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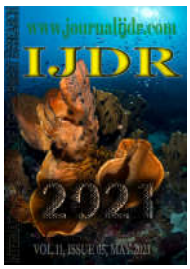

REVIEW ARTICLE OPEN ACCESS

MAJOR APPROACHES OF MOLECULAR AND PHYSIOPATHOLOGICAL MECHANISMS FOR HORMONAL TREATMENT OF MELASMA: A SYSTEMATIC REVIEW

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ABSTRACT

Introduction: Epidemiological data showed that melasma occurs in 14.5% -56% of pregnant women and in 11.3% -46% of individuals who take oral contraceptives in different countries. In this respect, by inducing the synthesis of melanogenic enzymes, such as tyrosinase and proteins related to tyrosinase 1 and 2, estrogens stimulate melanogenesis in human melanocytes. The increase in progesterone levels that occurs during pregnancy and the increase in estrogen production that occurs from the eighth to the thirtieth week of pregnancy reflects the progression of hyperpigmentation. **Objective:** The main predictors, pathophysiological mechanisms, and experimental and clinical results of melasma were addressed through a systematic literature review, discussing the main outcomes of clinical studies. **Methods:** The present study followed a systematic review model. After literary search criteria using MeSH Terms, a total of 98 clinical studies were compared and submitted to eligibility analysis and, after that, 70 studies were selected, following the rules of PRISMA. The search strategy was carried out in the databases PubMed, Embase, Ovid and Cochrane Library, Web Of Science, ScienceDirect Journals (Elsevier), Scopus (Elsevier), OneFile. **Results:** Sex hormones, such as estrogens, especially 17-β-estradiol (E2) and progesterone, are factors involved in the regulation of pigmentation. Levels of estradiol, luteinizing hormone (LH) and follicle-stimulating hormone (FSH) were found to be higher in the serum of women with melasma. Estrogen and progesterone receptors are expressed differently in melasma skin than in perilesional or non-lesional skin. Few authors have analyzed the effects of progesterone on pigmentation, and no data has been reported with concentrations of progesterone found in non-pregnant men and women. An increase in keratinocyte proliferation was observed with baseline progesterone concentrations. It is well known that keratinocytes secrete exosomes and factors that regulate melanogenesis, differentiation, and proliferation of melanocytes. Progesterone is involved in the pathogenesis of melasma, stimulating melanogenesis in epidermal melanocytes. **Conclusion:** The prevention of melasma can occur by progesterone components in oral contraceptives since progesterone can reduce melanocyte proliferation without significant effects on tyrosine activity. Estrogen can increase melanogenesis in the melanocyte monolayer and induce the production of melanogenic factors by keratinocytes. Estrogen can support hyperpigmentation, increasing the number of blood vessels and, thus, stimulating the secretion of endothelin-1.

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INTRODUÇÃO

Epidemiological data showed that melasma occurs in 14.5% -56% of pregnant women and in 11.3%-46% of individuals who take oral contraceptives in different countries [1,2]. Hispanic and Asian women are most commonly affected by melasma [3]. This disorder affects most patients in the third or fourth decade of life. The onset of the disease occurs earlier in light-skinned types, while those with dark skin are generally associated with a late-onset [4].

Still, in pregnancy, this pigmentary alteration is more likely to be associated with circulating female hormones than with the peptides of the melanocyte-stimulating hormone. In this respect, by inducing the synthesis of melanogenic enzymes, such as tyrosinase and proteins related to tyrosinase 1 and 2, estrogens stimulate melanogenesis in cultured human melanocytes. The increase in progesterone levels that occurs during pregnancy and the increase in estrogen production that occurs from the eighth to the thirtieth week of pregnancy reflects the progression of hyperpigmentation [1]. In this sense, it can be said that

