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Evaluation of the Relationship between Melasma and Female Sex Hormones (Estrogen and Progesterone) Levels

Aya Khudhair Khalaf[1], Staar Rasheed[2], Khudhair Kh. Al-Kayalli[3] and Sarmad, Y, Abbood[4]

[1, 3] Diyala University, College of Medicine

[2, 4] Baqubah Teaching Hospital

Abstract: **Background:** Uneven brown macules symmetrically distributed over sun-exposed parts of the face are the hallmark of melasma, a chronic acquired hypermelanosis of the facial skin. Melasma is known to be triggered by a number of conditions, including sun exposure, pregnancy, the use of oral contraceptives and other steroids, ovarian tumors, intestinal parasites, hepatopathies, hormone replacement therapy, the use of cosmetics and photosensitizing medications, procedures, inflammatory processes of the skin, and stressful events. **Aim of the study:** To evaluate the relationship between melasma and female sex hormones (estrogen and progesterone) with some epidemiological data. **Material and methods:** Two hundred and forty-four female patients with melasma were seen in a private clinic in Kalar City and Bquba Teaching Hospital during the period from 15th January 2018 to 15th October 2018. Their ages ranged from 20 – 45 years, with a mean age of 29.38 years. They were fully interrogated regarding age, occupation, outdoor working, marital status, number of pregnancies, menstrual cycle, uses of contraceptive pills, any history of hormonal and corticosteroid therapy, and family history of the same disease. Forty patients were investigated for female sex hormone levels. **Results:** The study shows normal values of both estrogen and progesterone levels at different phases of the menstrual cycle, which means female sex hormones had no role in the etiology of melasma in non-pregnant women, and the other etiological factors were important, particulary sunlight exposure. Fifty percent had a positive family history of melasma, (71%) centerofacial, (21%) malar, (8%) mandibular, (70%) had frequent sunlight exposure, (20%) pregnant, and (10%) used compound contraception pills (COC). **Conclusion:** The values of female sex hormones were normal, which means of no important role in the etiology of the disease.

Keywords: UV radiation, Melasma, UV index, Contraceptive pills, Female sex hormones.

INTRODUCTION

Uneven brown macules symmetrically distributed on sun-exposed facial skin are the hallmark of melasma, a chronic acquired hypermelanosis of the face (Handel, A.C. *et al*., 2014). Melasma is known to be triggered by a number of conditions, including sun exposure, pregnancy, the use of oral contraceptives and other steroids, ovarian tumors, intestinal parasites, hepatopathies, hormone replacement therapy, the use of cosmetics and photosensitizing medications, procedures, inflammatory processes of the skin, and stressful events (Tamega, A. de A. *et al*., 2013). Although the pathogenesis is uncertain, UV exposure, along with genetic and hormonal factors, is important (Handel, A.C. *et al*., 2014).

The clinical appearance is characterized by symmetrical organization, irregular borders, and asymptomatic light-to-dark brown hyperpigmentation. The condition's nearly constant deterioration over the summer is one of its characteristics (Kang, H.Y. *et al*., 2010). Histological analysis of melasma may reveal perivascular lymphohistiocytic infiltration, solar elastosis, larger melanocytes, increased melanosomes, and enhanced epidermal and dermal pigmentation (Ogbechie-Godec, O.A. *et al*., 2017). The centrofacial pattern is the predominant clinical pattern in 50–80% of cases, affecting the forehead, nose, and upper lip with the exception of the philtrum, cheeks, and chin in 65% of cases; malar in 20% of cases, and mandibular in around 15% of patients (Tamega, A. de A. *et al*., 2013). While mandibular melasma is present on the jawline and chin, the malar pattern is restricted to the malar cheeks. The latter may be associated with significant photodamage and is believed to be more prevalent in older adults (Sánchez, J.L., 2000). A new kind of melasma that can develop on non-facial body parts is called extra-facial melasma (Ritter, C.G. *et al*., 2013).

People of all races and ethnicities can have melasma, but those with darker skin phototypes who reside in areas with high UV radiation, like Asians, Latin Americans, and Afro-descendants, are more likely to get it (Taylor, S.C., 2003). Geographical differences are clearly characterized, and it is more prevalent in young women, with men making up about 10% of all cases (Sarkar, R. *et al*., 2010). The development of melasma has been linked to female hormone stimulation and a predisposed genetic background (Ogbechie-Godec, O.A. *et al*., 2017).

Melasma, which is classified into three types—epidermal, dermal, and mixed—can be detected by Wood's mild examination of the skin (Pandya, A.G. *et al*., 2000). While progesterone levels were the same in both groups, women with melasma had

***Corresponding Author:** Aya Khudhair Khalaf

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higher levels of estradiol, luteinizing hormone (LH), and follicle-stimulating hormone (FSH) in their sera than women without the condition (Hassan, I. *et al*., 1998). While FSH levels were comparable and testosterone levels were lower, luteinizing hormone levels were higher in the sera of males with melasma than in those of controls without the condition (Sarkar, R. *et al*., 2010).

