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Dermatologic Medication in Pregnancy

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SUMMARY In female body, a vast number of skin changes occur during pregnancy. Some of them are quite distressing to many women. Therefore, performing treatment for physiologic skin changes during pregnancy with antiinfective agents, glucocorticosteroids, topical immunomodulators, retinoids, minoxidil, etc., is discussed. Drug administration during pregnancy must be reasonable.

KEY WORDS: dermatologic medication, pregnancy, physiologic skin changes, treatment

INTRODUCTION

In female body, a vast number of changes occur during pregnancy. Some of them are quite distressing to many women. Therefore, performing treatment for these changes during pregnancy is discussed. Normal pregnancy needs to avoid harmful drugs, both prescribed and over-the counter, and drugs of abuse, including cigarettes, alcohol as well as occupational and environmental exposure to potentially harmful chemicals. Sufficient and well-balanced nutrition is essential. Nutritional deficiencies and toxic effects during pregnancy predispose the future adult to some diseases such as schizophrenia (1), fertility disorders (2), metabolic imbalances (3), diabetes and cardiovascular diseases (4). Pregnancy extends and alters the impact of sex differences on absorption, distribution, metabolism and elimination (5). Cardiac output is elevated early and remains elevated for the remainder of pregnancy. Regional blood flow can change, with some areas of the skin having substantial increases in blood flow during the course of pregnancy. It is not clear if these pregnancy-induced changes in blood flow alter transcutaneous absorption. Renal flow and glomerular filtration increase early in pregnancy, having substantial impact on the clearance of water-soluble molecules

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that are eliminated by renal mechanisms. During pregnancy there are changes in both oxidative and conjugative metabolism. These changes are typically unpredictable. It is necessary to understand how these metabolic and physiologic changes influence pharmacokinetics and pharmacodynamics (what the body does to the drug and what the drug does to the body) to enhance therapeutics during pregnancy.

There are typical morphological and functional changes in the skin during pregnancy. They include physiologic changes such as pigmentation, striae, fibroma, acne, blood vessel changes, and changes of skin glands, hair and nails, as well as specific lesions of pregnancy, i.e. pruritic urticarial papules and plaques of pregnancy, prurigo, herpes gestationis, impetigo herpetiformis, pruritus gravidarum or contact dermatitis, toxic drug eruptions, viral eruptions, etc. (7). We will focus on most frequent dermatologic lesions in pregnancy and their treatment.

In pregnant women, hyperpigmentation may appear on the face and disappear spontaneously after deliver (Figs. 1 and 2); it is intensified by exposure to UV light. Pigmentation of the nipples and the areola, the area around the navel, the armpits, and the genital and anal regions is also increased. Pregnant women are more sensitive to light. Hyperpigmentation can also occur in the axillae as well as in the upper inner aspects of the thighs (8). Recent studies have demonstrated that the placenta is rich in bioactive molecules other than estrogens and progesterone, which can induce pigmentation *in vitro* in human cells and *in vivo* in animal models (8).

Melasma (chloasma), also known as 'the mask of pregnancy', appears as irregularly shaped patches of light to dark-brown hyperpigmentation

