A Study of the Role of Vaso-Active Prostaglandins (PGI_2 and TXA_2)in Pathophysiological Changes in Pre-Eclampsia

Malee Juengjaroen PhD,*
Athiwat Thaworn Cert in MST,+
Sirikul Chotewuttakorn MSc.+

*Department of Microbiology, Faculty of Science,
+Department of Pharmacology, Faculty of Medicine Siriraj Hospital,
Mahidol University, Bangkok 10700, Thailand

Abstract : *The plasma levels of 6-keto-$PGF_{1\alpha}$ and TXB_2 were assessed by RIA in 7 severe and 19 mild pre-eclampsia (PE). These levels were compared with the levels in 9 normal pregnancies (NP) , both antepartum and postpartum. It was found that the levels of 6-keto-$PGF_{1\alpha}$, TXB_2 in mild and severe pre-eclampsia were 578.9 ± 26.9, 43.3 ± 16.5 and 517.6 ± 76.6, 26.8 ± 5.0 pg/ml while in normal pregnancy were only 458.4 ± 36.8, 18.6 ± 2.2 pg/ml respectively. However, they did not show any significant difference. (Thai J Obstet Gynaecol 1993;5: 63-66.)*

Key words : prostaglandins, pathophysiological changes, pre-eclampsia

Pre-eclampsia (PE) is an obstetric complication of unclarified aetiopathogenesis. It could be considered as a disorder of platelet and vessel wall interaction during pregnancy. Platelet activation and the imbalance of prostacyclin (PGI_2) and thromboxane (TXA_2) in maternal circulation have been suggested as the important roles in this pathology[1,2]. There is evidence not only for deficient PGI_2 production but also exaggerated TXA_2 synthesis in PE[3,4]. Since PGI_2 promotes vasodilatation and opposes platelet aggregation and adhesion while TXA_2 induces vasoconstriction and enhances platelet aggregation and adhesion to the vascular wall, the combined actions of TXA_2, if unopposed, will lead to maternal hypertension, increased platelet aggregation and decreased utero-placental blood flow which are commonly found in pre-eclamptic patients. Moreover, There is evidence indicating that anti-platelet therapy may protect against PE[5-7]. The roles of platelets and these 2 prostaglandins are, therefore, more reliable. It is worthwhile to study the activity of platelets as well as the plasma levels of PGI_2 and TXA_2 in parallel. However, both PGI_2 and TXA_2 are labile substances. Their stable metabolites, i.e. 6-keto-$PGF_{1\alpha}$ and TXB_2 were studied instead. Platelet aggregation

and plasma levels of 6-keto-$PGF_{1\alpha}$ and TXB_2 in pre-eclamptic patients were then studied and compared with normal pregnant subjects. The results of the platelet study are presented in a separate paper[8], but are also discussed in this paper.

Materials and Methods

Pre-eclamptic patients and normal pregnant subjects were screened by an obstetrician from admitted patients and the antenatal care unit (ANC) of Siriraj Hospital. Two kinds of PE, mild and severe PE, were defined by the development of diastolic blood pressure between 90-100 mmHg with edema and/or proteinuria 1^+ -2^+ and more than 100 mmHg with edema and proteinuria 2^+ or more, respectively during the third trimester of pregnancy. Normal pregnancy was normotensive pregnant subjects with the same compatible age and gestational age as the pre-eclamptic groups. None of the subjects had NSAIDs or were taking any drugs known to effect prostaglandins synthesis for at least 2 weeks before the study. They also should not have any history of hypertension, any suspected renal disease or diabetes mellitus.

Plasma levels of 6-keto-$PGF_{1\alpha}$ and TXB_2 of these subjects were assessed by [^{125}I] 6-keto-$PGF_{1\alpha}$ and [^{125}I] TXB_2 assay system (RIA) after these plasma was extracted by Sep-pak C_{18} cartridge[9]. Extracted plasma could be kept at -20°C until used if RIA process had not yet been performed.

Kruskal-Wallis or Wilcoxon Matched-Pair Signed Rank test were employed to test the difference of variable among/or within subject groups.

Results

Thirty-five subjects were recruited in this study. They were 9 NP, 19 mild and 7 severe PE. Their clinical characteristics are shown in Table 1.

Plasma levels of 6-keto-$PGF_{1\alpha}$ and TXB_2 of NP, mild and severe PE, are shown in Table 2. These levels of each metabolite were not significantly different among the 3 groups of subjects and also were not significantly changed after delivery although the levels of 6-keto-$PGF_{1\alpha}$ and TXB_2 were found slightly higher in mild and severe PE than in NP.