The onset of melasma in women of reproductive age and the use of oral contraceptives suggest that female sex hormones have the onset and progression of the melasma (Passeron, T., 2013). The levels of placental, ovarian, and pituitary hormones, which stimulate melanogenesis, rise throughout pregnancy, especially in the third trimester. Various observations have been made, and melasma in pregnancy is more likely to be linked to circulating female hormones than to peptides of the melanocyte-stimulating hormone (MSH) (Muller, I. *et al*., 2014).

Melasma is found in 14.5%–56% of pregnant women and 11.3%–46% of people who use oral contraceptives in various nations, according to epidemiological data (Krupa Shankar, D.S.R. *et al*., 2014).
It is necessary to determine the role of progesterone in skin pigmentation. Progesterone has been discovered to play a role in the development of melasma by promoting melanogenesis in epidermal melanocytes (Lee, A., 2015).

There were differences in the levels of 17-β-estradiol at the start of the menstrual cycle between the groups in an Indian study that compared FSH, LH, prolactin, estrogen, and progesterone among 36 women with melasma and control of the same age. This suggests that circulating estrogens may be a risk factor and maintainer of the disease (Kang, H.Y. *et al*., 2010).

Estradiol, progesterone, and prolactin levels were measured in the serum of 138 women in a different study carried out in Pakistan; the results indicated that patients with melasma had significantly higher levels of estradiol in both the follicular and luteal phases in comparison to the controls (Jang, Y.H. *et al*., 2010). Both the dermis and the epidermis express receptors that are used by estrogen and progesterone. Only estrogen receptor (ER) β was found in the epidermis of adult human scalp skin (male and female).

Melasma is caused by UVA and UVB radiation, as well as less typically infrared and visible light, which induce melanogenesis. Sun exposure (without burning) is the most essential triggering factor. Melasma is more likely to form in the winter and worsen in the summer. People who live at high elevations are also more likely to get melasma (Jablonski, N.G. *et al*., 2012).

There is a stimulant for melanogenesis during pregnancy, especially in the third trimester, and elevated levels of placental, ovarian, and pituitary hormones may justify melasma associated with pregnancy. Elevated transcription of tyrosinase and dopachrome tautomerase, which may be implicated in the development of pigmentation in this phase, is also caused by increased levels of MSH, estrogen, and progesterone (Costin, G.-E. *et al*., 2007).

MATERIAL AND METHODS

Study protocol

This study was carried out in Kalar City, Sulaymania Governorate (private clinic) and Baaquba Teaching Hospital from 15 January to 15 October 2018.

Study design: 244 patients with facial hypomelanosis who had been clinically diagnosed with melasma were recruited. A full medical history was taken, including information on age, occupation, marital status, menstrual cycle, number of pregnancies, and any drug history. Blood samples were randomly drawn from 40 patients to check the levels of oestrogen and progesterone.

Study population: A cross-sectional study was conducted on patients with facial hypomelanosis, with some patients being randomly selected for a blood investigation in a biochemistry laboratory to assess serum levels of oestrogen and progesterone using an automated enzyme immunoassay analyser (AIA-360), Tosoh Bioscience Corporation, 2010.

Ethical considerations: Informed consent was obtained from the patients and from Baquba Teaching Hospital.

Statistical Analysis: Excell 2010, SPSS version 20 statistical program used for analysis, Chi-square and P-value for analysis data.

RESULTS

A total of 244 female patients were observed and diagnosed with melasma on clinical grounds. The patients' ages ranged from 20 to 45 years, with a mean age of 29.38 years. As demonstrated in Table 1, the disease manifested most frequently in patients between the ages of 20 and 30 (65.6%),

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followed by those between the ages of 31 and 40 (24.6%), and least frequently among those between the ages of 41 and 45 (9.8%). A total of 40 patients were investigated for serum levels of oestrogen and progesterone at varying phases of the menstrual cycle. The results demonstrated that these hormones were within normal parameters. In the investigation of oestrogen, 30% of patients were in the follicular phase, 30% in the ovulation phase, and 40% in the luteal phase. For progesterone, 35% of patients were in the follicular phase and 65% in the luteal phase (see Table 2).

Table -1: Distribution of patients according to age

Age group	No. of patients	Percent
20-30	160	65.6%
31-40	60	24.6%
41-45	24	9.8%
Total	244	100%

Table -2: Distribution of patients according to values of estrogen and progesterone according to the phase of the menstrual cycle

Hormones	Cycle Phase	No. of patients	Tested values Ng	Normal values Ng
Estrogen	Follicle	12	8 –49.7	20 – 300.8
	Ovulation	12	7 – 180	41.3 – 527.4
	Luteal	16	13.7 – 237.8	20 – 349.1
Progesterone	Follicle	14	0.1 – 0.35	≤ 0.97
	Luteal	26	0.25 – 17.92	0.37 – 18.4

Thirty patients (75%) of those tested for hormonal levels were married, and all of them had childbearing (1-4 childbearing), and 10 (25%) were not married. None of them was pregnant at the time of examination (Table 3).