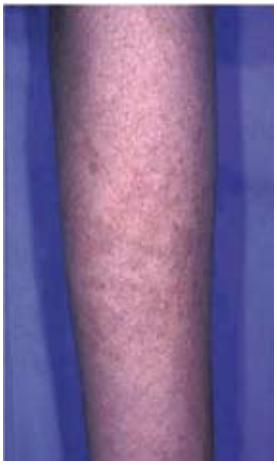

Figure 1. Hyperpigmentation

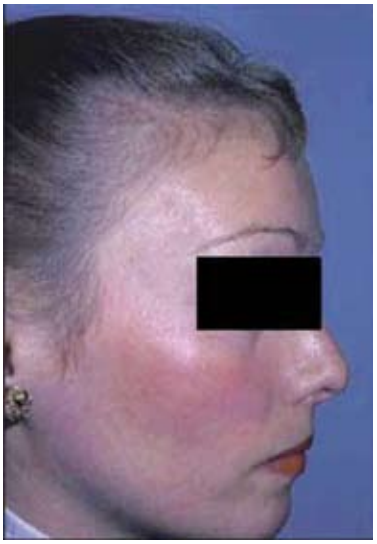

Figure 2. Mottled pigmentation

with very well demarcated borders affecting the cheeks and upper lip (Fig. 3) (9). Treatment for melasma is deferred until after delivery. During the second half of pregnancy, striae distensae appear relatively often on the stomach, hips, thighs and breasts (Fig. 4). There is no known physical measure or drug that is effective as prophylaxis.

Soft fibroma more frequently occurs in the neck and auxiliary regions during pregnancy. Blood circulation of the facial vessels increases and can lead to quick blushing and blanching, and to increased dermographism. The veins in the breast and stomach skin are much more visible, and varicosities in the legs and vulva as well as hemor-

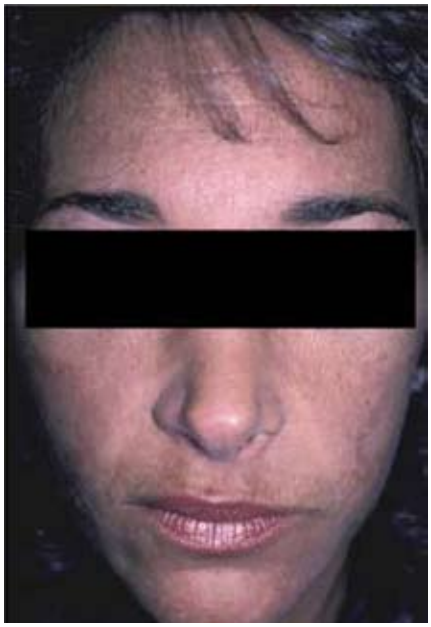

Figure 3. Melasma

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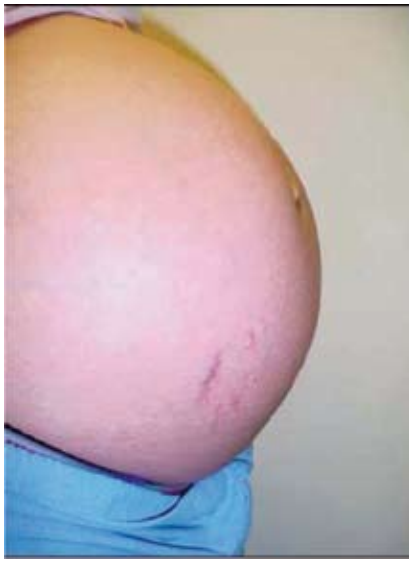

Figure 4. Striae gravidarum

rhoids may appear (Fig. 5). In early pregnancy, the secretion of sebaceous glands can increase significantly, while acne frequently shows improvement. Acne gravidarum can occur during the third month of pregnancy (Fig. 6). During pregnancy, the growth of hair and nails is generally enhanced. After delivery, hair loss often seems quite threatening. However, this synchronic transition from anagen to telogen hair is fully physiologic and usually returns to normal over the next few months postpartum (Fig. 7). Substances applied topically are absorbed in greater quantities during pregnancy. This can lead to an increased exposure to the system and thus to the fetus.

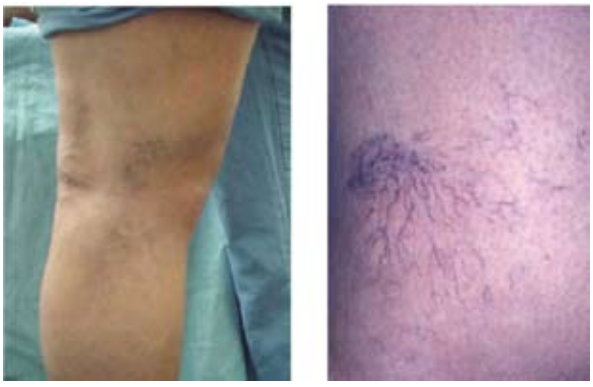

Figure 5. Varicose and spider veins secondary to pregnancy

TREATMENT IN PREGNANCY

Conservative therapies are usually sufficient for most of dermatoses in pregnancy to control the symptoms before delivery: bland topical emollients and antimicrobial topical agents and topical corti-

