

# Analysis Level of Serum Estradiol Hormone of Pregnant Women with Melasma

Andi Miranti<sup>1</sup>, Anis Irawan Anwar<sup>1</sup>, Khairuddin Djawad<sup>1</sup>, Ilhamjaya Patellongi<sup>2</sup>,  
Siswanto Wahab<sup>1</sup>, Nusratuddin Abdullah<sup>3</sup>

<sup>1</sup>Department of Dermatology, Medical Faculty, Hasanuddin University, Makassar, South Sulawesi, Indonesia

<sup>2</sup>Faculty of Public Health, Hasanuddin University, Makassar, South Sulawesi, Indonesia

<sup>3</sup>Department of Obstetric and Gynecology, Medical Faculty, Hasanuddin University, Makassar, South Sulawesi, Indonesia

## Email address:

miranti\_rm@yahoo.com (A. Miranti), anisianwar@yahoo.co.id (A. I. Anwar), duddin@ymail.com (K. Djawad),  
siswantowahab@ymail.com (S. Wahab), ilham\_pt@yahoo.com (I. Patellongi), nusraya@yahoo.com (N. Abdullah)

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**Abstract:** Hormonal changes in pregnancy are the important etiology of melasma. The presence of melasma in more than 75% of pregnancies. At the end of pregnancy, estrogen levels increase. Estrogen, especially estradiol triggers increased synthesis of melanin. This paper is aimed to determine the relationship between estradiol hormone with melasma and the type of melasma in pregnant women. This study used a cross-sectional study design to determine the relationship of estradiol hormone with melasma. It was conducted from September-November 2015. Skin examination was performed on 64 pregnant women (15-49 years old) who suffered from melasma in the third trimester and who did not, and the blood was drawn to measure the level of serum estradiol hormone. The study results that the levels of estradiol was slightly higher in women with melasma than those without melasma (13811.7 vs 12820.5), but not statistically significant ( $p > 0.05$ ). There was slightly higher levels of estradiol in women with the mixed type of melasma than the other types (14444.10 vs 14047.25 and 12243.50), but it was not statistically significant ( $p > 0.05$ ). Estradiol levels correlated significantly ( $p < 0.05$ ) with maternal age ( $r = 0.238$ ) and gestational age ( $r = 0.435$ ); but did not correlate significantly ( $p > 0.05$ ) with MASI (Melasma Area Severity Index) score and the type of melasma. The study concluded that estradiol levels in women with melasma are higher than not melasma and in mothers with type mix melasma were higher than other types, but not statistically significant. Estradiol level correlated with maternal age and gestational age.

**Keywords:** Estradiol, Melasma, Pregnant

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## 1. Introduction

Melasma is a common pigmentary disorder that manifests as symmetric hyperpigmented macules and patches on the face. It typically affects women of reproductive age with Fitzpatrick skin type IV-VI. [1]

The etiology of Melasma is multifactorial such as pregnancy, sun exposure, hormonal therapy, the use of cosmetics, racial or genetic effects, phototoxic drugs and antiseizure. The majority of melasma cases is associated with sun exposure, pregnancy or oral contraceptives. [2, 3]

In melasma pigmentation occurs as a result of increased

production of melanin or the increased proliferation of active melanocytes. Increased production of melanin have occurred without changes in the number of melanocytes. Mechanism incidence of melasma occurring in a formation process of melanin, melanosomes production may increased, increased melanisasi melanosomes, the formation of larger melanosomes, the increase in transfer of melanosomes from melanocytes to keratinocytes, as well as increased durability of melanosomes in keratinocytes.[4]

In pregnancy, particularly in the third trimester, there is stimulus for melanogenesis, and the increased levels of placental, ovarian and pituitary hormones may justify the

association between melasma and pregnancy. [5]

Hormonal changes are also important etiologies. In particular, the presence of melasma in up to 75% of pregnancies, the increased incidence of the disease in women on oral contraceptive pills (OCP), the histological finding of increased estrogen receptor expression in affected skin, the strong correlation between estradiol levels and melanogenesis, and the association of melasma with hormone replacement therapy in post-menopausal women all support this theory [6] Athar Moin et al, found that pregnant women who suffer from melasma is more common in third trimester and the higher parity, melasma is also increasing. [7]

Estradiol levels regarded as estrogen levels with the highest potential to melanogenesis, melanositosis, and deposition of melanin pigment. [8]

Wiedemann et al. (2009), conducted the research on the analysis of differences in the effects of progesterone and chlormadinone acetate (CMA) in melanocytes compared to estrogen. Obtained melanocyte proliferation induced by 17 $\beta$ -estradiol (0.1 and 1 nM) in about half of the experiment, whereas progesterone (100 nM) and CMA (100 nM) reduced the proliferation rate respectively 38% and 27%. Activity pigmentation slightly stimulated by 17 $\beta$ -estradiol, while progesterone has no effect on the activity of tyrosinase. [9]

Based on the above research, a study is needed to see the extent of the relation between the levels of the estradiol hormone to melasma and type of melasma.

