Comparation of Estradiol and Estriol Serum Levels in Different Degrees of Melasma Severity in Pregnant Women

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Abstract: Estrogen, estradiol and estriol, is known to be capable of inducing melanogenesis and have been held responsible for the pigmentation seen in pregnancy. This study was conducted to analyse serum levels of estradiol and estriol in different degree of melasma severity in pregnant women. A cross-sectional study using continuous sampling in pregnant women with melasma conducted in June - July 2017 at Dr Saiful Anwar Regional General Hospital Malang, Indonesia. Inclusion criteria include pregnant women with melasma (15-49 years). Pregnant women with previous history of non-pregnancy melasma, who are taking hormonal contraceptives or taking hormonal drugs containing estrogen and taking phototoxic drugs excluded from the study. History, physical examination, Wood Lamp, and measurement severity melasma using MSS (Melasma Severity Score) was performed. Blood samples were drawn for serum estradiol and estriol serum examination using ELISA method. Result from 25 pregnant women with melasma divided into four groups, clear (6 subjects), mild (5 subjects), moderate (9 subjects) and severe (5 subjects). Estradiol serum levels mean were 417.80 (clear), 836.60 (mild), 793.58 (moderate) and 891.00 (severe). Estriol serum levels mean obtained on clear (94.67), mild (149.88), moderate (199.64) and severe (141.17). Significant different serum levels of estradiol found in each group of MSS (p=0.015) and serum levels estriol did not significantly differ in each group of MSS (p=0.454). This study concluded that estradiol serum levels in pregnant women with melasma were different in melasma severity degrees, but estriol serum levels were not different in melasma severity degrees.

1 INTRODUCTION

Melasma is also known by the name of chloasma or mask of pregnancy (Newcomer et al, 1961) as it may appear during pregnancy and is characterised by symmetric hyperpigmentation lesions (Grawkrodjer et al 2002) (Hindrtiatini, 2015). The incidence of melasma is estimated to be about 0.2-4% of total patients with skin disease in Indonesia (Praskoeswa, 2002). Data obtained at dr Saiful Anwar Regional General Hospital Malang, in 2014 melasma reached 338 (3.4%) patients from total of 9736 patients per year, as the seventh of ten most common diseases in the Dermatology and Venereology Outpatient. In 2015, the incidence of melasma decreased to 226 (2.7%) incidence of total 8310 patients per year. The latest data obtained from Saiful Anwar's Dermatology and Venereology Outpatients in 2016, the total number patients of melasma as many as 185 (2.3%) of total 7945 patients per year.

The predominance of melasma in women supports the role of female sex hormones in one of the pathogenesis of melasma, but the mechanism is unclear (Handel et al, 2014). Estrogen enhancement that increases α-MSH (Melanocyte-Stimulating Hormone) expression in keratinocytes is thought to be an essential key to explain the process of hyperpigmentation occurring in the skin with melasma (Im S et al, 2002). Estrogen is a steroid hormone formed primarily of androstenedione. There are three types of estrogens namely estrone, estradiol and estriol.The potential of estradiol is 12 times the estrone potential and eight times estriol, so estradiol is considered the primary estrogen (Speroff et al, 2005). A study conducted by Gopichandani et al. (2015) supports that the pathogenesis of melasma is primarily affected by estradiol, evidenced by the high levels of these hormones in melasma in pregnancy was found to be lower than controls. Other estrogens such as estriol and estrone are said to affect the

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cytoplasm and estrogen core receptors that are known expressed in melanocytes (Gopichandani et al, 2015). In pregnancy especially in the third trimester, high levels of estriol and estradiol are associated with high levels of α-MSH which can increase tyrosinase and dopachrome tautomerase production so that melanogenesis increased and vulnerable to melasma (Ortonne et al, 2009).

Melasma Area Severity Index (MASI) is used to measure the clinical severity quantity of melasma (Kimbrough et al, 1994). In addition to the MASI scheme, a global degree of severity is also required to estimate treatment success in melasma clinical trials. Melasma Severity Score (MSS), used as a worldwide degree, is commonly used in clinical trials research and is expected to be clinically meaningful in describing the severity of disease that is easy to use in clinicians and patients (Rodrigues et al, 2016).

