Melasma: A Cosmetic Stigma During Pregnancy

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Abstract
Melasma represents the most common pigmentary disorder occurring in pregnancy. It mainly consists in a hyperpigmentation of the face and neck, due to an alteration of melanocytes’ density and of melanin’s concentration. At first sight it may appear to be a minor clinical condition, without vital risk, but clinicians consider it as an important cosmetic stigma difficult to treat and that may cause great emotional suffering.

Keywords: Melasma; Pregnancy; Pigmentation disorder; MelasQoL; Estrogen; Progesterone

Introduction
The term “melasma” derives from the Greek word *melas*, which means “black” in color. Melasma (also known as “chloasmagravidarum” or “mask of pregnancy” [1] is a common, acquired, mostly symmetric, hypermelanosis, which involves sun-exposed skin areas, especially the face and neck. Clinically, it is characterized by irregular, light- or dark-brown macules and patches with well-defined margins.

Typically, the disease affects women of reproductive age, from all racial groups [2]. Rarely, it has been described in men (10%).

Although the pathophysiology of melasma is uncertain, four are considered the main developing-factors: genetic predisposition, sun-exposure, estrogens, drugs. Among these, the sunlight’s exposure is the most important factor. Ultraviolet radiations (UV) cause the peroxidation of the membranous lipids and the generation of free radicals, which could stimulate melanocytes to produce excess melanin. Both UV-B and UV-A stimulate melanogenesis; the use of selective sunscreens, blocking only one type of radiation, is unsatisfactory.

The importance of a genetic predisposition is supported by the description of a more incidence in certain families and races.

Another important etiological factor is the female hormonal activity. Its importance in melasma’s pathogenesis has many evidences, such as prevalence in female gender, association with pregnancy and with treatment based on contraceptive pills.

Moreover, melasma may be associated to the topical application or the oral intake of photosensitizing drugs.

The action of one or more risk factors induces an increase in the number of melanocytes and in their function, which is clinically represented by the typical hyperpigmented macules. Lesions may be localized in certain areas of the face, such as centrofacial, malar and mandibular, or be diffuse like a “mask”.

Based on the cutaneous Wood’s examination, melasma can be classified into four major clinical types, each one with a specific histological pattern [2]:

1. Epidermal type: light brown macules, with enhancement of pigmentation under Wood’s light. Histologically it is characterized by a melanin increase in the basal, suprabasal, and stratum corneum layers.
2. Dermal type: ashen or bluish-gray patches. There is no enhancement of pigmentation under Wood’s light. Histologically, it is characterized by a preponderance of melanophages in the superficial and deep dermis.
3. Mixed type: dark-brown macules. Enhancement of pigmentation is present under Wood’s light only in some areas.
4. Indeterminate type: unapparent under Wood’s light.

The diagnosis of melasma is clinical and, usually, no laboratory test is indicated. The histological examination of a skin biopsy may confirm the diagnosis.

Melasma and Pregnancy
The mask of pregnancy is well known both to obstetric patients and medical doctors.

Despite its high incidence, the exact correlation between the cutaneous pigmentation and the hormonal activity is not well understood. Hyperpigmentation seems to be related to the high levels of estrogens, progesterone and melanocyte-stimulating hormone, which are normally increased during the third trimester of pregnancy. Environmental factors, photosensitizing drugs or other clinical condition (e.g. hyperthyroidism) may exacerbate a pre-existing condition.

Many data support the role of estrogen and progesterone in stimulating the normal melanogenesis. Sexual steroids stimulate the transcription of genes codifying for enzymes involved in the melanogenesis, such as Dopachrome tautomerase (DTC) and tyrosinase [3]. In particular, is now clear as tyrosinase hydroxylate estradiol to a catechol-like compound, which is involved in the regulation of the same enzymatic activity [4].

These results are consistent with the significant increases in melanin synthesis and in tyrosinase activity, which have been reported in cultur of human melanocytes under similar conditions.

As melanocytes contain both, cytosolic and nuclear estrogen receptors, it is possible that melanocytes in melasma patients are inherently more sensitive to the stimulatory effects of estrogens and other sex steroid hormones.

Recent studies suggest that estrogens exert their effect in the skin
through the same molecular pathways used in other non reproductive tissues. There is evidence that 17β-estradiol can use both signaling pathways (genomic and nongenomic) in epidermal keratinocytes. In the classical mode (or genomic one), the hormone enters the cell by passive diffusion, and interacts with its intracellular receptors. After such interaction, the receptor changes conformation, forming homo- or heterodimers. Finally, the complex hormone-receptor binds to specific regions of DNA, called estrogen response elements (ERE). ERE consist of 15 base pair inverted palindromes, localized within the regulatory region of the target gene. The nonclassical pathway (non genomic one) works faster. It consists on the ability of estrogen to interact with either membrane estrogen receptors or non-steroid hormone receptors (e.g., G-protein-coupled receptor, GPR30). The non-classical pathway acts via different conventional second messengers (e.g., cAMP) and activates mitogen-activated protein kinases, which regulate the transcription of specific genes [5] (Figure 1).

