

T Helper 1/T Helper 2 Cell Immunity in Preeclamptic Twin Pregnancy

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Abstract

Preeclampsia has been classified into two types on the basis of the T helper (Th)1/Th2 balance: Th1-predominant type and Th2 predominant type. In this study, we examined the Th1/Th2 ratio in peripheral Th cells in 11 patients with preeclamptic twin pregnancies, 11 normal (nonpreeclamptic) twin pregnancies, 11 preeclamptic singleton pregnancies, and 11 normal singleton pregnancies. The average Th1/Th2 ratio in the patients with preeclamptic twin pregnancy was 8.3 ± 3.4 (mean \pm SD), which was similar to those in patients with normal singleton and twin pregnancies and significant lower than that in patients with preeclamptic singleton pregnancies ($p = 0.003$). The present results suggest that the mechanisms of preeclampsia differ between singleton and twin pregnancies.

(J Nippon Med Sch 2007; 74: 434–436)

Key words: twin pregnancy, T helper cell, preeclampsia

An immune disorder has been implicated in the development of preeclampsia (gestational hypertension with proteinuria). Recent studies have suggested that in women with normal pregnancies, cytokines produced by T helper (Th)2 cells predominate over those produced by Th1 cells, protecting the fetus and placenta from rejection, whereas Th1 cells predominate in women with preeclampsia^{1,2}. The predominance of Th1 cells is closely related to inflammation, endothelial dysfunction, and poor placentation in preeclampsia. Thus, a bias toward a Th1 response is believed to be harmful for fetal survival, whereas a Th2 response is beneficial.

In this study, we examined the Th1 and Th2 percentages and the Th1/Th2 ratio in peripheral Th cells in 11 patients with preeclamptic dichorionic twin pregnancies, 11 normal (nonpreeclamptic) dichorionic twin pregnancies, 11 preeclamptic

singleton pregnancies, and 11 normal singleton pregnancies with methods reported previously^{3,4}. Patients gave oral informed consent for all examinations.

Flow-cytometric determination of interferon (IFN) γ and interleukin (IL) 4 in the cytoplasm of peripheral CD4⁺ T cells was performed with the FastImmune™ Cytokine Detection System (BD Biosciences Immunocytometry Systems, San Jose, CA, USA)⁴. The typical forward and side-scatter gates for lymphocytes together with CD4⁺ gate (logical gate) were set to exclude contaminating monocytes from the analysis. Fifty thousand cells were acquired in the list mode and analyzed with CELL Quest software (BD Biosciences Immunocytometry Systems). The percentage of cells positive for IFN- γ and IL-4 (%IFN- γ and %IL-4) were counted with a fluorescence-activated cell sorter (BD Biosciences Immunocytometry Systems). In this

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Table 1 Description of patients, Th1 and Th2 percentages, and Th1/Th2 ratio in peripheral Th cells

	Singleton pregnancy		Twin pregnancy	
	(-)	(+)	(-)	(+)
Preeclampsia number of cases	11	11	11	11
Maternal age (y)	27 ± 5	29 ± 5	29 ± 4	31 ± 6
Parity	0	0	0	0
Gestational age at study (weeks)	30 ± 2	30 ± 3	28 ± 3	30 ± 3
Systolic blood pressure (mmHg)	—	149 ± 9	—	146 ± 7
Diastolic blood pressure (mmHg)	—	91 ± 10	—	89 ± 9
Proteinuria ≥ 300 mg/dL	—	3	—	2
Th1 (%)	16.7 ± 5.0 *	22.1 ± 5.8	13.0 ± 4.2 *	16.4 ± 5.4 *
Th2 (%)	2.2 ± 0.6	2.0 ± 0.5	2.4 ± 0.4	2.1 ± 0.6
Th1/Th2 ratio	7.8 ± 2.4 *	11.6 ± 2.8	6.4 ± 2.9 *	8.3 ± 3.4 *

* $P < 0.05$ compared with preeclamptic singleton pregnancy.

study, CD4⁺ Th cell subsets were classified as Th1 (IFN- γ positive, but IL-4 negative) or Th2 (IL-4 positive, but IFN- γ negative), and the Th1: Th2 cell ratio was defined as the ratio of %IFN- γ to %IL-4 (IFN- γ : IL-4).

Data are presented as mean \pm SD. Statistical differences among subjects were evaluated with the Mann-Whitney U test, and differences with p values < 0.05 were considered significant.

As shown in **Table 1**, the average Th1/Th2 ratio in patients with preeclamptic twin pregnancies was 8.3 ± 3.4 , which was similar to that in patients with normal singleton pregnancies or twin pregnancies but was significantly lower than that in patients with preeclamptic singleton pregnancies ($p = 0.003$).

Preeclampsia has been classified into two types on the basis of the Th1/Th2 balance: a Th1-predominant type and a Th2-predominant type¹². Th1-predominant immunity, which is observed in preeclamptic singleton pregnancy, is closely related to poor perinatal outcomes¹. In 2006, Luo et al⁵ observed that gestational hypertension has a much more benign effect on neonatal outcomes in twin pregnancies than in singleton pregnancies. Although maternal-fetal systemic immune interactions are mediated by T cells and by natural killer cells¹⁶, we hypothesize that the Th1/Th2 cell immunity with a shift to Th2-predominant immunity is an important factor in successful neonatal outcomes in preeclamptic twin pregnancies.

The causes of the difference in Th1/Th2 balance

between preeclamptic singleton pregnancies and twin pregnancies are not clear. However, some possible mechanisms leading to these consequences can be proposed. First, the changes in Th1/Th2 cytokine balance in normal pregnancy have been suggested to be mediated by changes in steroids, such as estrogen, which is a potent inhibitor of Th1 cytokine production⁷⁻⁹. In 2002, we observed that maternal 24-hour urine estriol levels in twin pregnancies are higher than those in singleton pregnancies³. In the present study, unfortunately, we did not measure maternal estrogen levels. However, steroids such as estrogen may play important roles in the decrease in Th1 cytokine production in preeclamptic twin pregnancies. Second, we have suggested that elevated adenosine levels inhibit the activation of Th1 cells and regulate Th1/Th2 immunity during normal (twin) pregnancies¹⁰. In 2002, we also observed that changes in plasma adenosine levels differ between preeclamptic singleton pregnancies and twin pregnancies¹¹. Thus, a further study may be needed to examine the role of adenosine in the difference in neonatal outcomes of preeclampsia between singleton pregnancies and twin pregnancies.

In conclusion, the present results suggest that the mechanisms of preeclampsia differ between singleton pregnancies and twin pregnancies.

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(Received, August 10, 2007)

(Accepted, September 18, 2007)