Miranti et al. (2016) reported that serum estradiol levels were slightly higher in pregnant women with melasma than pregnant women without melasma, but this increase in numbers was not significant. That is, serum estradiol levels are associated with the age of pregnant women and gestational age, but not related to MASI score or melasma types. Meanwhile, no literature has examined serum estriol, which produced only during pregnancy against the severity of melasma. The study objective is to compare serum estradiol and estriol levels in degrees of melasma severity in pregnant women.

2 METHOD

This study used cross-sectional observational analysis in Pregnancy Outpatient Clinic, Dermatology and Venereology Outpatients Clinic in dr Saiful Anwar Regional General Hospital Malang and Physiology Laboratory Faculty of Medicine Universitas Brawijaya Malang, East Java, Indonesia. After Hospital Ethics Committee approvement, this study carried out from June to July 2017. Calculation sample was using single population proportion at a precision of 5%, 95% confidence interval and prevalence of melasma in pregnancy 43,5% (r=0,435).[9] This study population was 25 pregnant women with melasma visited Outpatient Clinic. Samples in this research are all population that fulfil the criteria of inclusion and exclusion. Inclusion criteria including pregnant women with melasma aged 15-49 years, pregnant women with melasma that appear during pregnancy either primigravida or multigravida and willing to be the subject of research and signed informed consent. Exclusion criteria for pregnant women with prior history of melasma that appear not during pregnancy, pregnant women using hormonal contraceptives and hormone replacement therapy (estrogen, progesterone or both), pregnant women taking phototoxic drug (antibiotics, NSAIDs, diuretics, retinoids, epidermal growth factor inhibitors, anti-fungal, tranexamic acid, antihistamines and neuroleptics), and Gemelli pregnancy.

The diagnosis of melasma and determination of severity made by anamnesis, physical examination with a typical clinical picture then calculated Melasma Severity Score by converting MASI score into MSS. Melasma Severity Score divided into clear (0-6.9), mild (> 6.9), moderate (>12,4) and severe (>20,2).[11] Measurements made by three consecutive examiners on the same day. Collect 5cc of blood samples in a tube of SST (Serum Separator Tubes) then centrifuge for 10 minutes at 2000-3000 rpm within 20 minutes. After all samples collected, serum estradiol and estriol levels evaluated by ELISA method. After filling the data on the data collection sheets, then the data is processed using the Statistical Package for Social Sciences (SPSS) version 18. Test the normality of population data comparability using Kolmogorov-Smirnov test. The difference analysis serum estradiol and estriol level in each group of MSS using One-Way ANOVA.

3 RESULT

In this study, the samples obtained as many as 25 pregnant women with melasma with the age range 15-49 years. The mean age of the study subjects was 32.50 with a standard deviation of 7.77. The age of majority of subjects with melasma is 31-40 years. Age of pregnancy obtained in the third trimester of 21 people (84%) followed by the second trimester as much as three people (12%) and one person (4%) first trimester of the 25 subjects, the duration of exposure to sunlight less than 6 hours as many as seven people (28%) and as many as 18 people (72%) experienced a duration of exposure to sunlight more than 6 hours a day. Followed by sun exposure time at 09.00 to 15.00 as many as 18 people (72%) and sunlight exposure time is less than 09.00 as many as seven people (28%).

Table 1: Baseline Characteristics.

	Group	Amount (n=25)	Percentage (n=100%)	p
Age	15-20 21-30 31-40 41-49	2 6 13 4	8% 24% 52% 16%	0.489
Gestational age (Trimester)	I II III	1 3 21	4% 12% 84%	0.206
Sunlight exposure duration (Hours)	< 6 > 6	7 18	28% 72%	0.861
Sunlight exposure timing	< 09.00 09.00 – 15.00	7 18	28% 72%	0.861
Genetic	Yes No	13 12	52% 28%	0.925
Co-existing Diasease	None Preecclampsia Hyperemesis gravidarum VSD Asthma Big baby Condylomata acuminata Anemia Hepatitis B	14 4 1 1 1 1 1 1 1	56% 16% 4% 4% 4% 4% 4% 4% 4%	0.399
Melasma type	Epidermal Dermal Mixed	17 3 5	68% 12% 20%	0.701
MSS	Clean Mild Moderate Severe	6 5 9 5	24% 20% 36% 20%	0.632