As well as stimulate melanogenesis, estrogens improve skin moisture and also increase its thickness and content in collagen. Therefore, estrogen plays a key role in the skin aging. Despite the knowledge that estrogens have such important effects on skin, their cellular and molecular mechanisms of action are still poorly understood and their influence on pigmentation is still far from clear [6].

Another interesting study shows how melanocytes of healthy

![Figure 1: Extra-nuclear signalling and transcriptional actions of estrogen receptors [5.]](image-url)
skin, incubated with MSH, ACTH, luteinizing hormone (LH), and follicle-stimulating hormone (FSH), increase in size and produce more tyrosinase [7].

Interestingly, estradiol, estriol, and progesterone incubation led to a less increased cell proliferation, and don’t increase tyrosinase activity.

Perez et al. [8] examined the link between circulating levels of hormones and their relationship to melasma. The authors found that nulligravid women with melasma have significantly higher serum levels of LH and lower levels of estradiol than normal controls. The authors also found that there was no difference in serum levels of beta MSH (b-MSH), ACTH, FSH, progesterone, prolactin, thyroid hormone, or cortisol between the two groups.

Recently, investigators found that a lipid extraction from the placenta may induce pigmentation both in vivo and in vitro. The placenta has been found to be rich in bioactive sphingolipids, which induce melanogenesis by the upregulation of melanogenic enzymes (e.g. tyrosinase and tyrosinase-related proteins 1 and 2) [9].

Another important issue concerns the particular localization of lesions in melasma.

Wade et al. [10] have suggested that the reason why only certain body areas, but not the entire body, are affected by hyperpigmentation is that melanocytes in the areas affected are more sensitive to hormonal stimulation. Another explanation may be the greater population of melanocytes in the affected sites [11]. An investigation showed that there is a greater population of melanocytes in the skin of the face and forehead, than in the skin of the thigh and arms [12]. Finally, melasma may also have a vascular component, a neuronal component and stem cell factor in its pathogenesis [13]. Further research into the effects of hormones and environmental factors on melasma is needed.

In summary, there is some evidence of a hormonal component in the pathogenesis of melasma, but the available data are conflicting, possibly because of the varied genetic backgrounds of the different study populations. More studies are necessary to add more knowledge on melasma pathogenesis and maybe to improve therapeutic approach.

A Cosmetic Stigma

Like the majority of the skin changes pregnancy-related, melasma is benign condition, and usually resolves spontaneously within a year after delivery. On the other hand, in some cases melasma may persist longer. Even if persistence incidence has been reported to be less than 10% of all patients, one study found a persistence in 30% of cases after 10 years [14].

Although melasma has been usually considered as a minor clinical condition without vital risk, clinicians consider it as an important cosmetic stigma, often difficult to treat, psychologically distressing for patients.

Recent studies underline the psychological impact of melasma in the patients’ quality of life. The most commonly used tool for assessment of quality of life in patients with melasma is the Melas QoL [15-16] (Table 1).

Affected women are usually frustrated or embarrassed, and refer difficult interpersonal relationships 3. Interestingly, the effect of melasma on quality of life doesn’t seem to be related with the severity of disease: even a small amount of pigmentation can be distressing.

### Table 1: Melas QoL scale description. The Melas QoL is scored from 7 to 70, with a higher score indicating worse melasma-related health-related quality of life.

| On a Like scale of 1 (not bothered at all) to (bothered at all), the subject rates how she feels about: |
|---|
| 1. The appearance of your skin condition |
| 2. Frustration about your skin condition |
| 3. Embarrassment about your skin condition |
| 4. Feeling depressed about your skin condition |
| 5. The effects of your skin condition on your interactions with other people (e.g. interactions with family, friends. Close relationship, etc.) |
| 6. The effects of your skin condition on your desire to be with people |
| 7. your skin condition making it hard to show affection |
| 8. Skin discoloration affecting your sense of freedom |
| 9. Skin discoloration making you feel unattractive to others |
| 10. Skin discoloration affecting your sense of freedom |

Interestingly, after the treatment, the number of women, who still report distress, reduces significantly.

Unfortunately, treatment of melasma in pregnancy is difficult, often unsatisfactory, and preventive measures are limited.

### Conclusion

Melasma is the most common pigmentary disorder occurring in pregnancy. It is a cosmetic problem, with a great psychological impact, which involves a complex, not completely understood, interaction between environmental, hormonal, and cellular factors. Additional studies to understand the exact etiopathogenesis are needed, because these may serve as new targets for therapy.

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