

Role of estrogen, progesterone and prolactin in the etiopathogenesis of melasma in females

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Abstract *Background* Melasma is a commonly acquired hypermelanosis of facial skin due to various etiological factors including hormonal imbalance.

Objectives To find out the relationship between hormonal imbalance and melasma in females.

Patients and methods One hundred and fifty female patients suffering from melasma, between the ages of 17-45 years, were enrolled in the study. They were examined by Wood's lamp to see the type of melasma whether epidermal, dermal or mixed (dermoepidermal). Patients were investigated for levels of estrogen, progesterone and prolactin in two consecutive follicular and luteal phases on 9th and 18th day of cycle, respectively. Forty control cases were also investigated for the aforementioned hormonal levels in their follicular and luteal phases.

Results Out of 150 patients, 138 completed the study while 12 patients were lost to follow up. Amongst the 138 evaluable patients, there were only 4 patients who had normal values for all the three hormones i.e. estrogen, progesterone and prolactin in all four phases. Fifteen patients (10.9%) had normal values of estrogen in both follicular (F1 & F2) and luteal phases (L1 & L2) while the remaining 123 patients (89.1%) had deranged values of estrogen (mostly increased) in any of the four phases. The values of progesterone were normal in 62 (44.9%) patients while they were deranged in 76 (55.1%) patients in all four phases. The levels of prolactin were normal in 134 (97.1%) patients while deranged in 4 (2.9%). Out of 40 controls, only 3 (7.5%) had increased values of estrogen in both follicular and luteal phases.

Conclusion Estrogen is found to be the causative agent of melasma.

Key words

Melasma, estrogen, progesterone, prolactin.

Introduction

The term melasma is derived from the Greek word 'melas' meaning black.¹ It is a disorder of pigmentary system characterized by irregular brown or greyish-brown, acquired hypermelanosis of sun-exposed areas especially the face.^{2,3} The exact mechanism of

hyperpigmentation in melasma is not known, as the synthesis of melanin is a complex process involving tyrosinase activity, formation of melanosomes, their transfer and organization in keratinocytes.⁴ However, various contributing factors have been identified including genetic predisposition,^{1,5} oral contraceptive pills,^{1,3} pregnancy,⁶ hormonal therapy,^{7,8} ultraviolet light^{9,10} and phototoxic and antiepileptic drugs.^{1,3,5}

Although, melasma can occur in both sexes and any skin type, it is more commonly seen

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in women (90%) especially with darker complexions (Fitzpatrick's skin types IV to VI) and those living in areas of intense ultraviolet radiation.^{1,5} The condition usually develops slowly and symmetrically, lasting for years, worsening in summers and improving in winters.¹⁰ There are three well recognized clinical patterns of melasma which include centrofacial, malar and mandibular. Centrofacial variety is the most common clinical pattern.¹¹ There are also three histological patterns of melasma including epidermal, dermal and mixed type.^{3,5} The diagnosis of melasma is classically clinical while Wood's lamp is used to identify the depth of melanin pigmentation.^{12,13}

The levels of estrogen, progesterone and prolactin in melasma patients have not yet been investigated in Pakistani patients. So, the present study was planned to determine the role of different hormones particularly estrogen, progesterone and prolactin in the causation of melasma.

Patients and methods

The study was carried out over a period of one year in the Department of Dermatology Unit-I, KEMU/Mayo Hospital, Lahore. One hundred and fifty female patients of melasma (any type), with age between 17-45 years, presenting to the outpatient department were enrolled, after getting approval from the ethical committee of the institution and a written informed consent. Forty females of matched criteria, who had no melasma or any hyperpigmentary disorder, were also enrolled as controls for comparison of hormonal levels. None of the patients or control subjects was on any oral/ local medication. The pregnant and lactating females or patients on any hormonal therapy (contraceptive pills) were

excluded from the study. Patients with other systemic diseases like diabetes, hypertension, Cushing syndrome etc. or on drugs for any underlying disease were also excluded.

A detailed history and clinical examination of each patient was carried out. The personal data like family history of melasma, marital status, number of children, age of onset, use of drugs (anovulatory) and cosmetics, exposure to sunlight and use of veil was recorded. Patient's skin type, area and extent of involvement of melasma were also noted. Wood's lamp examination was performed to see the type of melasma i.e. epidermal, dermal, mixed and Wood's lamp inapparent type. The results of routine investigations (complete blood and urine examinations, random blood sugar, renal and hepatic profiles and thyroid function tests) were recorded. Biochemical parameters including serum estradiol, progesterone and prolactin levels were performed at the Centre for Nuclear Medicine (CENUM), Mayo Hospital, Lahore. Two samples were drawn during the follicular phase (9th day of menstrual cycle) while the two during the luteal phase (18th day of menstrual cycle) in two consecutive months for both haematological & biochemical levels. Estradiol and progesterone were estimated by radioimmunoassay (RIA) and prolactin was estimated by immunoradiometric assay (IRMA) techniques.