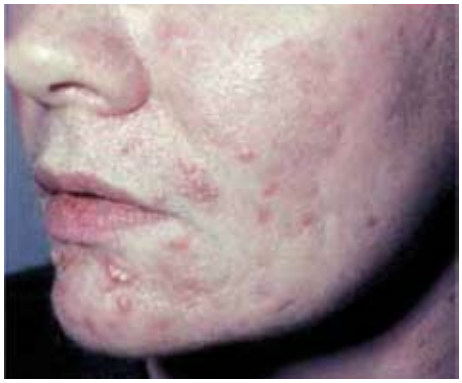

Figure 6. Acne secondary to pregnancy

costeroids (9). Therapy with oral antihistamines is unsuccessful and must be avoided as well as tetracycline, retinoids and cytostatics. In local therapy, mercury compounds, salicylate agents, phenol and menthol should be avoided (10). Oral corticosteroids have been prescribed less often than topical ones (10,11).

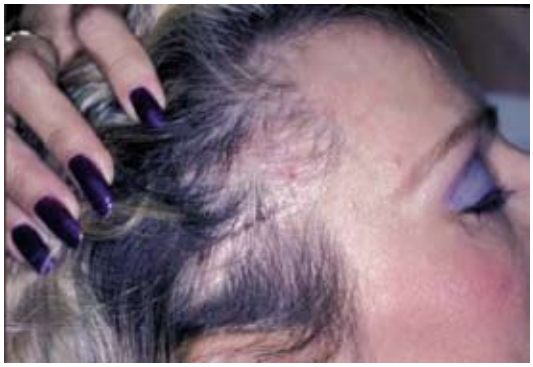

Figure 7. Telogen effluvium

Antiinfective agents

Every external antibiotic therapy must be critically examined from the perspective of whether there is a bacterial infection that might possibly be more effectively treated systemically. Sensitization and the development of bacteriological resistance need to be considered with topical antibiotic treatment. Chloramphenicol should not be used in the last weeks of pregnancy. For usage over wide skin areas, preparation should be viewed as criti-

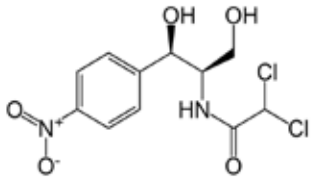

Figure 8. Structural formula of chloramphenicol

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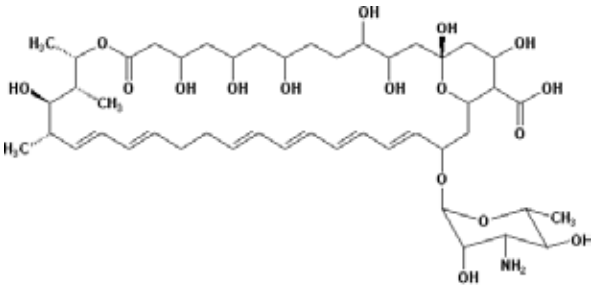

Figure 9. Structural formula of nystatin

cally as systemic usage because of the changes of absorbing larger amounts of the agent (Fig. 8) (11). Nystatin (Fig. 9) can be used through pregnancy without restriction. It is the drug of choice for the treatment of superficial Candida infections of the mucous membranes of the mouth, intestine and vagina but may be less effective than newer agents (12). Clotrimazole and miconazole are topical antimycotics of choice in pregnancy (13-15). Bifonazole, croconazole, econazole, fenticonazole, isoconazole, ketoconazole, omoconazole, oxiconazole, sertaconazole, salconazole and tioconazole are second choice antimycotics for local therapy. They are structurally and functionally related to clotrimazole. No teratogenic effects have been observed as a result of local treatment with these antimycotics. Amphotericin B can be applied locally or can be used as a systemic therapy for mycosis. Local application is considered safe. Therapy with griseofulvin is contraindicated in pregnancy. It is used as an oral preparation for the treatment of dermatophytosis of the skin, hair and nails. It is suitable for therapy of nail mycosis because it is deposited in keratin. Rosa *et al.* report on two pairs of conjoined twins after use of griseofulvin in pregnancy. The birth rate of conjoined twins might be 1:100000 births (16). For condylomata acuminata, cryotherapy or trichloracetic acid is the treatment of choice during pregnancy.

