Research Article

The Salivary Estriol Level was Higher in Preterm Delivery Compared to that in Preterm Pregnancy

Kadar Estriol Saliva pada Persalinan Kurang Bulan lebih Tinggi Dibandingkan dengan Kadarnya pada Kehamilan Kurang Bulan

Erwin Purba, Tita H. Madjid, Adhi Pribadi

Department of Obstetrics and Gynecology
Faculty of Medicine University of Padjadjaran/
Dr. Hasan Sadikin Hospital
Bandung

Abstract

Objective: To know the difference of salivary estriol level between patients with preterm birth and preterm pregnancy of 32-36 weeks and to determine the correlation between the level of estriol in saliva and the incidence of preterm delivery.

Methods: This research was a cross-sectional studies of 80 patients in Dr. Hasan Sadikin Hospital and its networks. The subjects are 40 patients in labor and 40 patients in preterm pregnancy, that met the inclusion criterias during the period September 2011 to November 2011. We took the salivary sample and examine the level of estriol. The data were analyzed by Shapiro-Wilk and Mann Whitney test.

Result: The study found that the difference of salivary estriol levels in preterm labor and preterm pregnancy groups was statistically significant ($p<0.05$). The mean salivary estriol levels in preterm labor group was 3438.75 while the mean value of estriol levels in preterm pregnancy group was 686.10 and ranges of each group is 1188-16338 and 88-1180.

Conclusion: The value of salivary estriol levels were higher in preterm labor compared to the level in preterm pregnancy.

[Indones J Obstet Gynecol 2012; 36-2: 66-70]

Keywords: preterm labor, salivary estriol

Abstrak

***Tujuan**: Untuk mengetahui perbedaan kadar estriol saliva pada persalinan kurang bulan dan kehamilan kurang bulan pada usia 32-36 minggu dan menentukan hubungan kadar antara estriol saliva terhadap kejadian persalinan kurang bulan.*

***Metode**: Penelitian ini merupakan penelitian potong lintang terhadap 80 orang pasien di RS Dr. Hasan Sadikin dan beberapa rumah sakit jejaring, 40 orang pasien dalam masa persalinan dan 40 orang pasien dalam masa kehamilan yang memenuhi kriteria inklusi selama periode September 2011 sampai November 2011. Dilakukan pemeriksaan kadar estriol saliva pada subjek penelitian. Data yang diperoleh dianalisis dengan uji Shapiro-Wilk dan Mann Whitney.*

***Hasil**: Didapatkan perbedaan kadar estriol saliva yang bermakna secara statistik ($p<0,05$) antara kelompok persalinan kurang bulan dan kelompok kehamilan kurang bulan. Rerata kadar estriol saliva pada kelompok persalinan kurang bulan adalah 3438,75 dengan simpang baku 3283,03 sedangkan nilai rerata kadar estriol pada kelompok kehamilan kurang bulan adalah 686,10 dengan simpang baku 279,22 serta rentang masing-masing kelompok adalah 1188-16338 dan 88-1180.*

***Kesimpulan**: Dari hasil penelitian dapat ditarik kesimpulan bahwa kadar estriol saliva pada persalinan kurang bulan lebih tinggi dibandingkan dengan kehamilan kurang bulan.*

[Maj Obstet Ginekol Indones 2012; 36-2: 66-70]

***Kata kunci**: estriol saliva, persalinan kurang bulan*

Correspondence: Erwin Purba, Department of Obstetrics and Gynecology, Faculty of Medicine University of Padjadjaran. Bandung. Telephone : 08127230702, Email : milovan_purba@yahoo.