## 2. Patients and Methods

This study used a cross-sectional study design. Selection of sample was performed in consecutive sampling. The Research was conducted at the Antenatal Care Clinic of RSIA Siti Fatimah, Ujung Pandang Baru health center, Kassi-Kassi health center. The Examination was carried out in the Laboratory of Microbiology Hospital UNHAS during the period of September to November 2015. Thirty-two patients were third trimester pregnant women aged 15-49 years who were diagnosed with melasma and 32 pregnant women who did not suffer from melasma as the control group. Patients who experienced post-inflammatory hyperpigmentation, were taking medications that are phototoxic, suffering from thyroid disease, and who refused to participate were excluded from the study.

The research subjects were given a description of the research to be carried out; if they were willing to participate in research, they were asked to sign an informed consent. The patients were further selected according to the inclusion and exclusion criteria. The data collection performed, covering the history, physical examination, and picture taking using the camera canon ixus 130 14.1 megapixels, usual lighting, and dark blue background. The patients were then examined in order to differentiate between the epidermal, dermal and mixed type of melasma with the use of wood's lamp. Examination to differentiate melasma and post-inflammatory hyperpigmentation by using the dermoscopic tool was carried

out using anhandyscope connected with iphone 4S. After that, the patients had their blood taken from the vena cubiti as many as 3 cc, which then stored in the blood bank. After all the samples were collected, it was examined for the hormone estradiol serum using ELISA method.

A Descriptive analysis and distribution of serum estradiol hormone levels were conducted. The data was analyzed by using the Statistical Package for Social Science (SPSS). Statistical test used are the correlation of Spearman test and Mann Whitney U test with significance level  $p < 0.05$ .

## 3. Result

**Table 1.** Comparison of estradiol levels between mothers with and without melasma.

Melasma	Estradiol Level(pg/mL)			Value p*
	Min/Maks	Mean (SD)	Median	
Yes (=32)	6382,5/18874,1	13319,52 (3081,39)	13811,7	p= 0,128
No (n=32)	389,1/18728,0	11924,76 (4078,81)	12820,5	

\*Mann Whitney

In table 1 show that the estradiol level was slightly higher in women with melasma than without melisma (Median; 13811.7 vs12820.5), but it was not statistically significant ( $p > 0.05$ ).

**Table 2.** Comparison of estradiol levels based on the type of melasma in women with melasma.

Type of Melasma	Estradiol Level(pg/mL)			Value p*
	Min/Maks	Mean (SD)	Median	
Epidermal (n=12)	6382,5/15900,2	12414,16 (2851,18)	14047,25	p=0,441
Dermal (n=6)	7599,3/16014,3	13132,18 (3463,16)	12243,50	
Mixed (n=14)	8497,7/18874,1	14175,84 (3096,43)	14444,10	

\*Kruskal Wallis test

Table 2 present there were slightly higher levels of estradiol in women with the mixed type of melasma compared to the other types (Median; 14444.10 vs 14047.25 and 12243.50), but it was not statistically significant ( $p > 0.05$ ).

**Table 3.** Correlation of maternal age, gestational age, MASI scores and type of melasma with estradiol levels.

Variable	Estradiol Level(pg/mL)		
	n	R	Nilai p*
Age (year)	64	$r = 0,238$	$p = 0,012$
Gestational age (month)	64	$r = 0,435$	$p < 0,001$
MA SI Score	32	$r = 0,187$	$p = 0,153$
Type of Melasma	32	$r = 0,230$	$p = 0,103$

\*Spearman Correlation

Table 3 shows that estradiol levels correlated significantly ( $p < 0.05$ ) with maternal age ( $r = 0.238$ ) and gestational age ( $r = 0.435$ ); but did not correlate significantly ( $p > 0.05$ ) with MASI score and type of melasma.

## 4. Discussion

This study chose estradiol hormone as its subject, as it is one of the most active forms of estrogen associated with the appearance of melasma, based on previous research and supporting journals which showed that estrogen increases the activity of tyrosinase and the number of melanocytes. [10]

High estrogen levels in serum have been reported to be associated with increased skin pigmentation. However, it is not clear whether the sex hormones play an important role in the proliferation of melanocytes from human culture and the activity of its tyrosinase [11]. In this study (Table 1) we obtained that the estradiol levels are slightly higher in women with melasma than women without melasma (median; 13811.7 vs 12820.5), but it was not statistically significant ( $p > 0.05$ ).