melasma is a common acquired hyperpigmented disorder that occurs mainly in photo exposed areas (face, neck, forearms, back, and neck) and affects mainly women of reproductive age. It can occur in all skin types, but it is more common in intermediate phototypes (Hispanic, Asian, African Mediterranean, Middle Eastern populations) and rare in extreme phototypes (I,VI) [5,6]. In this context, although there is a predominance of the indication of melasma in women, the female/male prevalence differs according to the ethnic group [5]. Also, genetic predisposition [7], hormonal influence, especially female sex hormone (use of oral contraceptives, hormone replacement therapy, pregnancy) [8], and exposure to solar radiation seem to be the most important triggers [5,9,10]. In this scenario, the epidermal type occurs in 72% of the melasma associated with pregnancy [8], and the melasma induced by pregnancy is associated with early-onset [5]. Histologically, epidermal melasma is characterized by an increase in melanin in all layers of the epidermis and an increase in the number and transfer of melanosomes [9]. However, in Caucasoid women, melanosomes are transferred more individually than as polymelanosomes [9,11,12].

As a photoaging disorder, melasma is also characterized by solar elastosis [10-12]. Other characteristics, such as damage to the basement membrane [10], increase in blood vessels and dermal mast cells [10,15] and lymphohistiocytic infiltration have been described [16]. Another photoaging disorder, which can be attributed mainly to UVA-induced fibroblast dysregulation [17]. Chronic exposure to UVA and visible light appears to be implicated in damage to the dermal and basal membranes [13]. Also, sex hormones, such as estrogens, especially 17-β-estradiol (E2) and progesterone, are factors involved in the regulation of pigmentation [18], collagen content, skin aging, skin moisture, and skin thickness [19]. Also, estradiol, luteinizing hormone (LH), and follicle-stimulating hormone (FSH) levels were found to be higher in the serum of women with melasma than in those of control women without melasma, while progesterone levels were similar in two groups [20,21]. In the same sense, in the serum of men with melasma, luteinizing hormone levels were higher than in controls without melasma, while FSH levels were similar and testosterone levels were lower [22,23]. Also, a testosterone metabolite, 5α– androstane-3β-diol, competes with E2 to bind ERβ and thus triggers an estrogenic response in cells [24]. Therefore, estrogen and progesterone act through receptors expressed in both the epidermis and the dermis. In the adult scalp skin in humans (male and female), only the estrogen receptor (ER) β was observed in the epidermis, fibroblast blood vessels, and hair follicles, while in the human neonatal foreskin both RE-α and RE-β were detected [19,25]. Estrogen and progesterone receptors are expressed differently in melasma skin than in perilesional or non-lesional skin. Thus, the present study approached, through a systematic literature review, the main predictors, pathophysiological mechanisms, and experimental and clinical results of melasma, discussing the main outcomes of clinical studies. The present study aimed to present, through a systematic review, the main predictors, pathophysiological mechanisms, experimental and clinical results of melasma, discussing the main outcomes of clinical studies.

METHODS

Study Design: The present study followed a systematic review model. After literary search criteria using the MeSH Terms that were cited in the item below on "Search strategies", a total of 98 clinical studies were compared and submitted to the eligibility analysis and, after that, 70 studies were selected, following the systematic review rules – PRISMA (Transparent reporting of systematic reviews and meta-analyzes-HTTP: //www.prisma-statement.org/).

Search Strategy and Information Sources: The search strategy was carried out in the databases PubMed, Embase, Ovid and Cochrane Library, Web Of Science, ScienceDirect Journals (Elsevier), Scopus (Elsevier), OneFile (Gale) followed the following steps: -Search by MeSH Terms: *Melasma; Pathophysiological mechanisms; Treatments; Experimental studies; Clinical studies*, and the use of Booleans "and" between mesh terms and "or" among historical findings.

Risk of Bias: According to the Cochrane model for the risk of bias in the present study, the global assessment resulted in 7 studies with a high risk of bias and 4 studies with uncertain risk. Also, the funding source was absent in 3 studies and 5 studies did not disclose information about the conflict of interest statement.

