Conference Paper

Increase of PlGF (Placental Growth Factor) Level After Administration of Dydrogesterone in Pregnancy

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Abstract

Aim. To observe the effect of Dydrogesterone administration in pregnancy on PlGF level. **Methods.** This is a randomized controlled clinical trial. Study population has been divided into two groups. Group A consists of 20 women who receive only Folic acid 5 mg a day for 4 weeks time. Group B consists of 20 women who receive Dydrogesterone 2x10 mg a day and Folic acid 5 mg a day for 4 weeks. PlGF has been measured twice. First measurement was done before drug administration, while the second measurement has been done during 18^{th} weeks of pregnancy. The changes on PlGF level before and after treatment from each group has been analyzed using SPSS 17. **Results.** 40 pregnant women have been recruited for this study. There are no differences based on the patient's age, number of pregnancy and parity, gestational age and body weight between each group. The mean levels of PlGF in both groups before intervention shows no significant difference ($p = 0091$ or $p > 0.05$), 40.80 pg/mL vs. 25.95 pg / mL. The mean levels of PlGF in group A after 4 weeks administration of Folic acid is 89.60 pg / mL. It shows the escalation of 48.8 pg / mL. The elevation of PlGF level in group A shows significant difference ($p = 0.000$ or $p < 0.05$) after 4 weeks Folic acid treatment.The mean levels of PlGF in group B after 4 weeks administration of Dydrogesterone and Folic acid is 212.15 pg / mL. It shows the escalation of 186.20 pg / mL. The elevation of PlGF level in group B shows significant difference ($p = 0.000$ or $p < 0.05$) after 4 weeks Dydrogesterone and Folic acid treatment. **Conclusion.** Dydrogesterone treatment can increase the level of PlGF.

Keywords: Dydrogesterone, pregnancy, PlGF

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1. Introduction

The incidence of spontaneous miscarriage occurs more than 80% at less than 12 weeks gestation recently.At least 1 of 6 couples who has successfully conceive is going to have a miscarriage. However 40-50% incidence of miscarriage causes are not yet known. Lately, there is a popular suggestion concerning a possible link between the incidence of miscarriage with maternal immune response to fetal antigen. Maternal immune system response against fetal antigen can occur because fetus and placenta consist of paternal antigens. Progesterone can induce tolerance of maternal immune

system to the fetal paternal antigens. Progestin use during first trimester of pregnancy has widely used either by physicians or midwives. However, routine progestin use in normal pregnant women has never been investigated before. Placental growth Factor (PlGF) is a homodimer glycoprotein that is homologous to Vascular Endothelial growth Factor (VEGF) produced by throphoblastic cells. Therefore, currently PlGF commonly used as an indicator on placental development and can also being used as predictor on obstetric complications related to placental disorders such as preeclampsia and inter-auterine growh retardation (IUGR). This study is trying to observe the increasing of PlGF (Placental Growth Factor) Level as the measurement of the placental development after administration of dydrogesterone in the pregnancy .

2. Material and Methods

This is a double blind randomized clinical trial (Randomized Controlled Clinical Trial) held at Antenatal Care clinic (ANC) at the General Hospital dr. Zainoel Abidin (RSUZA), Banda Aceh to all pregnant women undergoing first trimester ANC in RSUZA. Study population has been divided into two groups. Group A consists of 20 women who receive only Folic acid 5 mg a day for 4 weeks time. Group B consists of 20 women who receive Dydrogesterone 2x10 mg a day and Folic acid 5 mg a day for 4 weeks. PlGF has been measured twice. First measurement was done before drug administration, while the second measurement has been done during 18^{th} weeks of pregnancy. The research undergone nonprobability sampling by consecutive sampling. Data analysis is done by using bivariate analysis between supplementation didrogesteron and PlGF levels using SPSS 17. Analysis of the data for comparative analytical numerical information unpaired two groups: Group A: the results in the form of PlGF levels in pregnant subjects were given progesterone and Group B: this results in a level of PlGF in pregnant patients given a placebo. If one of these groups there were no normal distribution of data, the statistical tests performed were the Mann-Whitney. If both groups have a normal distribution of the data will lead to the identification variance between groups. If the same variance (p values at variance test > 0.05), the statistical test to be used is the unpaired t test for equal variances. When variants are not the same (p value on the test variant < 0.05), the statistical test used is the unpaired t test for unequal variance. In this study all the data so that the normal distribution of data is followed by a test using unpaired t-test because it has the same variance (p values at variance test > 0.05).

