

## The Correlation Between Melasma, Ovarian Cysts and Androgenic Hormones (A Case-Control Study)

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**Abstract:** Melasma is a common acquired hypermelanosis that occurs exclusively in sun exposed areas; it is exacerbated by sun exposure, pregnancy, oral contraceptives and certain Anti-epilepsy drugs, but the exact correlation with endocrine factors is still unknown. The aim of this study was to evaluate the correlation between polycystic ovarian diseases, sex hormones and melasma. This case-control study was performed on 101 subjects who had melasma and 101 control subjects referred to the dermatology clinic of Ardabil university of Medical Sciences. Serum levels of Prolactine (PL), testosterone, 17 hydroxy progesterone, Follicle Stimulating Hormone (FSH) and Luteinizing Hormone (LH) and Dihydroepiandrosterone Sulfat (DHEAS) were measured by using an Radio Immuno Assay Gammacounter machine in Ardabil nuclear medicine laboratories. Sonography of ovaries were either done. Data were analyzed using SPSS 13 statistical package. the age range of the study subjects was 15-45 years old. There was only, significant difference in mean serum levels of DHEAs between cases and controls ( $p = 0.013$ ) and no difference in others. Ovarian cysts were found in 65.3% of patients and 47.5 % of controls ( $p = 0.01$ ). There was Hirsutism and Acne in 23.8 and 64.4% of patients, respectively. The results confirm the possible role of ovarian cysts and androgenic hormone or another endocrine etiologic factor in melasma. More studies is required for more perception.

**Key words:** Melasma, ovarian cysts androgenic hormone, correlation, DHEAS

### INTRODUCTION

Melasma is an acquired, brown hypermelanosis of the face seen mainly in women. Lesions are irregular light to dark brown macules and patches, usually involving the forehead, temples, upper lip and cheeks (Victor *et al.*, 2004).

It has been reported in 50-70% of pregnant women (Wong and Ellis, 1992; Winton and Lewis, 1982; Black and Wilkinson, 1987) and in 8-29% of non pregnant women who are taking birth control pills (Sanchez *et al.*, 1995; Resnick, 1967). It has also been reported to exist in 10% of men (Champion *et al.*, 1997). Melasma in men shares the same clinical pathologic characteristics as in women, but hormonal factors do not seem to play a significant role. While all races are affected, there is a particular prominence among Latinos, especially of Caribbean origin and among Asians (Victor *et al.*, 2004; Kang *et al.*, 2002; Fitzpatrick *et al.*, 1997). Melasma is more apparent during and after periods of solar exposure (Arndt *et al.*, 1996; Riley *et al.*, 1962). It has been considered to arise from pregnancy, oral contraceptives, Endocrine dysfunction, cosmetics, genetic factors, medications, nutritional deficiency, hepatic dysfunction

and other factors (Fitzpatrick *et al.*, 1997; Farhana *et al.*, 1998). Melasma has also a coincidence in other members of family and inheritance susceptibility has been reported in twin sisters. Melasma Hyperpigmentation has been seen in patients who receiving phenytoin or mephenytoin pills (Odom *et al.*, 2000). Progesterone and estrogens stimulate melanogenesis and have been implicated in pregnancy and Oral Contraceptives usage (Snell and Bischoff, 1960; Snell, 1964). Plasma levels of immune reactive melanocyt stimulating factor ( $\beta$ -MSH), plasma  $\alpha$ -MSH, urine 17- Hydroxy Steroids and 17-Ketosteroids, Serum Cortisol, Follicle Stimulating Hormone (FSH) and Adrenocorticotrophic Hormone (ACTH) are normal in patients (Smith *et al.*, 1977; Perez *et al.*, 1983). As some old studies have been conducted focusing on role of sex hormones in melasma are very nonspecific, very little is known about role of androgens any relation between ovarian cysts and hirsutism with melasma, so we started a new field of melasma research aimed at checking coincidence of some conditions like ovarian cysts, acne and hirsutism along with melasma and comparing some hormonal levels through a case control methodology.