RESULTS AND DISCUSSION

Major experimental studies

Effects of steroid hormones on melanocytes: After the literary search criteria, a total of 98 studies were found that were submitted to the eligibility analysis and, after that, 70 studies of high to medium quality and with risks of bias were selected that do not compromise the scientific basis of the studies, as presented in Figure 1. After a complete analysis of these selected studies, it was observed that estrogen can increase melanogenesis in the melanocyte monolayer and induce the production of melanogenic factors by keratinocytes. In vitro, it appears that melanocytes with high phototypes are more sensitive to progesterone, while those with low phototypes are more sensitive to estrogen. This may explain why melasma occurs earlier in low phototypes than in higher ones. Thus, it can be postulated that a local increase in estradiol in the papillary dermis induces the proliferation of endothelial cells. This local increase in blood vessels can modify the local levels of estrogen, progesterone, ET-1, and SCF, increasing the number of endothelial cells that can induce local hyperoxia that stimulates melanogenesis. In general, the data suggest that sex steroid hormones in melasma, especially estrogen, are not able to induce hyperpigmentation but act in synergy with UVB. However, estrogen can support hyperpigmentation, increasing the number of blood vessels and thus stimulating the secretion of endothelin-1.

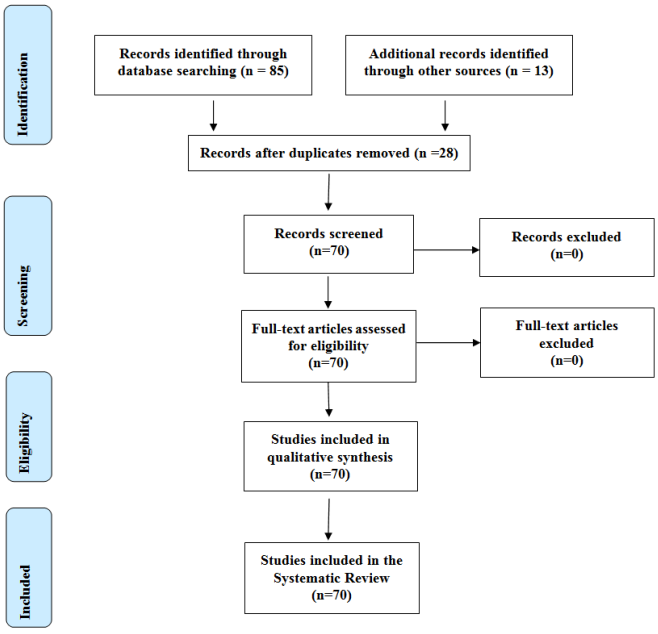

Figure 1. Flow Chart of Study Eligibility

In women, estradiol and progesterone concentrations vary according to age, menstrual cycle, pregnancy, and menopause. Men have lower levels of plasma estradiol and progesterone than women. Exposure to 17-β-estradiol in concentrations found in non-pregnant men and women (10-PDZ11 to 10-9 mol / L) may induce an increase in the melanin content in responsive melanocytes 3 days after treatment, whereas, decreased after 10 days [26-28]. In experimental studies in vitro, under stimulation with 25 nmol/L (2.5,10-8 mol/L) 17β-estradiol, a concentration observed during pregnancy [29] or 2.5,10-8 mol / L of ethinylestradiol (oral birth control pills), melanin synthesis

can be increased in melanocytes grown in monolayers [18]. Changes in melanin production were inversely correlated with melanocyte proliferation [26,28]. Experiments carried out with several strains of melanocytes showed that some melanocytes did not respond to estrogen stimulation, even at a high dose (10−7M) [30]. Also, few authors have analyzed the effects of progesterone on pigmentation, and no data has been reported with progesterone concentrations found in non-pregnant men and women. Progesterone at 5.10−7M, a physiological concentration observed in the third trimester of pregnancy [29], decreased pigmentation in melanocytes cultured in monolayers [18]. Female melanocytes derived from iPS (induced pluripotent stem cells) and male melanocytes from various body locations (facial vs. foreskin) and of different ages (adult vs. newborn) had a similar response to estrogen and progesterone (n = 3 for each group) [18]. In this sense, estrogen and progesterone can act through several receptors.