3. Result and Discussion

40 pregnant women were recruited for this study. The mean age between group A and B is 28.60 vs. 27.85, which is not statistically significant (p > 0.05). The mean number of pregnancy between group A and B is 2.35 vs. 2.15, which is not statistically significant (p > 0.05). The mean number of parity between group A and B is 1.35 vs. 1.15, which is not statistically significant (p > 0.05). The mean of gestational age between group A and B is 6.85 vs. 7.25 weeks, which is not statistically significant (p > 0.05). The

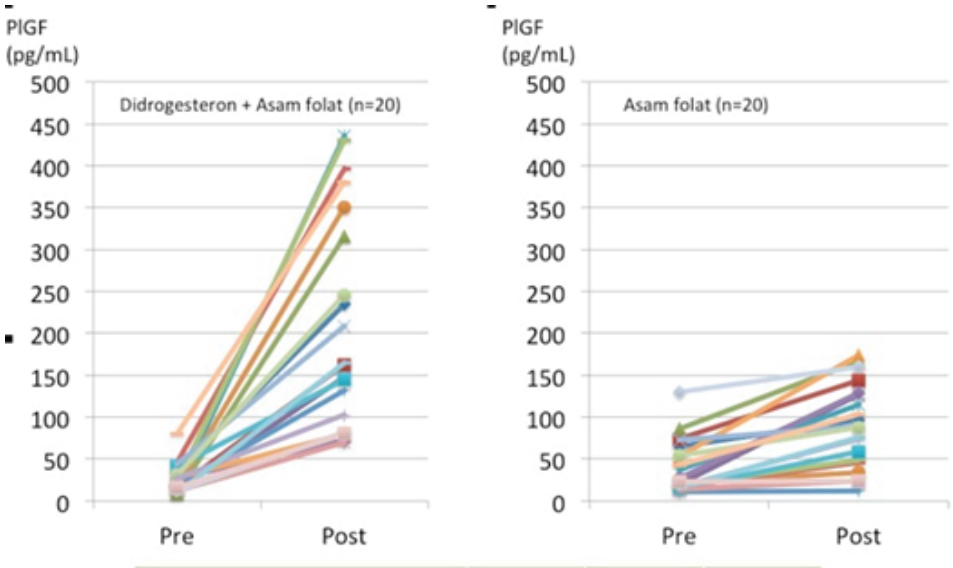

Figure 1: Individual changes on PlGF level between each group before and after treatment.

	Group A	Group B	P Value
The level of increase on PlGF level	186.20	48.80	0.000 (p< 0.05)

Table 1: Data on PlGF level increase after treatment.

mean body weight between group A and B is 58.95 and 56.85 kilogram, which is not statistically significant ($p > 0.05$).

The mean levels of PlGF between each groups before medication shows no significant difference 25.95 vs. 40.80 pg/mL ($p = 0.091$ or $p > 0.05$). The mean levels of PlGF in group A after receiving medication is 212.15 pg/mL, which shows an elevation of 186.20 pg / mL. The results of a paired t test for PlGF levels in group A before and after treatment shows significant difference ($p = 0.000$ or $p < 0.05$). The mean levels of PlGF in group B after receiving medication is 89.60 pg/mL, which shows an elevation of 48.8 pg/mL. The results of a paired t test for PlGF levels in group B before and after treatment shows significant difference ($p = 0.000$ or $p < 0.05$). Group A shows higher increase on PlGF level increase compared to group B after medication (186.20 vs. 48.80 pg/mL), and the difference on PlGF level after being treated between each group shows significant difference ($p = 0.000$ or $p < 0.05$).

4. Conclusion

The administration of Dydrogesterone during first trimester of pregnancy in normal pregnant women can increase PlGF level.

References

[1] W. D. Billington, The immunological problem of pregnancy: 50 Years with the hope of progress. A tribute to Peter Medawar, *Journal of Reproductive Immunology*, **60**, no. 1, 1–11, (2003).