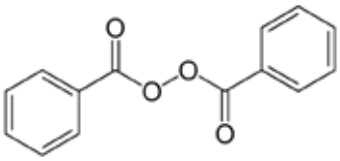

Figure 10. Structural formula of benzoyl peroxide

Antiseptics and disinfectants should have strong bactericidal or bacteriostatic action, and the skin, mucosa and wounds should tolerate them well. They should not cause systemic toxic effects when they are absorbed. Alcohols may be used topically as disinfectants during pregnancy.

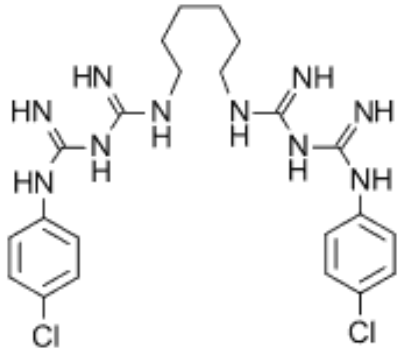

Figure 11. Structural formula of chlorhexidine

Benzoyl peroxide (Fig. 10) is used for external treatment of acne. Concurrent topical therapy with retinoid increases the absorption of these agents. There are no experimental or epidemiological risk data and no case reports indicating teratogenic effects. Benzoyl peroxide in therapeutic concentration may be used topically on a limited area to treat acne (the face). When povidone iodine is used on intact skin, transfer to the fetus must be assumed and can lead to functional disturbances in the fetal thyroid gland. Retrospective evaluation of children born to mothers who applied iodine vaginal douching did not show any indication of teratogenic effects (14,15). Iodine disinfectants may only be used during pregnancy on small areas for a few days. Phenol derivatives used in over-the-counter preparations for rinsing the mouth and disinfecting the skin are relatively safe during pregnancy (17). They should only be used on intact skin and in concentration not higher than 2%. Chlorhexidine (Fig. 11) is effective as a disinfectant of the skin and mucosa in pregnant women (18). Hexachlorophene should be avoided during pregnancy. In some animal studies hexachlorophene was found to be teratogenic (19). In a study of occupational exposure (occupationally exposed pregnant women) performed in Sweden, there was no increase in congenital malformations or perinatal death (20). Mercury compounds are contraindicated because they can be absorbed after external use (10,21). Limited accidental application justifies pregnancy interruption. Animal studies demonstrated carcino-

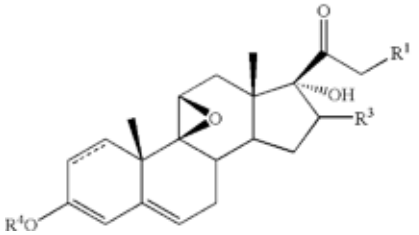

Figure 12. Structural formula of corticosteroids

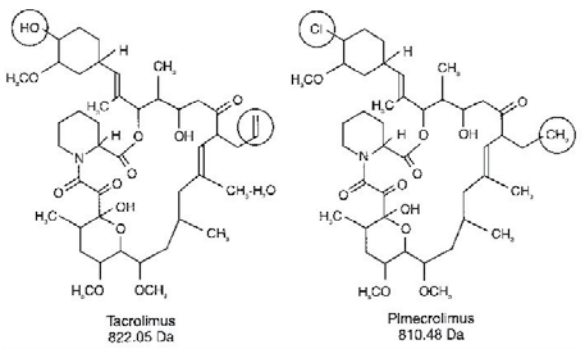

Figure 13. Structural formula of the local immunomodulators

genic activity and contradictory data on teratogenicity for gentian violet and crystal violet (22,23).

