] | C | Use with caution, might be prescribed if there is more benefit than its risk. |
| Azelaic acid | Summarized in Table 2 | | | | |
| Salicylic acid | Various systemic absorptions, depend on vehicle and occlusion.[54] | Embryo malformation is associated with systemic administration of salicylic acid.[54] | Most of the studies revealed that low dose of asetylsalicylic acid which administered during pregnancy was not associated with the increase of side effects, such as malformation, prematurity, and low birthweight.[39] | C | Risk during pregnancy is low if use is restricted to local areas for a limited duration. Broad use of salicylic acid, either with high concentration or under occlusion, should be avoided due to the increase risk of salicylic toxicity.[55] |
| Glycolic acid | Very minimal[56] | Side effect on reproduction system has been reported after the use of high dose.[56] | Study of glycolic acid usage in pregnant woman is not available yet. No adverse effects observed in this population ever reported.[39] | - | Considered safe for use during pregnancy due to its minimal absorption.[48] |

However, it is still not recommended for women during pregnancy and lactation since US FDA classifies it as category C.[4] There are some risks for fetus and breastfed neonates although the systemic absorption of tretinoin is very minimal. Therefore, the benefit-risk ratio to use of tretinoin for stretch mark post delivery should be well considered.

**Nail and hair concerns.** Due to physiological changes during pregnancy, high intake of protein, vitamins, and minerals are required to maintain fetomaternal health status. Nail and hair changes during pregnancy are often caused by low intake of those nutrients. Therefore, it is necessary to routinely give sufficient supplementation of nutrients, multivitamin, and minerals for pregnant women. Furthermore, hair loss and fragile nail often cause anxiety among pregnant women, even though these conditions resolve within three months post delivery.[4] Therefore, the selection of nail and hair care during pregnancy should be done properly since some commercial products have side effects and insufficient safety profile for this population.

*Minoxidil.* Minoxidil 1-5% solution is generally well tolerated by patients, without any hazardous risks to health. This drug acts by inducing vasodilatation to increase the blood circulation of hair follicles to stimulate its growth. Systemic absorption is estimated around 2 to 3%. The topical application of minoxidil should be avoided since US FDA classified this drug as category C. Although the animal study did not reveal any evidences of teratogenicity, but it is known to reduce the conception rate and increasing the incidence of fetal absorption in rabbits.[65]

*Hair dye.* Pregnant mothers sometimes undergo cosmetic hair treatment such as hair dye. Permanent hair color products usually contain phenylenediamine, 3-aminophenol, resorcinol, toluene-2,5-diaminesulphate, sodium sulfite, oleic acid, sodium hydroxide, ammonium hydroxide, propylene glycol, and isopropyl alcohol. Experimental animal studies showed risks of teratogenicity of phenylenediamine, aminophenols, and ethanolamine, when used in very high doses. Human studies revealed that exposure to these chemicals results in very limited systemic absorption, unless there are burns or abscesses on the scalp. Therefore, these chemicals are unlikely to reach the placenta in substantial amounts to cause harm to the unborn fetus.[66] Until present, there are no reports regarding the hazardous effects of hair dye to pregnancy. In fact, there is only small amount of chemical compound within hair dye, which is absorbed into the body. However, Organization of Teratology Information Service (OTIS) is still recommending the postpone the hair dyeing until second trimester.[67]

*Other hair treatment care products.* Thioglycolic acid with concentration less than 5% and pH 7 – 12.7 is approved as hair depilatory products.[4] Sodium, calcium, and potassium hydroxide are found abundantly in many hair removal products, which are also normal ions in the human body. Systemic absorption of these ions is very minimal. Therefore, its use during pregnancy should not cause any side effects.[68]

Hair straighteners or relaxers, bleaching agents, and permanent dyes usually contain sodium hydroxide, guanidine hydroxide, ammonium thioglycolate, ammonium hydroxide, petroleum, and hydrogen peroxide.[66] Hair bleaching cream contains small concentration of hydrogen peroxide, with minimal systemic absorption. Once it is absorbed, this substance will undergo rapid metabolism. Therefore, it is concluded that it brings no harm to mother and fetus.[69] Blackmore-Prince et al. found that no increased risk for preterm delivery or low birth weight in 525 pregnant Black women exposed to chemicals used to straighten and curl hair.[70] Furthermore, Rosenberg et al. also revealed no association between preterm deliveries and the use of hair relaxers during pregnancy in 5,944 Black women.[71] Until recent, there are no studies on occasional use of hair products during pregnancy. For the average pregnant women, receiving hair treatments 3 to 4 times during pregnancy does not appear to increase risk of adverse effects on the fetus.[66]

*Nail treatment products.* The pregnant women's nails often become fragile. Although there are no recommendations for specific treatment, this changes may cause psychosocial effect due to its appearance.[15] Pregnant women should avoid any products which increase the sensitization risk, and should opt for hypoallergenic materials, such as replacing acetone with hypoallergenic nail cleanser.[4] Nail polishes may contain phthalates which are absorbed systemically.[72] However, no reports of birth defects have been associated with the exposure of this substance. Therefore, recent studies suggested to avoid the use of leave-on phthalates containing products such as nail polishes during pregnancy to minimize the risk of fetal exposure.[73]