[2] F. G. Cunningham, et al., Williams Obstetrics. 23 ed., Mc. Graw Hill, New York, p. 47-72, 2010.

[3] R. Druckmann and M.-A. Druckmann, Progesterone and the immunology of pregnancy, *Journal of Steroid Biochemistry and Molecular Biology*, **97**, no. 5, 389–396, (2005).

[4] J. Espinoza, R. Romero, J. K. Nien, R. Gomez, J. P. Kusanovic, L. F. Gonçalves, L. Medina, S. Edwin, S. Hassan, M. Carstens, and R. Gonzalez, Identification of patients at risk for early onset and/or severe preeclampsia with the use of uterine artery Doppler velocimetry and placental growth factor, *American Journal of Obstetrics and Gynecology*, **196**, no. 4, 326–e13, (2007).

[5] J. S. Hunt, D. K. Langat, R. H. McIntire, and P. J. Morales, The role of HLA-G in human pregnancy, *Reproductive Biology and Endocrinology*, **4**, no. 1, article no. S10, (2006).

[6] R. W. Kelly, Pregnancy maintenance and parturition: The role of prostaglandin in manipulating the immune and inflammatory response, *Endocrine Reviews*, **15**, no. 5, 684–706, (1994).

[7] G. E. Lash, K. Naruse, B. A. Innes, S. C. Robson, R. F. Searle, and J. N. Bulmer, Secretion of Angiogenic Growth Factors by Villous Cytotrophoblast and Extravillous Trophoblast in Early Human Pregnancy, *Placenta*, **31**, no. 6, 545–548, (2010).

[8] YS. Lin and CH. Liu, Prediction of early pregnancy outcomes, *Int J Gynaecol Obstet. Oct*, **51**, no. 1, p. 33, (1995).

[9] D. R. Mishell Jr., D. Shoupe, P. F. Brenner, M. Lacarra, J. Horenstein, P. Lahteenmaki, and I. M. Spitz, Termination of early gestation with the anti-progestin steroid RU 486: Medium versus low dose, *Contraception*, **35**, no. 4, 307–321, (1987).

[10] E. R. Norwitz, D. J. Schust, and S. J. Fisher, Implantation and the survival of early pregnancy, *New England Journal of Medicine*, **345**, no. 19, 1400–1408, (2001).

[11] H. Pearson, Immunity's pregnant pause, *Nature*, **420**, no. 6913, 265–266, (2002).

[12] N. S. Qureshi, Treatment options for threatened miscarriage, *Maturitas*, **65**, no. 1, S35–S41, (2009).

[13] D. P. Robinson and S. L. Klein, Pregnancy and pregnancy-associated hormones alter immune responses and disease pathogenesis, *Hormones and Behavior*, **62**, no. 3, 263–271, (2012).

[14] K. Sumapraja, Dasar-dasar Imunologi Dalam Bidang Kebidanan, in *Ilmu Kebidanan Sarwono Prawirohardjo., , PT Bina Pustaka Sarwono Prawirohardjo*, AB. Saifuddin, Ed., 97–111, Jakarta, 4 edition, 2010.

[15] O. Thellin, B. Coumans, W. Zorzi, A. Igout, and E. Heinen, Tolerance to the foeto-placental 'graft': Ten ways to support a child for nine months, *Current Opinion in Immunology*, **12**, no. 6, 731–737, (2000).

[16] J. C. Ullery, J. C. DeNeef, and J. H. Holzaepfel, Dydrogesterone therapy: Clinical observations and laboratory findings in 61 patients, *Obstetrics and Gynecology*, **22**, no. 1, 38–45, (1963).

[17] B. M. Polliotti, A. G. Fry, D. N. Saller Jr., R. A. Mooney, C. Cox, and R. K. Miller, Second-trimester maternal serum placental growth factor and vascular endothelial growth factor for predicting severe, early-onset preeclampsia, *Obstetrics and Gynecology*, **101**, no. 6, 1266–1274, (2003).

[18] A. E. Schindler, Progestational effects of dydrogesterone in vitro, in vivo and on the human endometrium, *Maturitas*, **65**, no. 1, S3–S11, (2009).