

Melasma and Endocrine Disorders

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Abstract

Melasma is an acquired and chronic disorder characterized by a localized symmetrical hypermelanosis of the face or, less frequently, involving the neck and forearms. It occurs with a high prevalence during pregnancy, especially during the second half of the gestational period, and in women taking exogenous female hormones. Melasma has also rarely been described in males, especially those affected by primary hypogonadism or taking estrogens for prostatic cancer. Melasma thus appears to be pathologically related to female sex hormones, but this is not consistently reflected in high circulating levels of estrogens or progesterone. This implies that other factors are likely to be relevant, including genetic predisposition, exposure to ultraviolet light, cosmetics and some medications. Melanocortins play a key role in melanogenesis but no cases of melasma have been described in pituitary or adrenal diseases, including those associated with an increase in serum ACTH. An association between melasma and thyroid disorders has been reported only once and not confirmed in subsequent studies. The skin is both a source of, and a target for vitamin D; however, no cases of melasma have been described in association with disordered vitamin D production. Finally, clinicians should distinguish the localized hypermelanosis of melasma from general hyperpigmentation occurring in pregnancy or in pituitary and adrenal diseases associated with a raised serum ACTH.

Keywords: Melasma; endocrinology; endocrine disorders; female hormones; pregnancy; oral contraceptives; hormone replacement therapy; estrogens; progesterone

Abbreviations: ACTH: Adrenocorticotrophic Hormone; CRH: Corticotropin-Releasing Hormone; DHEA: Dehydroepiandrosterone; FSH: Follicle-Stimulating Hormone; HRT: Hormone Replacement Therapy; LH: Luteinizing Hormone; MSH: Melanocyte-Stimulating Hormone; OCP: Oral Contraceptive Pill; POMC: Proopiomelanocortin; SERM: Selective Estrogen Receptor Modulator; TRP-1: Tyrosinase-Related Protein-1; TRP-2: Tyrosinase-Related Protein-2; TSH: Thyroid-Stimulating Hormone; T3: Triiodothyronine; T4: Thyroxine; UV: Ultraviolet; VDR: Vitamin D Intracellular Receptor; 1,25(OH)₂D₃: 1,25-Dihydroxyvitamin D3 (Calcitriol)

Introduction

Melasma, also named chloasma or mask of the pregnancy [1], is an acquired and chronic disorder characterized by a symmetrical hypermelanosis of the face [2], although it may be localized also on the neck and forearms [3,4]. There are 3 major clinical patterns: centrofacial, malar and mandibular [5].

Melasma is histologically characterized by excessive melanin deposition in the epidermis (epidermal type, 70%), dermal macrophages (dermal type, 10%) or both (mixed type, 20%) and can be clinically demonstrated by Wood's light examination [5,6].

Melasma is a common condition which affects millions of people worldwide [7]. Melasma does not spare any sex or race, although it appears to be more common in females and people of Hispanic origin [5].

Risk factors include darker skin types (particularly Fitzpatrick skin types III and IV), genetic predisposition and exposure to ultraviolet (UV) light, pregnancy, exogenous female hormones, cosmetics and some medications [5,7,8].

The aim of this review is to focus on the relationship between melasma and endocrine disorders.

Melasma and Female Hormones

Melasma is clearly related to female hormones since it often appears during pregnancy or Oral Contraceptive Pill (OCP) use, but the etiopathological mechanisms involved are unclear [7]. It is important

to distinguish melasma from general hyperpigmentation during pregnancy that may be seen in up to 90% of pregnant women, and is characterized by accentuation of normally hyperpigmented areas such as the areolae, nipples, genital skin, axillae and inner thighs [6]. Both melasma and hyperpigmentation in pregnancy are thought to share a similar pathogenesis.