## MATERIALS AND METHODS

The study conducted in Ardabil in the Iran on female patient who attended dermatology clinic in 2001. the study was designed as a case-control study.

**Subject selection:** Cases chosen in this case-control study were 101 female patients having a melasma diagnosis. Controls were 101 age-matched patients referred to dermatology clinic and lacked melasma. Melasma was defined as the presence of acquired, brown hyperpigmented patches on the face. Participants were interviewed and taking a medical history and physical examinations were done. Hirsutism was defined as the presence of excessive body Hair in androgen dependent area and was evaluated using a modification of the ferriman-Gallwey score quantitating the presence of terminal hairs over nine body areas (i.e., upper lip, chin, chest, upper and lower abdomen, upper and lower back, upper and lower thighs).

Acne was defined as presence of either comedones, characteristic erythematous papules and pustules, nodules or pseudocysts and scars. Ovarian cysts were diagnosed by a radiologist through sonography. Ovarian size was also measured.

The inclusion and exclusion criteria were as follows:

### Inclusion criteria:

- Adult females aged 15-45 years
- Iranian nationals
- All clinical types of melasma in face

### Exclusion criteria:

- Pregnancy
- Oral contraceptive users, mephenyion, phenytoin and spironolacton users during the last 6 months.
- Lacking Addison disease, Cushing's syndrome and Hyperthyroidism.
- Lacking hirsutism and melasma.

**Procedures and instruments of data collection:** Serum levels of luteinizing hormone follicle stimulating homon, prolactin, testosterone, dihydro epiandrosteron sulfat and 17 Hydroxy-progesteron were measured in the mid-follicular phase of patients and controls. Ovarian sonography was done by an expert radiologist for patients and controls.

**Assays:** Serum LH, FSH, prolactine, testosterone, dihydroepiandrosteron sulfat and 17 hedroxy progesteron were analysed by Radio Immuno Assay (RIA), Picker Gammacounter. The lowest detection limit of the assay was 0.01ng mL<sup>-1</sup>.

Table 1: The frequency of sonography results for patient in two groups

	Group ovarian condition	Case		Control	
		Frequency	(%)	Frequency	(%)
Cysts	Single cyst	18	17.8	15	14.8
	Multiple cyst	48	47.5	33	32.6
Ovary size	Cyst+Enlarged size	42	63.6	26	54.1
	Cyst+Normal size	24	36.4	22	45.9

Table 2: The descriptive statistics of study variables in two group

Sig	St.dev	Mean	Group	Variables
0.63	6.3	28.5	Case	Age
7.1	29	Control	Control	
0.15	287.3	403.02 mIU L <sup>-1</sup>	Case	Prolactine
	319.5	341.1 mIU L <sup>-1</sup>	Control	
0.07	0.95	1.08 ng mL <sup>-1</sup>	Case	17-(OH) Progesteron
	0.88	1.3 ng mL <sup>-1</sup>	Control	
0.2	4.57	0.89 ng mL <sup>-1</sup>	Case	Testosterone
	0.19	0.32 ng mL <sup>-1</sup>	Control	
0.013**	66.5	108.7 Ug 100 mL <sup>-1</sup>	Case	DHEA.s
	83.2	135.3 Ug 100 mL <sup>-1</sup>	Control	
0.73	22.3	9.4 IU L <sup>-1</sup>	Case	LH
	9.9	8.6 IU L <sup>-1</sup>	Control	
0.21	10.6	6.4 IU L <sup>-1</sup>	Case	FSH
	2.3	5.03 IU L <sup>-1</sup>	Control	

\*\*: Significant in 0.05 (95% CI)

**Data processing and analysis:** Data were entered into the computer and analyzed by Statistical Package for Social Science (SPSS) software package release 13. Chi-square ( $\chi^2$ ) and one way ANOVA were the main tests used to determine associations between qualitative and quantitative variables.