INTRODUCTION

Preterm delivery is a problem in the field of obstetry and perinatology due to the high incidence of infant morbidity and mortality. Seventy percents of neonatal mortality and morbidity were caused by prematurity, with the mortality rate of 19,000. Prematurity is also as the most important risk factor for neurologic disorder and infant developmental disorder.[1-5]

The incidence rate of preterm delivery is 7-10% (mean, 11%) of overall pregnancy.[3] In the United States, the incidence rate of preterm delivery is 12% and it causes 75% of neonatal death, whereas in the developing countries, the incidence ranges from 5% to 10%.[3,6] In Indonesia, the prematurity incidence ranges from 10 to 20%; while from January 1998 to December 2000, at Dr. Hasan Sadikin Hospital Bandung, it was 8.2% of overall delivery with perinatal death rate by 53.6%.[5-7]

A healthy pregnancy, when reached full term, is a large scale of hyperestrogenic state. The amount of estrogen produced daily by syncythiotrophoblast for the last gestational weeks is equal to that produced by ovaries of at least 1000 ovulatory women in a day. In similar analogic manner, the amount of estrogen produced by placenta within one normal pregnancy is greater than the amount that secreted by ovaries of 200 ovulatory women within the same 40-week period. Such hyperestrogenic state in pregnancy is an increasing condition that is in line with the continuing pregnancy and then halts promptly after labour.[8-10]

The estrogenic pathway in the human placenta is different from that in ovary follicles (granulosa cells) of non-pregnant women. Estrogen is produced in ovary de novo, from acetate or cholesterol. In the human placenta, acetate or cholesterol, even progresteron cannot function as precursor for estrogen biosynthesis. C19-steroid consists of dehydroepiandrosteron, androstenedion, and testosteron are the precursors for estrogen biosynthesis. In the human placenta, estradiol-17 is a product of secretory estrogen. Besides, 16-hydroxyandrostenedion is altered into 16-hydroxyestron, which will be turn into estriol before secreted by trophoblast. Thus, syncitiotrophoblast secretes two type of estrogen, i.e., estradiol-17 and estriol. In non-pregnant women, urine estriol to estron plus estradiol-17 concentration ratio is less than one. This ratio increases up to 10 folds or more by aterm, consequently occurring profound increased and imbalanced in estriol formation during pregnancy. This can be accounted for the metabolic change of estron or estradiol-17 leading to estriol due to pregnancy. Moreover, neither estron nor estradiol-17 are changed into estriol in the placenta.[8,11-12]

Estriol for the first time was detected in the maternal blood at 9th weeks pregnancy and the level continues increasing in plasma during pregnancy. Three to five weeks before delivery, there is a surge of blood estriol level.[4] Subsequently, miometrial estrogen-receptor binding estriol gives rise uterotrophic response that when it continues it will promote the production of prostaglandin from endometrial cells. The salivary estriol level indicates free plasma estriol level. The examination of salivary estriol is easier than that plasma estriol, non-invasive, and more stable during transportation.[13-15]

The early study by Dame et al. indicated that the salivary estriol/progesteron ratio was greater than normal in the pregnant women who suffered preterm spontaneous delivery. It was concluded that idiopathic preterm delivery of the women with intact membrane were preceded by the increased salivary estriol level since 5 weeks before delivery, leading to increased salivary estriol/progesterone ratio.[16-17]

The latter study by an author's team based on Lanchelin's study, suggested for the first time that the salivary estriol level = 2.1 ng/ml after 22-weeks pregnancy was the risk factor for preterm delivery.[18-19] In the study by McGregor et al, involving 956 singleton-gravid mother, the salivary estriol levels were examined weekly. They found that the increased salivary levels were associated with the increased risk for premature delivery. The study concluded that the salivary estriol level that was more than 2.3 ng/ml were a risk factor for premature delivery.[5,19-20]

METHOD

This research was a cross-sectional studies conducted in Dr. Hasan Sadikin Hospital and its networks, including RSKIA (Mother and Child Hospital) Astana Anyar, RSU (General Hospital) Ujungberung, RSUD (Regional Hospital) Garut, RSUD Sumedang and RSU Cibabat, from September to November 2011. During this period, 80 study subjects were recruited, consisting of 40 subjects in the preterm gestation group and 40 subjects in the preterm delivery group that met the inclusion criteria.