When glucocorticoids (Fig. 12) are applied regularly over large skin areas, absorption through the skin and transfer to the fetus must be assumed. With oral intake, there was a risk in animals for cleft palate, placental insufficiency and intrauterine growth retardation (24). There is a report on intrauterine growth retardation after massive topical use of triamcinolone (25). Data in animals and in humans suggest that repeated exposure during pregnancy to glucocorticoids that are not metabolized by placental 11β-HSD-2 dehydrogenase, such as dexamethasone or betamethasone, might reduce birth weight and predispose children to cardiovascular, metabolic or neuroendocrine disorders later in life (26). Topical therapy with glucocorticoids as long as the treatment time is brief and the area is moderately sized is acceptable for relevant indications. Pregnant women may use polidocanol in case of itching. Polidocanol is a combination of benzethonium and carbamide (urea). No teratogenic action has been observed to date either in animal or human studies. Applied to the skin, a small amount of camphor has a cooling and local anesthetic effect and enhances the circulation to the skin. Camphor and other essential oils are included in a large number of hyperemia-causing dermatologic products. No teratogenic action has been observed in animal or human studies for topical application of menthol. Coal tar preparations should ideally not be used in pregnancy; however, accidental use does not require any action. Coal tar products have demonstrated mutagenic or carcinogenic properties experimentally, but in well-tried use of the group of substances employed therapeutically in humans there has not yet been any indication (27). Tacrolimus and pimecrolimus are immunomodulators often used in dermatotherapy (Fig. 13). They are mostly used in the treatment for atopic dermatitis and psoriasis inversa. These agents can be used topically when there are no acceptable alternatives on a small surface. Salicylates are used as keratolytics in 2%-20% (solution or ointment). Topical use of keratolytics mentioned above is not a cause for concern in pregnant women when the medications are used over a limited period of time. Azaleic acid has antiinflammatory, antibacterial and keratolytic effects; it is used in acne therapy, and 4%-8% of the topically applied substance is absorbed systemically. Azaleic acid is only to be used in pregnancy when absolutely necessary on small skin surfaces and not during the first trimester. Sulfur is present in lotions, creams and powders; it is used as a mild keratolytic and bacteriostatic agent. There are no data on its use during pregnancy (28). It can be used on a small skin area in pregnancy. Resorcin (Fig. 14) is an aromatic alcohol that is used in local acne therapy and in other dermatoses as a bactericidal, fungicidal, keratolytic, exfoliative and antipruritic agent, and also for seborrheic dermatitis and psoriasis. Topical treatment on a small area with resorcinol is acceptable during pregnancy. Isotretinoin and tretinoin (Fig. 15) are natural vitamin A derivatives; in the form of synthetic derivatives they have been used to treat cystic acne. In the skin retinoids loosen the keratin layer and in this way ease the scaling process. Isotretinoin can also cause sebaceous glands atrophy. Today retinoids should be considered as the most teratogenic medication since thalidomide. If used in pregnancy, it increases the risk for spontaneous abortion and leads to characteristic retinoid embryopathy with anomalies of the ears (including agenesis or stenosis of the auditory canal), facial and palatine defects, micrognathia, cardiovascular defects, defects of the thymus (with possible immune sequences)

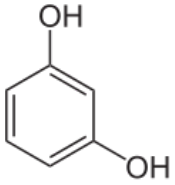

Figure 14. Structural formula of resorcinol

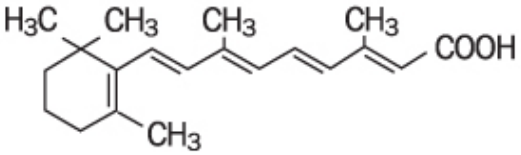

Figure 15. Structural formula of tretinoin

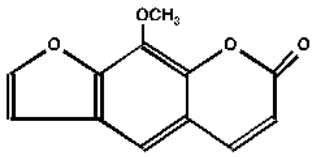

Figure 16. Structural formula of psoralen (8-methoxypsoralen)