## RESULTS

Housewives constituted 65.3% of the subjects, 15.3% were students and 19.3 % were employees. 63.4% of the case group had a history of one or more pregnancies. 60.4% of the case subjects had never used contraceptive pills.

Centrofacial and malar patterns involved 89.1 % and 10.9% of melasma patients, respectively. There was positive family history in 36.7% of subjects. Mean and standard deviation of time length from onset of the lesions was 4.2±3.6 years. 23.8% of patients had some grades of hirsutism with a score of 6 or more. Frequency of hirsutism was similarly distributed among different age groups among the melasma patients. 64.4 % of them were affected by acne lesions. Acne lesions were higher in the patients compared with controls (64.4 vs.9/9 %, (p<0.05)). The highest frequency of acne patients in control group belonged to 25-35 years age group and was as high as 32%, while in case group the highest frequency was equal to 5.9% and belonged to 15-25 years age group. In both groups the lowest frequency belonged to 35-45 years age group and was less than 1% in control group versus 11.9% in case group patients. Ovarian cysts were found

in 65.3% of patients and 47.5% of controls. 47.5% of cysts in cases and 33% in controls were small, multiple cysts. 63.6% of cystic ovaries among patients and 54.1% among controls were enlarged. All mentioned differences were shown to be statistically significant (Table 1). Mean serum value of hormone levels are given in Table 2 showing that only the mean serum level of DHEA.s between cases and controls was statistically significant. It was 135.3 in control group compared to 108.7 in case group patients.

### DISCUSSION

Recent studies have shown that the areas of hyperpigmentation in melasma exhibit increased deposition of melanin in the epidermis and dermis (Kang *et al.*, 2002; Grimes *et al.*, 2005). No increase in the number of melanocytes in these areas was noted, but these cells were larger, more dendritic and showed increased melanogenesis producing especially eumelanin (Grimes *et al.*, 2005).

Multiple etiologic factors including pregnancy genetic, race, endocrine, contraceptive pills, etc. have been implicated in melasma. Riley and Pathak considered sunlight as a provocative factor in the appearance of melasma (Riley *et al.*, 1962). Snell mentioned that progesterone and estrogen stimulate melanogenesis as observed during pregnancy and oral contraceptive usage (Snell and Bischitz, 1960; Snell, 1964). Smith, found plasma levels of  $\beta$ -Melanocyte Stimulating Hormone ( $\beta$ -MSH) normal (Smith *et al.*, 1977). An increased level of luteinizing hormone and lower levels of serum estradiol in melasma patients has also been reported which may represent evidence of a mild ovarian dysfunction (Perez *et al.*, 1983). Hassan reported increased serum levels of luteinizing hormone and lower levels of prolactin in melasma patient (Farhana *et al.*, 1998). In our survey there was statistically significant difference only in mean serum levels of DHEA.s between cases and controls while, no significant difference was found in mean serum levels of prolactin, testosterone, 17 Hydroxy progesterone, Luteinizing hormone and Follicle stimulating hormone between cases and controls. In our survey, the rate of enlarged and multicystic ovaries were higher in melasma patients. Although we did not find similar results in any other survey. In our survey, the rate of hirsutism in melasma subjects was higher than standardized rate in society as 23.8% of melasma patients had Hirsutism. While standard rate in Iran has been reported to range from 6-10% (O'driscoll *et al.*, 1994). In UK and U.S.A the prevalence rate of hirsutism has been reported 5-10%

(Burton *et al.*, 1971). Also similar surveys were not found about hirsutism in melasma patients. Therefore, more studies are needed to explain cause or causes in detail. 64.3% of melasma subjects and only 9.9% of control subjects had acne lesions more than one third of melasma subjects have had familial history for melasma, which may confirm a genetic predisposition to melasma. Hughes mentioned genetic predisposition in monozygotic twins (Hughes, 1987) whereas some other studies did not confirm this (Fitzpatrick *et al.*, 1997). In any case, all of the above explanations to show one or more common causes between melasma, Hirsutism and Acne probably in genetic background. This common factor may be androgenic hormonal or may be a common receptor for them.

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