The data were collected and transferred to SPSS version 11 and analyzed accordingly. Paired "t-test" was used to compare the means and to find out the significance of difference. A *p* value <0.05 was considered significant.

Results

Out of 150 patients, 12 (6 married and 6 single) were lost to follow up while the remaining 138

completed the study.

Out of 138 patients, 75 (54.3%) were married and 63 (45.7%) unmarried. Seventy nine (57.2%) patients belonged to age group of 17-25 years, 54 (39.1%) were of 26-35 years and 05 (3.7%) were in the age range of 36-45 years. The mean age of married patients was 33.86 ± 4.55 years and that of unmarried 23.91 ± 3.21 years while the mean age of all patients was 29.28 ± 6.37 years. Regarding occupation, there were 99 (71.7%) housewives and 39 (28.3%) professional ladies. Frequency of low socioeconomic status was 111 (80.4%) while 27 (19.6%) belonged to middle class. All the patients had regular menstrual cycles.

There were 69 cases of epidermal melasma followed by 49 dermal and 20 mixed type with a percentage of 50.0, 35.5 and 14.5, respectively. The number of cases with epidermal, dermal and mixed melasma in married patients were 31, 33 and 11, respectively. Among unmarried patients, 38 were suffering from epidermal, 16 from dermal and 9 from mixed type of melasma. Almost double the number of married patients had dermal melasma as compared to unmarried patients while epidermal and mixed types had almost the same distribution in both married and single subjects. The malar pattern was observed in 98 (71%) patients while centrofacial pattern was seen in 40 (29%) cases.

The levels of different hormones in 138 cases in all the four phases are shown in **Figures 1** and **2**. Comparison of these hormonal levels in follicular and luteal phases in patients of melasma and controls revealed that the concentration of estrogen was raised in melasma patients ($p < 0.001$).

Out of 138 patients who completed the study, there were only 4 patients who had normal

values of estrogen, progesterone and prolactin in all four phases. The remaining 134 patients showed deranged values in any of the follicular or luteal phase, with either an increase or decrease in the hormonal assays particularly of the estradiol, showing its significant effect on causation of melasma. Regarding estradiol, only 15 (10.9%) patients had normal values in all four phases i.e. F1, L1, F2 and L2. The remaining 123 (89.1%) patients revealed deranged values of estradiol in any of the four phases (**Table 1**). The maximum number of patients had raised values between 228-500 pg/ml, however, some patients had raised values above 501 pg/ml (normal range 57-227 pg/ml). The comparison of married patients with married controls did not have any significant difference in the levels of estrogen and progesterone in F1 and L1. However, the comparison of single patients with single controls had a significant difference of estrogen in the above mentioned two phases while progesterone levels were in normal range with no significant difference. The comparison of estrogen levels of married patients with single patients had a significant difference in only F1 and L1 while no significance in F2 and L2 indicating that levels may vary in different phases and this irregular increase or decrease of these hormones influence the pigmentary changes.

The levels of progesterone were deranged in 76 (55.1%) patients in any of the four phases (F1, L1, F2 and L2), however when compared with all controls, a non-significant difference was seen. No role of prolactin was seen as 134 (97.1%) patients had normal values of this hormone. Only 4 patients had increased values of prolactin in any of the four phases. The mean levels of progesterone and prolactin were in normal range in almost all patients showing no role in melasma. The control subjects had