Female hormone activity on normal human melanocytes

Since 1964 high estrogen levels have been reported to be associated with an increase in skin pigmentation [9]. In 1994 Jee et al. were the first authors to demonstrate the presence of estrogen receptors (both nuclear and cytosolic) in normal human melanocytes, with nuclear localization 10 times higher than cytosolic [10]. The presence of estrogen receptors has since been confirmed in human melanocytes from both healthy subjects [11] and melasma patients [12].

Jee et al. reported a dose-dependent proliferation of melanocytes in culture after 17 β -estradiol addition, despite a decrease of tyrosinase activity and melanin content [10]. A similar proliferation without increased tyrosinase activity after incubation with ovarian hormones (estradiol, estriol and progesterone) was shown by Maeda et al. [13].

Jee et al. results are in contrast to findings obtained by 2 different studies by the same Australian group, in which incubation with β -estradiol, at the physiological concentrations seen in pregnancy, of *in vitro* cultured melanocytes from normal human skin resulted in a dose-dependent stimulation of tyrosinase activity, increase in melanin extrusion and a 50% reduction in cell numbers [14,15]. In 1998 Kippenberger et al. confirmed an up-regulation of tyrosinase activity

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Received: October 12, 2014; **Accepted:** October 16, 2014; **Published:** October 18, 2014

Citation: Muller I and Rees DA (2014) Melasma and Endocrine Disorders. Pigmentary Disorders S1:001. doi: [10.4172/2376-0427.S1-001](https://doi.org/10.4172/2376-0427.S1-001)

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and expression of tyrosinase-related protein-1 (TRP-1) and TRP-2, in melanocytes isolated from human fetal back skin cultured with estradiol [16].

Human progesterone receptors have also been identified in normal human keratinocytes [17] and melanocytes [11], whilst progesterone stimulates proliferation of *in vitro* cultured human melanocytes [13]. Snell et al., using guinea pigs as a model, showed that estrogen increased both melanocytes' output of melanin and count in a dose-dependent manner, an effect that was augmented by simultaneous administration of progesterone [18].

The effects of female hormones on *in vitro* cultured human normal melanocytes are thus discrepant but in all cases they appear to exert an effect on cell proliferation or activity. These results thus support the role of female hormones, especially estrogens, in the pathogenesis of melasma, although the precise mechanisms involved are still unknown. It is also unclear why certain areas of the face are predisposed to melasma while others are not involved. Hormone receptor, blood vessel and sebaceous gland density and activity are all likely to play a role [7] since estrogens appear to increase the vascularization of the skin and suppress sebaceous gland activity [11], even if other factors such as phototoxicity and anti-oxidants are also likely to be involved [7].

Melasma, pregnancy and the role of oral contraceptives

During pregnancy, especially in the 3rd trimester, women have increased levels of placental, ovarian and pituitary hormones that represent a stimulus for melanogenesis, which may explain the association of melasma with pregnancy [19,20]. Elevation of melanocyte-stimulating hormone (MSH), estrogens and progesterone also lead to increased transcription of tyrosinase and dopachrome tautomerase, which may be involved in the development of pigmentation in this period [21].

In 1976 Thody et al. found no differences in levels of plasma β -MSH measured by specific radioimmunoassay between pregnancy and the postpartum period, both of which were within the normal range [22]. In 1978, Clark et al. observed significantly higher levels of immunoreactive α -MSH levels during late pregnancy than in control populations, despite no differences during the first trimester. Since hyperpigmentation in pregnancy usually begins early and is normally focal, the authors excluded a role of circulating α -MSH in pigmentation during pregnancy. This contrasts with its clear role in generalized hyperpigmentation such as in Addison's disease and Cushing's syndrome [23].

These observations imply that melasma in pregnancy is more likely to be associated with circulating female hormones than MSH peptides. Indeed, the increase in progesterone levels that occurs throughout pregnancy and in estrogen production that occurs from the eighth until the 30th week of pregnancy mirrors the typical progression pattern of hyperpigmentation [21,24]. The crucial role of female hormones in melasma onset is also suggested by its high prevalence among women taking exogenous estrogens and/or progesterone and its correlation with menstrual periods [25].