**Vascular lesions.** Edema and varices are two common vascular problems, which encountered during pregnancy with prevalence of 70% on second trimester.[74] The managements for these conditions include the use of elastic compression stocking, proper diet, leg elevation within proper duration, and manual lymphatic drainage. This therapy can relieve some symptoms, such as pain, tingling, and edema without exposing any high risks to patient.[4]

Some skin care products to relieve edema include relaxing gels and natural remedies such as extract of arnica flower, Hamamelis (witch-hazel), and *Aesculus hippocastanum* (horse chestnut). However, some of these substances possess hazardous risk to pregnant women. Arnica has an anti-inflammatory effect, healing capability, analgetic, and increasing blood circulation. The oral administration can induce abortion since it stimulates the uterus contraction. The topical formulation has lower risk, but its use during pregnancy should be avoided. Witch-hazel is a shrub whose flowers blossom in the autumn and possessing hemostatic effect, anti-inflammatory effect, and vasoconstrictor capability. Horse chestnut plant contains aescin, a natural mixture of triterpene saponins. It posseses the anti-inflammatory activity to relieve edema. It can be used safely for pregnant women. Aside from previous compounds, camphor and menthol with concentration more than 3% are often found in topical analgetics. However, those are not recommended during pregnancy since they can pass the placental barrier; causing toxic effect to embryo and has abortifacient effect.[4]

**Cellulite.** Cellulite is one of the aesthetic problems during and after pregnancy, which is caused by lipid accumulation within adipocytes, resulting in the retention of water. It leads to destruction of collagen and elastin fibers, which worsen the local circulation. Skin care products containing xanthine and methylxanthine derivates are used concurrently with lymphatic drainage massage to stimulate the restructuring of local skin tissue and lipodystrophy. The plant extracts containing xanthine derivate possess decongestant effect in drainage by improving the microcirculation. There is no available

data regarding its safety profile on fetus and pregnant women. It should be emphasizied that their active substances are often mediated by liposome to increase the absorption to deeper skin layer.[75] Methylxanthine group (caffeine, theobromine, theophylline, and aminophylline) act through lipolytic action in adipocyte tissue by combined mechanisms of cAMP increase and phosphodiesterase (PDE) inhibition, to stimulate the excess fat transformation into free fatty acid, which excreted through lymphatic system. Caffeine is relatively safe during pregnancy in concentration less than 5%. The concentration of other xanthines should be less than 4% if they are being used in the formula of cosmetic products. However, their use are still not recommended during pregnancy.[76]

**Other topical preparations in pregnancy**

*Insect repellents.* Since the outbreak of fatal diseases transmitted by the mosquito as vector, such as Zika virus infection, Dengue, and Chikungunya; the use of repellent during pregnancy has been recommended in many tropical countries, especially on second and third trimester. The use of repellent containing N-Diethyl-Meta-Toluamide (DEET) 10-30% is considered safe in pregnant women. Nevertheless, it is not recommended for children under 2 years old.[77] Aside from that, hydroxyethyl isobutyl piperidine carboxylate (Icaridin or Picaridin) 10-20%, ethyl butylacetlaminopropionate (EBAAP or IR3535), and essential oil like lemongrass are used too in repellent products, but the study about their safety profiles during pregnancy are not available yet.[78]

*Skin tanning agents.* Dihydroxyacetone is additive coloring agent in tanning products. It binds with amino acid in stratum corneum with its concentration ranges between 1% to 15%. As it is used topically, the systemic concentration is very minimal (0.5%). Therefore, the use of dihydroxyacetone during pregnancy is considered safe.[79]

*Personal care products containing phthalates.* Phthalates are commonly found in personal care products whether rinse-off or leave-on such as hair sprays, shampoo, nail polishes, perfumes, lotions, skin toners, lipsticks and some essential oils, which are well known for its endocrine disrupting potential.[73] Lin et al. found a significant correlation between urinary phthalate metabolite concentrations in pregnant women and their cord blood, which emphasizes the potential impact of maternal exposure on fetal health.[80] Phthalates have not been connected to birth defects in humans. However, studies in animals have shown these substances interfere with male sexual development, so caution is warranted. Recent study by Hsieh et al. suggested that pregnant women should reduce the frequency of leave-on phthalates containing products use during pregnancy to avoid higher risk of phthalate exposure compared to rinse-off products.[73]

## CONCLUSION

The selection of safe topical products for pregnant women with good efficacy is important for fetomaternal health. Evidence-based medicine reports on the use of topical products in pregnancy are important to provide safety treatment options in this special population. Therefore, updated reports and comprehensive information on safety profiles of topical products during pregnancy are crucial for physicians and the mothers to wisely choose treatment plan.

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