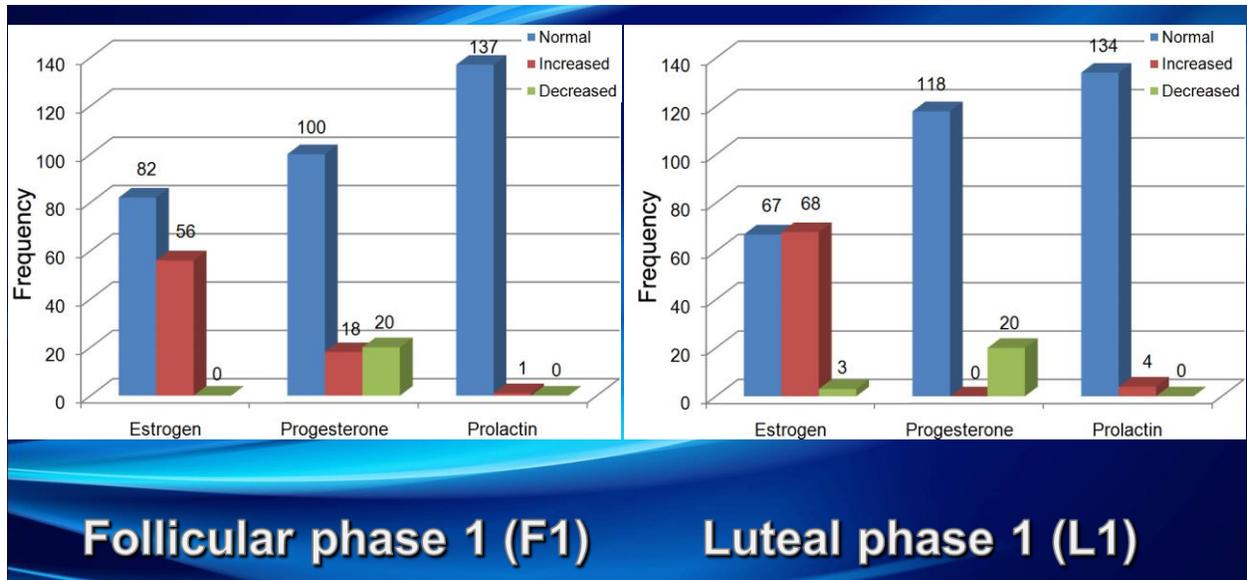


Figure 1 Levels of estrogen, progesterone and prolactin in follicular phase 1 and luteal phase 1 (n=138).

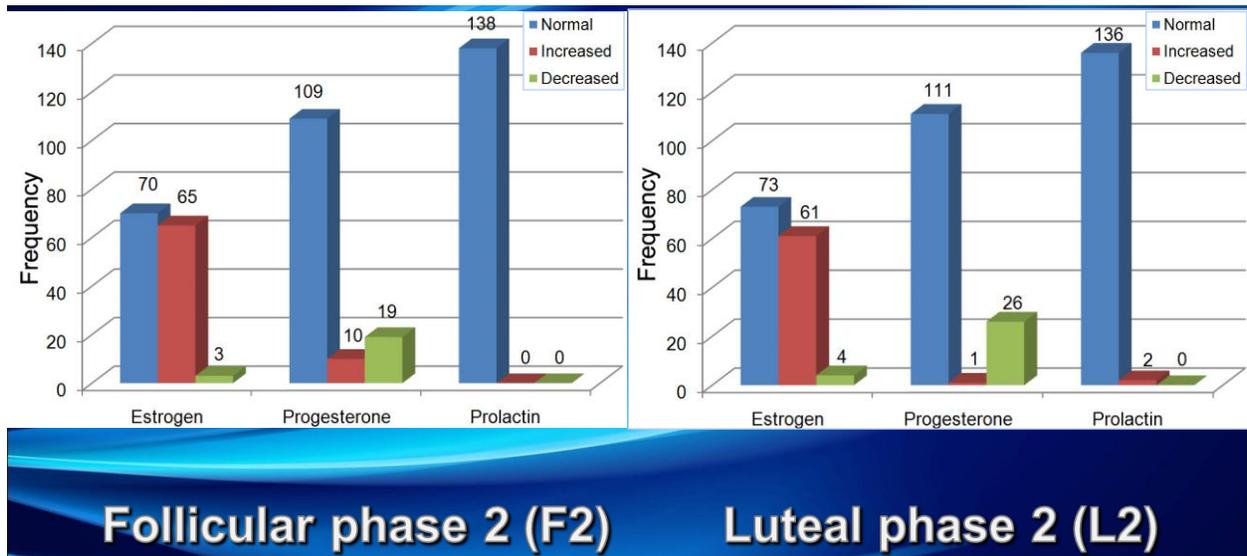


Figure 2 Levels of estrogen, progesterone and prolactin in follicular phase 2 and luteal phase 2 (n=138).

Table 1 Concentrations of estradiol in all four phases.

Phases	No. of patients	228-300 pg/ml	301-400 pg/ml	401-500pg/ml	500-700 pg/ml
F1	56	25	13	8	10
L1	68	23	24	13	8
F2	65	26	17	9	13
L2	61	19	26	9	7

F1=Follicular 1, F2=follicular 2, L1=luteal 1, L2=luteal 2. Normal level of estrogen 55-227 pg/ml.

Table 2 Effect of increased concentration of estradiol on progesterone level in all four phases.

Phase	↑ Estradiol	↓ Progesterone	↑ Progesterone	Normal Progesterone
Follicular 1	56	7	5	44
Luteal 1	68	10	0	58
Follicular 2	65	8	4	53
Luteal 2	61	6	1	54

normal values of hormones in 37 (92.5%) while the values were increased in only 3 (7.5%) cases in both follicular and luteal phases.

Many patients had a normal value of single hormone in one phase but a deranged value of the same hormone in another phase while many other patients had deranged values in two or more phases at the same time. The effect of increased estradiol concentration on progesterone level is shown in **Table 2**.