Melasma onset usually occurs during the second half of the gestational period and it can be found in 45–75% of pregnancies [26,27].

However, the prevalence of melasma among individuals taking OCP varies widely between different studies from 5 to 34 %, presumably depending on ethnicity and selection criteria [28]. For example, a relatively low prevalence of melasma, 8%, has been found in Cook's survey conducted on 350 Puerto Rican women on OCP [29]. Similarly,

Sanchez's study carried out on 76 Puerto Rican females with melasma observed that only 9% of them had a positive history for estrogen and/or progesterone use [5]. In contrast, Ortonne et al. in a survey conducted on 324 women being treated for melasma in nine clinics worldwide, found an onset of the disease in 25% of cases after use of OCP, in 26% of cases during pregnancy and in 42% of cases after pregnancy [30]. A similar percentage was found by Resnik et al. who reported a high incidence of melasma (29%) among 212 patients taking OCP [31].

In addition to OCP, hyperpigmentation of the face also occurs in some women during normal menstruation. Both may be predictive of potential melasma development during pregnancy [26]. For example, among the 61/212 (29%) patients with melasma in Resnik's study of women on the OCP, 87% of them also developed melasma during pregnancy [31]. Likewise, melasma during pregnancy indicates susceptibility to increased pigmentation with the OCP, although these drugs may also induce melasma when none existed in pregnancy [26,32].

Melasma associated with use of the OCP is usually persistent, while melasma of pregnancy usually fades within one year after delivery [26,31,32]. Melasma persists after pregnancy in less than 10% although one study found persistence in 30% cases after 10 years [19]. If melasma persists postpartum, some women note a premenstrual hyperpigmented flare [28].

Considering that UV light induces up-regulation of melanocytes and its role in melasma's pathogenesis, susceptible women should be advised to avoid unprotected heavy sun exposure and ensure protection with broad-spectrum (UVA and UVB) sunscreen and appropriate clothing [19,33].

Melasma in post-menopausal women

Since female sex hormones in the OCP appear to be important for the development of melasma, a similar relationship might be anticipated in postmenopausal women on Hormone Replacement Therapy (HRT). In fact, there are several case-reports of melasma occurring in postmenopausal women. In 1998 Johnston et al. reported a case of melasma of the arms occurring in a 54 year-old woman who had taken HRT continuously for 8 years [34]. Similarly, Varma et al. described a 46 year old woman who developed melasma on both forearms during sun exposure while receiving HRT [35]. Melasma of the forearms seems to be a relatively common sign especially in older patients and postmenopausal women on supplementary estrogen therapy. In 1997 O'Brien et al. reported 7 cases of melasma localized to the forearms at a later age. Since some of these patients had had facial melasma when they were younger, the authors proposed the existence of a population of estrogen-sensitive melanocytes in the forearm skin which mature at a later age [36].

A single case report is also described of melasma occurring in a post-menopausal 46-year-old woman after 1 month administration of tamoxifen for breast cancer [37]. Tamoxifen is a selective estrogen receptor modulator (SERM) [38] and exerts mixed estrogenic and anti-estrogenic effects depending on the tissue and cell type [39].

Idiopathic melasma

In 1983 Pérez et al. found decreased levels of serum estradiol and high values of luteinizing hormone (LH) in 9 patients with idiopathic melasma compared to 9 unmatched controls [40]. Considering the small number of patients evaluated and the use of unmatched controls, these results cannot necessarily be extended to patients affected by melasma in general.