The data collected includes maternal age, gestational age, parity, body mass index, and laboratory tests (hemoglobin, hematocrit, leukocyte, and thrombocyte) to exclude the occurence of infection; subsequently, followed with salivary sampling to measure the salivary estriol level at Laboratory Prodia Jakarta. All treatments were applied to all subjects. The data were then analyzed by Shapiro-Wilk and Mann Whitney test.

RESULTS

The characteristics of the subjects which was recorded included maternal age, parity, and body mass index. Table 1 indicates that the mean maternal age in the preterm delivery group was 28.35 (SD:5.84) and the range was between 17-38 years.

As many as 55% of the subjects in this group were in the age group of <24 years. In the preterm gestation group, the mean age was 27.3 (SD:5.29) and the range was between 16-37 years. As many as 67.5% of this population was in the age group of 24-34. Statistically, this differences were insignificant (p=0.402) . The characteristics of the subjects were shown at the following table.

Table 1. The Characteristics of the Subjects by Age, Parity, and Body Mass Index in the Mothers with Preterm Delivery and with Preterm Pregnancy

Characteristics	Group		Significance
	Preterm Delivery	Preterm Pregnancy	
Maternal Age(year)			
< 24	22	11	t=0.842
25-34	12	27	p=0.402
≥ 35	6	2	
$\bar{X}$(±SD)	28.35(5.84)	27.30(5.29)	
Median	29.00	28.50	
Range	17-38	16.37	
Parity			
0	18	8	
1	8	12	
2	7	14	p=0.365
3	3	4	
4	4	2	
Body Mass Index			
< 19.8	2	0	
19-26	10	9	t=2.69
26.01-29.99	3	4	p=0.006
>30	1	3	
$\bar{X}$(±SD)	22.7(2.6)	26.4(4.2)	
Range	19.6-28.1	21.8-37.0	

Note: t=t test, p=p-value

The most common parity history in the preterm delivery group was nulliparity (45%) and that in the preterm pregnancy group was 2 parity (35%). This difference was not statistically significant (p=0.365).

The mean body mass index (BMI) in the preterm delivery group was 22.7 (SD:2.6) and the range was 19.6-28.1. About 62,5% of this population was in the BMI group of 19.9. The mean body mass index in the preterm delivery group was 26.4 (SD:4.2) and the range was 21.8-37.0. About 56.25% of this population was in the BMI group of 19.9-26. Statistically, the difference was siginificant (p=0.006).

Table 2. Comparison of Salivary Estriol Levels between Preterm Delivery and Preterm Pregnancy

Level	Group		Signi-ficance
	Preterm Delivery	Preterm Pregnancy	
Estriol (pg/ml)			
$\bar{X}$(±SD)	3438.75(3283.03)	686.10(279.22)	t=0.000
Range	1188-16338	88-1180	p=0.000

Notes: t=Mann-Whitney test, p=p-value

Table 2 shows the comparison of salivary estriol level in preterm delivery and preterm pregnancy. In the preterm delivery group, the mean level was 3438.75 (SD:3283.03) and the range was 1188-16338. In the preterm pregnancy group, the mean level was 686.10 (SD:279.22) and the range was 88-1180. The table indicates that the mean salivary estriol level in the preterm delivery group was higher compared to that in the preterm pregnancy group. Based on the data, statistical tes indicated that t-value was 0.000 with the p-value was significant (p=0.000), showing that there was a difference of estriol levels between both groups.

Table 3. The Correlation of Age and Parity to Estriol Level in Preterm Delivery

Correlation of Age and Parity to Estriol Level	r_s	p
Between Age and Estriol Level	0.187	0.249
Between Parity and Estriol Level	0.294s	0.115

Notes: r_s=Pearson's correlation coefficient

Table 3 indicates that the comparison between age and estriol level showed a p-value of 0.249 (p>0.05), implying that it was not significant. This means that there was no correlation between age and estriol level in preterm delivery. Meanwhile, the relationship between parity and estriol level showed a p-value of 0.115 (p>0.05), meaning that there was also no significant correlation between parity and estriol level in preterm delivery.