Discussion

The exact cause of melasma is uncertain but a direct relationship with female hormonal activity appears to be significant because it commonly occurs in pregnancy and with the use of oral contraceptive pills.^{5,6} Other factors implicated in the etiopathogenesis are exposure to sunlight,^{7,9} photosensitizing medications,^{1,5} mild ovarian or thyroid dysfunction and certain cosmetics.^{14,15}

In the present study, majority of patients had an age range of 17-25 years with a mean of 29.28 ± 6.37 years which is in accordance with other studies.^{16,17} Most of our patients (71.7%) were housewives and (28.3%) were professionals. Majority (80.4%) belonged to a low socioeconomic status. This poor class of society usually lives in areas where the houses are open and there is an excessive exposure to sunlight. At the same time females are exposed to heat and light while engaged in their family work. The low socioeconomic status, large families and poor nutrition all affect their health as observed in other studies^{1,18} which is in accordance with our study.

There was no significant difference in melasma patients on the basis of their marital status i.e. 54.3% married and 45.7% unmarried. This is in accordance with other studies^{16,19} indicating that

it commonly occurs in females of reproductive age. In our opinion, there is no relation of melasma with menstruation, as most of our patients had regular cycles. But, it is thought that irregular menstrual cycles denote an imbalance in hormonal levels which may affect the causation or enhancement of melasma as compared to patients having normal cycles.

Malar pattern was the most common type of melasma seen in our study which is similar to other studies.^{7,12} However, our study differs from that of Liberrman and Moy¹¹ who reported that the most common pattern was centrofacial. Epidermal melasma was the commonest variety seen which is also in accordance with other studies^{7,11,12} while dermal melasma was noted to be more common in married patients. In our opinion, this may also be related to hormonal changes.

Relationship of melasma with the levels of hormones i.e. estrogen, progesterone and prolactin was determined in different follicular (F1, F2) and luteal phases (L1, L2). Levels of estrogen in 89.1% of patients were increased in any of the four phases (F1, L1, F2, L2) and when compared with controls, showed a highly significant difference ($p < 0.001$) indicating that raised estrogen levels must have some role in the causation of melasma although not established as yet by any other study.

In a study by Hassan *et al.* circulating prolactin and estrogen on day 5, 7, 9 and 11 of the menstrual cycle and progesterone on day 17, 19 and 21 were measured in thirty-six patients with melasma and twelve healthy controls, they observed significantly higher levels of estrogen on day 5, 7 and 9 in the study group than the controls.¹⁶ Serum prolactin was significantly lower on day 9 in the study group than in the control group while serum progesterone was

similar in patients and controls.¹⁶ These findings indicate a possible role of high estrogen in the maintenance of melasma.¹⁶ Some contradictory reports showed that there was a statistically significant decreased level of estrogen observed in melasma patients, which implies that melasma patients had some degree of mild endocrinopathy.⁸ The study proposed that some cases of idiopathic melasma may represent a symptom of mild subclinical ovarian dysfunction.⁸

Various research workers have demonstrated the association of melasma with hormonal imbalance, sun damage and genetic predisposition.^{22,21} Some dermatologists believe that melasma could be stress-induced, since the release of melanin is controlled by hormones which are easily influenced by stress.²² The pituitary and ovarian hormones possibly induce hyperpigmentation of skin by stimulating the melanogenesis in epidermal melanocytes and estradiol and progesterone may be involved in the pathogenesis of melasma, usually developing between early adulthood and menopause in which a high concentration of serum ovarian hormones is maintained.^{14,23}

Many cases appear to be related to excess estrogen, either produced endogenously during pregnancy or delivered exogenously through the use of oral contraceptive pills and hormone replacement therapy; however, the mechanism of this interaction has not been elucidated. In vitro studies^{24,25} have shown that cultured human melanocytes express estrogen receptors, and estradiol increases the levels of tyrosinase, tyrosinase-related-protein 1 and tyrosinase-related-protein 2, the enzymes involved in human eumelanogenesis within normal human melanocytes. Although, estrogen has been hypothesized to be central in the pathogenesis of melasma, there had been few studies to support

this view. It is known that melanogenesis is mediated, at least in part, by the binding of melanocyte stimulating hormone to the human melanocortin receptor 1 (MCR1) in normal human melanocytes while estradiol increases MCR1, mRNA levels and tyrosinase levels, although the mechanism of these responses has not been established.^{25,26,27}

The present study gives an understanding about the role of hormones, particularly estrogen, in the causation of melasma. Further studies are needed to explore their role.

Conclusion

It was concluded from the present study that raised estradiol (estrogen) levels contribute towards the development of melasma and it may serve as the basis for exploring any topical or systemic anti-estrogen therapies for melasma in future studies.

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