In 1998 Hassan et al. found a higher 17β -estradiol value at the beginning of the menstrual cycle in 36 ovulatory women with melasma compared to 12 healthy controls, with no differences in progesterone levels [41]. Similar results were obtained in 2011 in a Pakistani study conducted on 138 women (not pregnant and not taking any hormonal therapy) affected by melasma compared to 40 matched controls. The authors found significantly higher levels of estrogen in both the follicular and luteal phase in women affected by melasma compared to controls, with no differences in progesterone and prolactin levels [42]. These findings strengthen the role of circulating estrogens as risk factors for the initiation and maintenance of the disease [20].

Elevations in serum progesterone levels may also play a role in melasma pathogenesis [6,18]. In 1987 Sato et al. reported increased levels of progesterone in Japanese patients with melasma [43].

These studies suggest that estrogen levels tend to be increased in patients affected by idiopathic melasma, while data regarding progesterone levels are conflicting.

Melasma in males

There are few reports of melasma occurring in men. In 1957 the first case of melasma in a male was reported in a French man with primary hypogonadism, characterized by reduced testosterone levels and increased LH and follicle-stimulating hormone (FSH) [44].

Similarly, Sialy et al., in their study of 15 Indian men with idiopathic melasma, found reduced levels of testosterone and increased levels of LH compared with 11 age-matched controls; estrogen levels were not detected [45].

In 1997 O'Brien et al. reported a case of melasma of the forearms in a man who had been given exogenous estrogens for prostatic carcinoma [36] whilst Burkhart et al. (2006) reported a case of melasma after oral therapy with stimulators of testosterone production, a compound including dehydroepiandrosterone (DHEA), androstenedione, indole-3-carbinol and *Tribulus terrestris*, a gonadotropic stimulator that increases LH secretion [46].

Melasma and the Pituitary Gland

The intermediate lobe of the pituitary gland produces melanocortins, a class of peptide hormones crucial for melanogenesis which stimulate the production and release of melanin by melanocytes in skin and hair. The melanocortins include 3 different types of MSH (α -MSH, β -MSH, γ -MSH) and adrenocorticotrophic hormone (ACTH), all derived from the same precursor, the proopiomelanocortin (POMC) prohormone, whose secretion is induced by corticotropin-releasing hormone (CRH) produced in the hypothalamus [47]. In humans, α -MSH and ACTH are also produced locally in the skin (both in keratinocytes and melanocytes) and have a major role in pigmentation, presumably via paracrine and/or autocrine mechanisms [48-50]. Funasaka et al. also demonstrated the expression of CRH and CRH receptor in normal human melanocytes, nevus cells and melanoma cells [51].

Plasma immunoreactive β -MSH has been measured in patients with and without melasma taking progesterone only or combined progesterone-estrogen therapy; β -MSH levels did not differ from age and sex-matched controls [52].

Similarly, in 1983 Pérez et al. observed no significant differences in the levels of cortisol, ACTH, prolactin or β -MSH among 9 patients with idiopathic melasma compared to 9 unmatched controls [40]. However, these results may not be applicable to all patients affected by melasma because of the small number of patients evaluated and the use of unmatched controls.

No association between melasma and pituitary disorders has been reported in the literature, although the role of melanocortins in melanogenesis is clear. Maeda et al. reported increased melanocyte proliferation and an increase in both tyrosinase activity and TRP-1 expression in normal human melanocytes when incubated with pituitary hormones such as β -MSH, a potent analogue of α -MSH, ACTH, FSH and LH [13]. This suggests that the development of melasma does not involve circulating melanocortins produced by the pituitary gland but more likely those locally produced in the skin. This hypothesis is supported by the work of Im et al. who found an increased expression of α -MSH in lesional melasma skin [53].

It is important to distinguish melasma, localized mainly to the face or less frequently to the neck or forearms, from general hyperpigmentation caused by some pituitary or adrenal diseases leading to increased POMC-derived ACTH and MSH levels with consequent global skin hyperpigmentation. This is the case for patients affected by primary adrenal insufficiency, ACTH-dependent Cushing's disease and Nelson's syndrome, characterized by very high POMC-derived ACTH [54].