Discussion

The balance between PGI_2/TXA_2 is believed to be important in the control of the hemodynamic changes of pregnancy[1,10]. The imbalance of this ratio in favour of TXA_2 is also thought to be the cause of vasoconstriction of small arteries, activation of platelets and uteroplacental insufficieney in PE as well.[4,11] However, there is still controversy on this point. Our study is also in disagreement with this because the result of this study showed no significant difference in the levels of 6-keto-

Table 1 Characteristics of studied groups

Characteristics	NP	Mild PE	Severe PE
No. of subjects	9	19	7
Age (yrs)	20 ± 3	24 ± 7	26 ± 6
Gestational age (wks)	29 ± 3	36 ± 2	38 ± 3
Blood pressure:			
Systolic (mmHg)	112 ± 10	136 ± 17	156 ± 11
Diastolic (mmHg)	72 ± 8	91 ± 12	107 ± 8
Proteinuria (No.of positive subjects)	-	4	7
Edema (No.of positive subjects)	-	19	7
Parity:			
Nulliparous	8	13	4
Multiparous	1	6	3
Birth weight (kgs)	3281 ± 323	2601 ± 772	1977 ± 789

Table 2 Plasma levels of TXB_2 and 6-keto-$PGE_{1\alpha}$ in NP, mild and severe PE

	TXB_2 ($\bar{x}$ ± SE pg/ml)	6-keto-$PGF_{1\alpha}$ ($\bar{x}$ ± SE pg/ml)
Normal pregnancy	n = 9	n = 9
Antepartum	18.6 ± 2.2	458.4 ± 36.8
Postpartum	18.9 ± 2.4	474.6 ± 62.8
Mild PE	n = 16	n = 19
Antepartum	43.3 ± 16.5	578.9 ± 26.9
Postpartum	43.7 ± 9.8	560.6 ± 31.5
Severe PE	n = 6	n = 7
Antepartum	26.8 ± 5.0	517.6 ± 76.6
Postpartum	25.6 ± 3.9	537.8 ± 48.6

$PGF_{1\alpha}$ and TXB_2 between NP and the 2 groups of PE. Moreover, the plasma levels of these 2 metabolites in all 3 groups were not significantly changed after delivery even though it was found in the previous study on platelet that maximum aggregation of platelets in NP was significantly decreased after delivery[8,12]. Therefore, it seemed that TXA_2 which was proposed to be the important factor involving platelet activation during pregnancy may not be considered. However, in this study PGI_2/TXA_2 was still regarded as being an important factor in PE because their plasma levels of TXB_2 were noticeably higher than plasma levels of TXB_2 in NP but it did not show statistically significant difference which may be due to the

small number of subjects.

Based on our result, the use of anti-platelet durgs which have a primary mode of action such as a cyclo-oxygenase inhibitor i.e. acetylsalicylic acid, in preventing PE seemed not to be very impressive. Further studies on pathogenesis of this disorder as well as other anti-platelet durgs which have other mechanisms of action are still very much needed to establish the prevention and management of PE.

Conclusion

During pregnancy, plasma levels of 6-keto-$PGF_{1\alpha}$ and TXB_2 were higher in pre-eclamptic groups than in the normal group but not significantly different. After delivery, plasma levels of 6-keto-$PGF_{1\alpha}$ and TXB_2 were also insignificantly changed.

References

1. Friedman SA. Pre-celampsia: a review of the role of prostaglandins. Obstet Gynecol 1988; 71: 122-37.
2. Lindheimer MD, Katz AI. Pre-eclampsia: pathophysiology, diagnosis and management. Ann Rev Med 1989; 40: 233-50.
3. FitzGerald DJ, Rocki W, Murray R, Mayo G, FitzGerald GA. Thromboxane A_2 synthesis in pregnancy-induced hypertension. Lancet 1990; 335: 751-4.
4. Walsh SW. Low-dose aspirin: treatment for the imbalance of increased thromboxane and decreased prostacyclin in pre-eclampsia. Am J Perinatol 1989; 6: 124-32.
5. Schiff E, Peleg E, Goldenberg M, et al. The use of aspirin to prevent pregnancy-induced hypertension and lower the ratio of thromboxane A_2 to prostacyclin in relatively high risk pregnancies. N Engl J Med 1989; 321: 351-6.
6. McParland P, Pearce JM, Chamberlain GVP. Doppler ultrasound and aspirin in recognition and prevention of pregnancy-induced hypertension. Lancet 1990; 335: 1552-5.
7. Walsh SW. Physiology of low-dose aspirin therapy for the prevention of pre-eclampsia. Semin Perinatol 1990; 14: 152-70.
8. Ketsa-ard K, Chotewuttakorn S, Thaworn A, Anumanrajadhon Y. A study of the role of platelets and fibrinolytic activity in pathophysiological changes in pre-eclampsia. Thai J Obstet Gynaecol 1993; 5: 57-62.
9. Juengjaroen M. Determination of thromboxane B_2 in plasma. In: Visudhiphan S, ed. A laboratory manual of hemostasis. Bangkok: Ruen Daew Press, 1992.
10. Ylikorkala O, Makila UM. Prostacyclin and thromboxane in gynecology and obstetrics. Am J Obstet Gyecol 1985; 152: 318-29.
11. Wang YP, Walsh SW, Guo JD, Zhang JY. The imbalance between thromboxane and prostacyclin in pre-eclampsia is associated with an imbalanec between lipid peroxides and vitamin E in maternal blood. Am J Obstet Gynecol 1991; 165: 695-700.
12. Norris LA, Sheppard BL, Bonnar J. Increased whole blood platelet aggregation in normal pregnancy can be prevented in vitro by aspirin and dazmegrel (UK 38485). Br J Obstet Gynaecol 1992; 99: 253-7.