*p<0.05: significant different using Chi Square

Family history with melasma in 25 subjects found 13 people (52%) with positive family history with melasma, and 12 people (48%) did not get family history with melasma. In 25 subjects, there were other coexisting diseases of 4 persons (16%) followed by hyperemesis gravidarum, congenital heart disease Ventricular Heart Disease, asthma, large infants, condylomata acuminate, anemia and hepatitis B. Of the 25 subjects, the type of melasma epidermal epidermal (17%), dermal type 3 people (12%) and mixed type 5 people (20%). The degree of melasma severity obtained from 25 study subjects was 6 (24%) clear, 5 (20%) mild, 9 (36%) moderate, and 5 (20%) severe. Table 1 shows that age, the age of pregnancy, duration and time of sun-exposure, genetic, co-existing diseases, type of melasma and MSS (Melasma Severity Score) showed no significant difference (p> 0.05).

In Table 2, serum estradiol level in clear group was 417.80 ± 265.02, the mild group was 836.60 ± 390.89, the moderate group was 793.58 ± 189.87, and the severe group was 891.00 ± 194.89. Estriol serum levels obtained on average at the clear group of 94.67 ± 93.12, the mild group of 149.88 ± 109.87, the moderate group of 199.64 ± 46.52, and the severe group of 141.17 ± 98.69. Based on analysis difference from table 2, there was a significant different serum level of estradiol in each group of MSS (p=0.015) and serum levels estriol did not significantly differ in each group degrees of MSS (p=0.454).

Table 2:. Average of Serum Estradiol and Estriol Level in Groups of MSS.

MSS	Estradiol		Estriol	
	Mean	p-value	Mean	p-value
Clear	417.80	*0.015	94.67	0.454
Mild	836.60		149.88	
Moderate	793.58		199.64	
Severe	891.00		141.17	

*p<0.05 : signficant different

4 DISCUSSION

Melasma severity score obtained from the average of 25 subjects of the most moderate study (9 subjects), followed by clear (6 subjects), mild (5 subjects) and included severe (5 subjects). There were a significant different serum estradiol levels but not significantly different serum estriol levels in each MSS group. In melasma pathogenesis, increased estrogen will bind to the estrogen receptor on melanocytes thus stimulating the production of melanin. The increased estrogen will increase the stimulation of melanin production so that it is suspected to affect the severity of melasma. Estrogen levels in pregnant women dominated by forms of estradiol and estriol (Dameveska, 2014).

Estrogen receptor (ER) is a steroid hormone receptor in the cell nucleus. ER has two subtypes namely ERα and ER-β. Estradiol has a high affinity that activates both these receptors potentially. Activation of ER triggers the modulation of transcription and expression of genes in the melanocyte. The biologic effects of estradiol, is considered the most active form of estrogen and has a high potential for melanogenesis, are mediated by estrogen-alpha receptors (ER-α), and estrogen-beta receptors (ER-β) expressed by human skin cells. The physiological function of estriol is still not fully understood. Estriol is short-acting estrogen, meaning it has the lowest affinity for estrogen receptors alpha and beta compared with estradiol and estrone (Thornton, 2002).

Although estriol is an estrogen with the lowest affinity to estrogen receptors compared with estradiol, several theories mention the mechanism of action of estriol and estradiol. According to other literature by Cohen in 1985, said that estriol could compete with estradiol in binding to estrogen receptors in the uterus. This relationship evidenced by the physiological differences in the amount of estradiol and estriol. Also, physiologically estriol production is controlled by estradiol production, but when pregnant estriol production no longer controlled by estradiol evidenced by high estriol counts until the end of pregnancy (Cohen, 1985).

In this study, estradiol was significantly different in each group MSS while estriol was not significant difference may be due to the affinity of estriol bonds with estrogen receptors in melanocytes weaker than the affinity of estradiol bonds with estrogen receptors. The theory of estradiol and estriol work mechanisms according to Cohen can also support the results of research that estradiol has an important role in the severity of melasma. There is yet another study that measures serum estriol levels in pregnant women with melasma so that no data support the results of this study.

Several weaknesses in this study may be due to measurement MSS method is done through the conversion of MASI score measured subjectively depending on the examiner although it minimised by involving three examiners. More research is needed to determine the correlation between serum level estradiol in each group MSS. Also, melasma is a local hyperpigmentation disorder of the facial skin so that research variables may not be able to describe as taken from serum blood circulation. A histopathologic study of melasma skin lesions should be performed.

5 CONCLUSION

In pregnant women with melasma, the serum estradiol level was significantly different in degrees of melasma severity, while estriol did not differ.

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