Melasma and the Adrenal Glands

Levels of 17-ketosteroids have been consistently normal in patients with melasma [55] as well in the ratios of the fractionated estrogenic substances [56].

To date, no association has been found between melasma and adrenal disorders, either primary or secondary.

Melasma and Thyroid Disorders

Lutfi et al. in 1985 analyzed 84 non-pregnant women with melasma and 24 age- and sex-matched controls. They found a 4 times greater frequency of thyroid disorders (58.3%), both autoimmune and non-autoimmune, in patients with melasma compared to controls, suggesting an association between thyroid disorders and melasma [57].

However, there are no other reports of this association. Indeed, a small Iranian study conducted in 2010 found no differences in the levels of autoantibodies to thyroid peroxidase, triiodothyronine (T3), thyroxine (T4) or thyroid-stimulating hormone (TSH) between 45 females affected by melasma and 45 age-matched controls [58].

There is thus no strong evidence of a relationship between melasma and thyroid disorders. Both melasma and thyroid diseases are very common in young women hence this could erroneously lead to suggestions of a relationship between the two conditions when one does not really exist [20]. Larger studies are needed to clarify this.

Melasma and Vitamin D

Vitamin D₃ (cholecalciferol) is photochemically synthesized in the skin from 7-dehydrocholesterol [59] and its active metabolite 1,25-dihydroxyvitamin D₃ [1,25(OH)₂D₃; calcitriol] is formed by successive hydroxylation in liver and kidney [60]. Hormonal activity is carried out by 1,25(OH)₂D₃ via binding to its intracellular receptor (VDR); its principal function is to maintain calcium homeostasis [61,62].

However, the skin itself is a target for vitamin D since the VDR is also expressed in epithelial cells and melanocytes [14,63]. Studies with melanoma cells show an increase in tyrosinase activity in response to 1,25(OH)₂D₃, generally accompanied by a decrease in cell proliferation whether assessed *in vitro* [64,65] or *in vivo* [66]. Human melanocytes bind 1,25(OH)₂D₃ with affinities similar to those reported for human

melanoma cells [67]. Ranson et al. found a stimulatory activity of 1,25(OH)₂D₃ on tyrosinase activity in melanocytes from normal skin [14]. However, this is not a consistent finding [68].

Despite the active role that 1,25(OH)₂D₃ plays in the skin and the suggested use of vitamin D for the prevention or treatment of skin diseases such as melanoma and psoriasis [69], to our knowledge no case-reports of melasma associated with vitamin D disorders have been described so far.

Conclusions

Melasma is strongly associated with female sex hormones and may occur with a high prevalence during pregnancy or in response to treatment with estrogens and/or progesterone, such as the contraceptive pill or hormone replacement therapy. Melasma associated with the use of oral contraceptives is usually persistent, while melasma of pregnancy usually fades within one year of delivery. Melasma is usually localized to the face but in post-menopausal women taking hormone replacement therapy it tends to involve the forearms.

Despite the association between these conditions and melasma, the precise mechanisms by which female hormones, especially estrogens, are involved in its pathogenesis are still unclear. Moreover, serum levels of estrogens and progesterone have not been found to be consistently elevated in idiopathic melasma patients.

Melasma has also been described among men, especially with low testosterone and increased LH levels or taking exogenous estrogens.

Despite melanocortins playing an important role in melanogenesis, an increase in their serum levels seems not to be associated with melasma development, which is more likely to involve locally produced melanocortins in the skin.

No relationship between pituitary or adrenal disorders and melasma has been described so far.

An association between melasma and thyroid disorders has been reported in one study only and not confirmed in a subsequent one. Further larger studies are needed to clarify this association.

Despite the active role of 1,25(OH)₂D₃ in skin, to our knowledge no relationship between melasma and vitamin D disorders has been described so far.

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This article was originally published in a special issue, **Melasma** handled by Editor(s). Dr. Serena Gianfaldoni, University of Pisa, Italy