DISCUSSION

In this study, Table 1 indicates that in preterm delivery, the majority of subject was in the age group of less than 24 years; meanwhile, the mean maternal age was 29 years. The too young or too old maternal age was also became a risk factor for preterm delivery. A Sweden study suggested that the

mother's age between 13-17 years during pregnancy increased the risk for preterm delivery for two-fold than that at 20-24 years. Whilst, at 35 years old, the risk for preterm delivery increased two-fold than that in 20-30 years as control age.[21]

According to Creasy, the association between maternal age and preterm delivery was that the younger the preterm delivery was, the greater the possibility for preterm delivery. The mother's age less than 20 years and more than 40 years had a risk for preterm delivery. The age of the mother less than 18 years had a greater risk than that of 20 years old. The incidence of preterm delivery was found considerable in young-age group due to socioeconomic, education, and life-style factors.[4]

From this study results, the majority of parity history in preterm delivery was nulliparity (45%). According to several studies, preterm delivery was more frequent in primipara, and other several studies also suggested that the risk in preterm delivery increased after the fourth pregnancies.

The characteristics of the study subjects by body mass index showed that the mean of body mass index in the preterm delivery group was 22.7 with the range of 19.6-28.1. The majority of subject in preterm delivery had a body mass index between 19.96-26.

Table 1 indicates that the characteristics of subject, i.e., maternal age and parity, statistically showed no significant difference ($p>0.005$). it is concluded that both group were feasible to compare. Meanwhile, in the body mass index, statistical analysis showed a significant difference ($p<0.05$). This can be explained by Cohen et al that there was a significant association between mother's low body weight or body mass index during pregnancy with preterm delivery. Low body weight or BMI and poor nutrition in pregnancy are risk factors for preterm birth.[21-22]

The subjects in this study that met the inclusion criteria had received laboratory examinations to screen the existence of infection of the subjects. From the data in Appendix 7, the subject leukocyte level ranged from 9,100 to 13,900/mm^3; implying that the subjects were not being infected.

The previous study in 1980's concluded that there was a profile of estriol in the saliva during pregnancy. Some groups of author, including McGarrigle and Lachelin, Dame et al, and also Vining et al, indicated that the salivary conjugated/unconjugated estriol levels increased gradually up to the fifth week before delivery; and then increased more profound until the delivery time. By the delivery time, estriol was in an abundant form of free estrogen that elevated by 718% in the last 20-week of pregnancy and by 149% in the last sixth weeks before delivery. These increase were also seen in salivary estriol to progesteron ratio.[23]

In this study, as indicated in Table 2, there was significant different levels of salivary estriol ($p<0.05$) between the preterm delivery group and the preterm pregnancy group. The mean salivary estriol level in preterm delivery was 3438.75 (SD=3283.03), while the mean value of estriol in preterm pregnancy was 686.10 (SD:279.22); and the ranges were 1188-16338 and 88-1180 for each groups, respectively.

Table 3 in this study shows that the association of age to estriol level and of parity to estriol level had p-value of 0.249 and 0.115, respectively. These data implies that there were no correlation of age to estriol level and of parity to estriol level.

From this study, salivary estriol level range in preterm delivery was varied widely, i.e. 1188-16338. This condition indicates that prematurity was actually a multifactorial problem and there was no given factor that can solely cause it. Some factors that can influence the prematurity were parity, pregnancy interval, history of premature delivery, age, marital status, nutrition, body weight gain during pregnancy, pregestational body weight, socioeconomy, and physical fatigue.

Thus, this study's results can strengthen and conform the previous studies' results that the salivary estriol level was higher in preterm delivery compared to that in preterm pregnancy.

CONCLUSION

The mean value of salivary estriol level in preterm delivery was higher than that in preterm pregnancy.

The salivary estriol level can be applied as a predictor for preterm delivery.

REFERENCES

1. Cunningham FG, Gant NF, Leveno KJ, Gillstrap LC, Hauth JC, Wenstrom KT. Williams Obstetrics. 22nd edition. 2006. London: McGraw-Hill.