During pregnancy there is an increase in estrogen, progesterone and MSH, especially in the third trimester, which are often found associated with melasma. Estrogen and progestin may trigger the hyperpigmentation response by stimulating melanogenesis in melanocytes. Tyrosinase activity is increased and cell proliferation is reduced after treatment with  $\beta$ -estradiol-cultured melanocytes. Sex steroids increase gene transcripts for the enzyme of melanogenesis in normal human melanocytes, especially for DCT and tyrosinase. These results are consistent with an increase in melanin synthesis and significant tyrosinase activity. Tyrosinase has been proven using estradiol as a substrate for hydroxylate to catechol-like compound which can then regulate its enzymatic activity. When melanocytes contain estrogen receptors in its cytosol and nucleus, the pigmented cells in melasma patients are more sensitive to the stimulatory effect of estrogen and other sex steroid hormones. The existence of a second estrogen receptor (ER $\beta$ ) in human skin has a certain role that is different from the classical estrogen receptors (ER $\alpha$ ), which has the potential to increase the diversity in the mechanism of action of estrogen. [12] During the later stages of pregnancy the mother, placenta, and fetus collaborate to make large amount of steroids. Steroids are produced in a relatively larger amount isestriol. [13]

The production of estrogen by the placenta depends on precursors in the circulation, but in this situation either fetal or maternal steroids are important sources. Most estrogens derived from fetal androgens, particularly DHEAS. Dehydroepi androsterone sulphate fetus produced mainly by the adrenal fetus, the placenta converted by a sulfatase into DHEA, and further through enzymatic pathways common to steroid-producing tissues into androstenedione and testosterone. These androgens finally experienced aromatization in the placenta becomes consecutive estrone and estradiol. Most of DHEAS fetal is metabolized to a third

estrogen form that is an estriol. [13]

There are two subtypes of estrogen receptor and several isoforms and variants of each subtype connection. The first subtype, estrogen receptor  $\alpha$  (ER $\alpha$ ) classic, was first cloned in 1986; and the most recent discovery was the second subtype, estrogen receptor  $\beta$  (ER $\beta$ ). ER $\beta$  expression is clearly visible in the human epidermis, the cells located in the stratum basal and stratum spinosum become more immunoreactive than in the granular layer, while the stratum corneum is not immunoreactive. Strong staining in the nucleus for ER $\beta$  was also seen in the papillary dermis and blood vessels. [14] This may explain the obtained results (Table 2) which showed the slightly higher levels of estradiol in women with the mixed type of melasma than the other types (Median; 14444.10 vs 14047.25 and 12243.50), but it was not statistically significant ( $p > 0.05$ ).

The mechanism of induction of melasma by estrogen may be related to the presence of estrogen receptors on the melanocytes that stimulate cells to produce more melanin. [15] Histologically, women who have this condition develop an increased number of melanocytes, with the deposition of additional melanin and a background of solar elastosis, typically on the cheeks, forehead, and upper lip. [16]

In this study (Table 3) there was a significant relationship between levels of estradiol with gestational age, the mean estradiol levels in pregnant women got higher along with the more advanced gestational age. Estrogen produced by the placenta during pregnancy have higher levels in the second and third trimesters. At the end of the third trimester, estrogen reached its peak level of 6 ng/ml, which is 30 times higher than the concentration at the time of menstruation. [17]

The study did not examine the levels of the hormoneestriol, which is one form of estrogen which are relatively many in pregnancy due to lack of funding.

## 5. Conclusion

Estradiol levels in women with melasma are higher than not melasma (13811.7 vs 12820.5) and in mothers with type mix melasma were higher than other types (14444.10 vs 14047.25 and 12243.50), but not statistically significant. Estradiol level correlated with maternal age and gestational age. Further research is needed to prove the effect of hormonal melasma (MASI score and the type of melasma) with a cohort approach by observing the levels of the hormone estradiol in the final trimester I, II, and III as well as observing the type of melasma and score serum MASI.

## Abbreviation

MSH: Melanin Stimulating Hormone  
 Melanocortin 1 receptor (MC1-R)  
 Tyrosinase Related Protein 1 (TRP-1)  
 dopachrometautomerase (DCT)  
 keratinocyte growth factor (KGF)  
 estrogen receptor  $\alpha$  (ER $\alpha$ )  
 estrogen receptor  $\beta$  (ER $\beta$ ).

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