and central nervous system (ranging from neurologic damage through the eyes and inner ear to hydrocephalus) (29,30). Intelligence deficits have also been described (31). Topical use of retinoid is contraindicated during pregnancy. In case of such therapy in early pregnancy, interruption of pregnancy is unnecessary but detailed fetal ultrasound diagnosis should be planned. The European Network of Teratology Information Services (ENTIS) analyzed 41 pregnancies in which systemic PUVA therapy with 8-methoxypsoralen (Fig. 16) was administrated (31). No indications of embryotoxic effects were reported (32,33). Photochemotherapy with 8-methoxypsoralen and UVA irradiation is not recommended during pregnancy because of the possible mutagenic effects. If such treatment has been administered, it does not justify interruption of pregnancy or invasive diagnostic procedures. Sex hormones in acne therapy and their inhibitory substances are contraindicated during pregnancy. Local treatment of vaginal condylomata with 5-fluorouracil is contraindicated. Treatment of vaginal warts should be postponed until after the delivery.

Scabies should be treated with benzoyl benzoate because there is no toxicity observed after topical application (34). In a prospective study of 113 pregnant women using permethrine shampoo during pregnancy, 31 of them did not reveal prenatal toxicity during the first trimester (35,36). Lindane is potentially neurotoxic. Animal studies have demonstrated that it is stored in fat tissue and in the testes (Leydig cells) (37). Its use is not permitted after 2007 according to European environmental guidelines.

Pregnant women should be advised against use of insect repellents containing diethyltoluamide (DEET) on large areas of their bodies for a long time unless there is a strong indication. Sheafer and Peters describe a child with mental retardation born to a mother rubbing her arms and legs daily with a 25% DEET lotion (38). A randomized prospective study in 449 pregnant women with topical application of 1.7 g of DEET daily during the second and third trimesters did not demonstrate any difference in the newborns compared to control group (38).

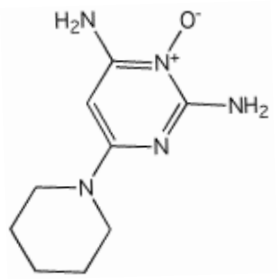

Figure 17. Structural formula of minoxidil

Icaridin should be chosen as a less toxic repellent with non-chemical protection like covering the skin.

Minoxidil (Fig. 17) is topically used in case of androgenic alopecia and other types of baldness. In a prospective study, 17 pregnant women were treated with minoxidil; one of 15 newborns had unspecified developmental disorder of the heart (39).

Smorlesi *et al.* describe women who applied minoxidil twice daily onto their scalp during pregnancy. Fetal pathology included heart enlargement with stenosis of the aorta, enlarged sigmoid colon and enlarged cerebral ventricles with brain hemorrhages. The placenta had ischemic and indurated areas, and there was a discrepancy between gestational age and villus maturation (40).

Rojanski *et al.* report malformations of lower extremities and esophagus in a severely hypertrophic fetus born to a mother who had used minoxidil for years. In pregnancy neither oral nor topical treatment with minoxidil is acceptable (41).

Cosmetic treatment with hyaluronic acid is to be avoided during pregnancy. Collagen injections have not been studied in pregnancy and the author advices against its use during pregnancy (42). Some literature data support the use of botulinum toxin A in pregnancy; however, general consensus is to avoid it for cosmetic purposes in pregnant women (42).

CONCLUSION

Pregnancy is associated with many physiologic changes in female body which will regress with parturition. Because many of them are cosmetic in nature and some are not harmful, the treatment must be reasonable. Drug administration during pregnancy means that both the mother and the unborn child are exposed. Women of reproductive age must be asked, prior to drug prescription, whether they are pregnant or they are planning pregnancy. Also, in chronic treatment of women

of reproductive age the possibility of pregnancy must be considered. Products proven to be safe in pregnancy are the drugs of first choice for long term treatment during the reproductive years. A healthy lifestyle during pregnancy can alleviate some of the physiologic changes, along with educating patients to follow a conservative approach.

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