2. Walkinshaw SA. Preterm labour and delivery of the preterm infant. In: Chamberlain G, Steer P, ed. Turnbull's Obstetrics. 3rd ed. 2002. London: Churchill Livingstone, Elsevier science limited.
3. Goldenberg RL, Rouse DJ. Prevention of premature birth. Med Prog. 1998; 339(5):313-20.
4. Stubblefield PG. Causes and prevention of premature birth: an overview. In: Fuch AR, Fuch F, Stubblefield PG, ed. Preterm birth causes, prevention and management. 2nd ed. 1993. New York McGraw-Hill.
5. Romero R, Chaiworapongsa T. Preterm labor, intrauterine infection and the fetal inflammatory response syndrome. Neo reviews. 2002; 3:73-81.
6. Morton H, Cavanagh AC, Athanasas-Platsis S, Quinn KA. Early pregnancy factor has immunosuppressive and growth factor properties. Reprod Fertil Dev. 1992; 4(4):411.
7. Morton H, Rolfe BE, Cavanagh AC. Pregnancy proteins: basic concepts and clinical applications. Sem Reprod Endocrinol. 1992; 10:72.
8. Hsueh AJW, Peck EJ, Clark JH. Progesterone antagonism of the estrogen receptor and estrogen-induced uterine growth. Nature. 1997; 254:337.
9. Chard T, Grudzinskas JG. Pregnancy protein secretion. Semin Reprod Endocrin. 1992; 10:61.
10. Handwerger S, Brar A. Placental lactogen, placental growth hormone, and decidual prolactin. Sem Reprod Endocrinol. 1992; 10:106.
11. Seppala M, Riittinen L, Kamarainen M. Placental protein 14/ progesterone-associated endometrial protein revisited. Sem Reprod Endocrinol. 1992;10:164.
12. Granner DK. Hormon gonad. In: Murray RK, Granner DK, Mayes PA, Rodwell VW, ed. Biokimia harper. 25th edition. 2003. Jakarta: EGC.
13. Editorial. Low Estrogen Level, Updated: http://www.Luhs.org/health/kbase/htm/nord/844/nord 844.htm (Diunduh 17 Maret, 2011).
14. The role of estrogen, tersedia dari: http://www.Paternity-angel.com/article_zone/hormones/hormon3.htm (Diunduh 17 Maret, 2011).
15. Tucker J, McGuire E. ABC of preterm birth: Epidemiology of preterm birth. BMJ. 2004; 329:675-8.
16. Yeast JD, Lu G. Biochemical markers for the prediction of preterm labor. Obstet Ginecol Clin North Am. 2005; 32:369-81.
17. Leung TN, Chung TK, Madsen G. Elevated midtrimester maternal corticotrophin releasing hormone levels in pregnancies that delivered before 34 weeks. BJOG. 2000; 106:1041-6.
18. Iams JD, Creasy RK. Preterm labour and delivery. In: Creasy RK, Resnik R, Iams JD, ed. Maternal fetal medicine. 5th ed. California: WB Saunders; 2004: 623-30.
19. McGregor JA, Jackson GM, Lachelin GL. Salivary estriol as risks assessment for preterm labor: a prospective tial. Am J Obstet Gynecol. 1995: 173;1337-42.
20. Norwitz ER, Robinson JN, Challis JRG. The control of labor. NEJM. 1999; 341(1):660-6.
21. Warren WB, Patrick SL, Goland RS. Elevated maternal plasma corticotrophin releasing hormone levels in pregnancies complicated by preterm labor. Am J Obstet Gynecol. 1992; 166:1198-204.
22. Horne AW, Stock SJ, King AE. Innate immunity and disorders of female reproductive tract. J Soc Reprod Fer. 2008; 135:739-49.
23. Puchner AM. Investigation of amniotic fluid factors as potential predictors of term and preterm deliveries. Med Inflam Hindawi. 2006; 2006:1-5.