For example, adult and foreskin melanocytes [28,30] or not [18] expressed ER and PR at mRNA and protein levels. However, while Natale et al did not find ER and PR, they found that melanocytes responded to estrogen via fixation to ERGP (estrogen receptor coupled to G protein) and to progesterone via fixation to PAQR7 (progestin and adipoQ 7 receptors), two G proteins Receptors coupled [18]. Since several factors such as TPA, PMA, CT, insulin, IGF-1, and EGF40-44 modulate ER and PR, it is hypothesized that melanocytes are capable of expressing ER, ERGP, PR, and PAQR7, but that their expression in vitro depends on stimulation by exogenous factors. Thus, the activation of ERGP and PAQR7 respectively stimulates or inhibits cAMP signaling, the same pathway used by melanocyte-stimulating hormone (α-MSH) to regulate pigmentation, so they neutralize [18]. Estrogen via REα fixation and in association with Sp1 can modulate the expression level of the progesterone receptor by binding to the ERE/Sp1 site (estrogen response element and sp1 sites) [31] and progesterone can inhibit the expression of ER [32]. Also, Smith et al raised the hypothesis that high levels of estradiol saturate the ER, inducing, in turn, a decrease in the ER synthesis [31,33]. Thus, in vitro, physiological doses of estrogen [12] stimulate the production of melanin by melanocytes, and these regulate the transcription of their ER to maintain their homeostasis. At doses found during pregnancy and with short-term exposure, estrogen-induced melanin production, while progesterone decreased it in vitro. Therefore, it is hypothesized that in vivo and under baseline conditions, a balance between the estrogen and progesterone pathways maintains pigmentation at its baseline level. However, during hormone replacement therapy and pregnancy, estrogen and progesterone levels can be modified and the ratio between the two hormones can vary. This would explain the appearance of melasma in women, who are more sensitive to sex steroid hormones or less able to regulate the level of their receptors.
Also, in the skin with melasma lesions, PDZK1 (PDZ domain renal protein 1), and estrogen-induced factor [34], are overexpressed in keratinocytes and melanocytes [35]. In a melanocyte-keratinocyte coculture, overexpression of PDZK1 increased estrogen (10–7–10–8M) and induced tyrosinase expression, while PDZK1 knock-down reduced estrogen-induced tyrosinase overload. This overexpression also stimulated the transfer of melanosome through increased phosphorylation of ERM (ezrin/radixin/moesin) and Rac1 (Ras-related botulinum toxin C3 substrate 1).

Effects of progesterone on melanocytes via keratinocytes: An increase in keratinocyte proliferation was observed with baseline progesterone concentrations (10–11–10–9M). The concentrations found during pregnancy and the luteal phase (10–8–10–7M) did not affect keratinocyte proliferation [36]. So far, there is no evidence indicating that progesterone stimulates the secretion of melanogenic factors by keratinocytes. Due to the expression of estrogen sulfotransferase in differentiated keratinocytes, the effect of estrogen is observed mainly in the basal layer [37], suggesting that estrogen mainly affects the epidermal melanin unit. In the epidermal melanin unit, the number of melanocytes and keratinocytes is tightly regulated [38], so if estrogen induces the proliferation of basal keratinocytes, the number of melanocytes increases. Also, it is well known that keratinocytes secrete exosomes and factors that regulate melanogenesis, differentiation, and proliferation of melanocytes [39,40]. Estrogen (10–7–10–8 mol/L) induces an increase in basal keratinocytes that, in turn, secrete factors that induce melanocyte proliferation, tyrosinase activity, and melanosome transfer leading to melasma. However, the melanocyte/keratinocyte ratio may vary according to the patient's sensitivity or the feedback control over the estrogen receptor. Also, progesterone does not appear to play a role in the modulation of pigmentation by keratinocytes in melasma [1].
Also, no evidence has been found that the effects of estrogen and progesterone on fibroblasts modulate pigmentation. Thus, in melasma, estrogenic modulation of fibroblasts does not appear to be involved in pigmentation. However, it is hypothesized that high doses of estrogen in some patients decrease collagen synthesis and thus facilitate melanocyte protrusion and melanin dermal deposition [41].
Also, in melasma, fibroblast-like cells, located around small blood vessels, expressed highly ERβ [42]. These cells are probably telocytes (Cajal interstitial cell, CD34 + stromal cells, or CD34 + fibrocytes). Telocytes are located in the papillary dermis just below the basement membrane [43], around blood vessels and surrounding sebaceous glands, express estrogen and progesterone receptors, and appear to play a role in angiogenesis [43,44] and tissue homeostasis [44]. They secrete extracellular vesicles that allow communication with neighboring cells, such as fibroblasts, immune cells, nerve endings, and endothelial cells [41,45,46]. Therefore, these cells participate in the increase in the number of vessels in the melasma.