Table -3: Distribution of patients tested for hormones according to marital status and childbearing

Status of patents	No.	Percentage	p-value
Married	30	75%	
not married	10	25%	
Childbearing in married	30	100%	

Regarding the clinical data (Table – 4), the study shows that 122 (50%) of patients had a family history of melasma, 173 (71%) of patients had centro facial type, 51(21%) had a malar type, and 20 (8%) had a mandibular type.

Table -4: Distribution of patients according to the clinical presentation.

Clinical type of Melasma	No. of patients	Percentage
Centro facial	173	71%
Malar	51	21%
Mandibular	20	8%
Total	244	100%

On the other hand, about 171 (70%) of patients were outdoors working with frequent and long exposure to sunlight; 49 (20%) were pregnant, and 24 (10%) were using oral contraceptive pills at the time of examination (Table 5).

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Table 5: Distribution of patients according to the aggravating factor

Aggravating factors	No.	%
Outdoor	171	70
Pregnant	49	20
Contraceptive pills	24	10

DISCUSSION

The study was done in Kalar city, which is one of the cities of Al-Sulaymania Province, Iraq, and its height from sea level was about 300 meters. I.e., it had a high UV index and UV radiation exposure, which was one of the major causes of melasma (9.(

Our study showed that melasma was more prevalent in the age group (20-30)years (65.6%) and in married patients (75%); these results are in agreement with other studies carried out in different cities of Iraq, such as a study carried out in Alkadhymia Teaching Hospital in Baghdad which showed that the majority of the patients were aged between (25-35) years, and (88%) of the patients were married (Mohammed, R. F), another study carried out in Basrah Medical College\ Basrah Governorate, Iraq showed that melasma was more prevalent in the age group (21-30) years (20). Our results showed normal values of female sex hormones, which were concordent to the results in a study done in Rio-de Janeiro in Brazil, in which the hormonal assay was normal, i.e., of no important role in the etiology of melasma, which means that other etiological factors were important particulary sunlight exposure and the female sex- hormons were of importance in the etiology of melasma in pregnant women's only (2.(

Although findings were opposite to those of two studies conducted in India and Pakistan, where hormonal levels were drastically elevated, approximately 27.3% of them had normal estrogen levels, whereas 72.7% had elevated levels (15,16). Still, 42.4% of the population had normal, and 57.6% had elevated levels of progesterone (21). One other study was done in Mayo Hospital showed only (3%) of patients had normal estrogen and progesterone levels. And one other study was done in Lahore-Pakistan, where (10.9%) had normal estrogen levels in both follicular and luteal phases, while the remaining (89.1%) had high estrogen levels in any of the four phases, while the progesterone levels were normal in (44.9%) (23). Regarding the clinical patteran of pigmentation, the Centro facial type was the most common in our study (71%), followed by the malar type (21%), then the mandibular type (8%). These results was different from that seen in Al-Kadhimia Medical City, in which most commonly the malar area was involved (44%), and in Medan-Indonesia studies in which centrofacial pattern was (52.9%), malar (47.1%), and non-showed mandibular type (24). A different study in which (45%) were centrofacial, and (39%) were malar type (13.(

While in Tunisian patients, the centrofacial type was frequently observed (76%), followed by malar (23%) and then mandibular (1%), concordant with our study (25). On the other hand, the current study showed that (70%) of patients were outdoor workers with frequent and prolonged sunlight exposure, (20%) were pregnant, and (10%) were on oral contraceptive pills; none of the pregnant and used oral contraceptives were included in hormonal assay because usually they had high female sex hormone content, this guideline was derived from the result seen in researches done in Baghdad where pregnancy was a related condition in (64%), while prolonged sun exposure (84%) was relatively concordant with our research (Mohammed, R. F). In Basrah also (37.9%) were pregnant (Al-Hamdi, K. I. *et al*., 2018). In Africa, (40%) of patients were pregnant, while prolong sun exposure were seen in (37%) (D'Elia, M. P. B. *et al*., 2017), and in Indenocia, melasma was seen in (20.5%) of patients who used contraceptive pillis (Tuntungan, M.-I, 2018). Variations in the results among the different study populations were most likely attributable to variations in social and ethnic hapets, sesonal variations of doing the studies, genetics, and character of the population, and other factors such as exposure to the sun throughout the year and the nature of work in the different population studies.

CONCLUSION

It was concluded that melasma was the most common type of facial melanosis in married, non-pregnant, and frequent child-peering females and most commonly aggravated by sunlight exposure, without any effect of female sex hormones.

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