Major Clinical Studies

A study of 324 women with melasma in nine different countries around the world found that melasma occurs only in 20% of cases during pregnancy and almost 10% begins after menopause. Also, the study showed that discontinuing the use of contraceptive pills weakly affects the development of the disease [47]. Progesterone is involved in the pathogenesis of melasma, stimulating melanogenesis in epidermal melanocytes [48]. Other studies have suggested the prevention of melasma by progesterone components in oral contraceptives since progesterone can reduce melanocyte proliferation without significant effects on tyrosinase activity. Considering that female sex hormones in oral contraceptive pills are factors involved in the development of melasma, a similar relationship can be anticipated in postmenopausal women with hormone replacement therapy [49]. In this context, melasma of the forearms has been described in postmenopausal women undergoing hormone replacement therapy [50]. Although a case-control study in 45 patients with facial melasma found no differences between groups with hormonal treatment, replacement of current oral contraceptive therapy is recommended [51]. There are several case reports of systemic hormones as triggers for the development of melasma. Besides, the development of melasma was observed after the application of topical estrogen cream [52]. The activities of estrogens and progesterone are mediated by pairs of specific human skin receptors, including ER, ER-alpha/ER-beta, and progesterone receptors (PRs) [53]. In vivo studies provide conflicting data on different expressions of ER and PR receptors in the lesional skin of melasma [54,55].

In this sense, the expression of ERs varies depending on the location and type of tissue, besides, it has been shown that the skin of the face expresses much higher concentrations of ERs than the breast or thigh [56]. Yet, ER-beta is more widely distributed in the skin and skin structures than ER-alpha. The variation in the distribution of receptors within the skin suggests that each of them plays a different role, specific to the cell, which has not been clarified so far [57]. Also, Perez et al. analyzing hormone levels in nine patients with melasma reported mild ovarian dysfunction with high LH, low mean follicular 17-β-estradiol, and normal plasma levels of α-MSH, FSH, progesterone, and prolactin. Furthermore, an ER sensitivity in both the thalamopituitary hypo-axis and melanocytes has been suggested as roles in the induction of melasma [58]. Also, differences in the levels of LH, FSH, and 17-β-estradiol at the beginning of the menstrual cycle between the groups were found in an Indian study

comparing FSH, LH, prolactin, estrogen, and progesterone among 36 women with melasma compared with controls of the same age. This suggests that circulating estrogens may be a risk factor and maintain the disease. Serum prolactin was lower on day 9 in the study group than in the control group, there was no difference in progesterone levels in patients with melasma on days 17, 19, and 21, compared to the control group [58]. Another study in 138 women reported a significant increase in estradiol levels, both follicular and luteal phases in patients with melasma when compared to controls [60]. In men, epidemiological studies have shown that melasma is not uncommon [61]. The first case of melasma in a male patient was reported in 1957 in a French man with primary hypogonadism, reproduced testosterone, and increased levels of LH and FSH [61]. Likewise, Sarkar [62] and Saily [63] reported reduced levels of testosterone and increased levels of LH in men with melasma compared to those related to the age of the control groups. Also, other authors have reported a case of melasma after oral therapy with a gonadotropic stimulator that leads to increased LH secretion and testosterone production, containing dehydroepiandrosterone (DHEA), androstenedione, indol-3-carbinol, and Tribulus Terrestris. Also, an increase in the number of male patients with melasma has been reported after the use of finasteride, an anti-androgen [64]. O'Brien reported a possible pathogenic role of estrogens, describing a case of forearm melasma in a man who was treated with exogenous estrogens for prostate carcinoma [65].

A study of 41 men with melasma reported hormonal changes in only 9.7% of patients, suggesting that exposure to the sun and family history were the main predictors of melasma [49]. Likewise, Handa [66] found no significant difference in circulating hormone levels between 50 men with melasma and healthy controls. Therefore, the role of hormones in the appearance of melasma in men is contrasting and needs to be verified in studies with larger samples. Although some triggering factors, such as sun exposure, pregnancy, use of oral contraceptives, ovarian tumors, liver disease, hormones replacement therapy, inflammatory skin processes, use of cosmetics, and photosensitizing drugs are described, the causes of melasma remain unknown [67, 68]. Also, the assumption of different and antagonistic hormonal therapies (anti-estrogen and anti-androgen) melasma may appear. This clinical evidence and the new data on melasma show that different predictors may play an important role in the pathogenesis of melasma. Besides, according to recent data analysis, genetic influences and exposure to UV radiation are likely to cause the pathogenesis of melasma. The increase in elastotic materials in skin biopsy samples indicates that the accumulation of sun exposure is necessary for the development of melasma [69]. In this context, paracrine associations between keratinocytes, fibroblasts, and melanocytes in the skin probably play an important role in regulating epidermal melanization [70]. In response to UV, keratinocytes and fibroblasts secrete one of the melanogenic cells that act on the melanocyte receptors, causing hyperpigmentation. Also, the predilection for melasma by the facial region, where the density of the sebaceous glands is greater, suggesting a possible association between sebaceous function and melasma. The sebaceous glands can synthesize various cytokines and growth factors, such as angiopoietin and adipokine. Also, sebocytes are under the control of αMSH, and therefore an overexpression of this hormone can influence cell types. Considering that pigmentation is strictly dependent on the cross-talk between different skin cells, other cells can be considered as a therapeutic target in the treatment of melasma [49].

CONCLUSION

Estrogen can increase melanogenesis in the melanocyte monolayer and induce the production of melanogenic factors by keratinocytes. In vitro monolayer studies have shown that the effect of sex hormones on cells, especially melanocytes and fibroblasts, varies according to the concentrations used. In vitro, it appears that melanocytes with high phototypes are more sensitive to progesterone, while those with low phototypes are more sensitive to estrogen. This may explain why melasma occurs earlier in low phototypes than in higher ones. However, it can be hypothesized that UV irradiation and sex hormones are necessary to maintain hyperpigmentation, especially estrogen in predisposed patients. In women, estrogen and progesterone levels vary during the menstrual cycle and pregnancy. It can be postulated that a local increase in estradiol in the papillary dermis induces the proliferation of endothelial cells. This local increase in blood vessels can modify local levels of estrogen, progesterone, ET-1, and SCF. Also, an increase in the number of endothelial cells could induce local hyperoxia that would stimulate melanogenesis, an effect already observed in melanocytes in both monolayers and 3D cultures and would support hyperpigmentation. In general, the data suggest that sex steroid hormones in melasma, especially estrogen, are not able to induce hyperpigmentation but act in synergy with UVB. However, estrogen can support hyperpigmentation, increasing the number of blood vessels and thus stimulating the secretion of endothelin-1. Since the sensitivity of cells to sex steroid hormones varies widely, it is hypothesized that these hormones are responsible for the difference in susceptibility to melasma.

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