CHAPTER I

INTRODUCTION

1.1 Background

Recurrent Pregnancy Loss (RPL), also referred to as recurrent miscarriage, is defined as two or more consecutive pregnancy losses prior to 20 weeks from the last menstrual period, it affects approximately 1% to 2% of women. [1,2] The incidence of RPL approximately 1 in 300 pregnancies.[2] One of the factor that may related to pregnancy loss is trombophilia. The mechanism thought that early fetal loss occurs as a result of damage to chronic vessels, reduced trophoblast invasiveness or apoptosis. Impaired uteroplacental circulation due to thrombosis on maternal side of the placenta may explain late fetal loss.[3] One example of hereditary trombophilic elements is methilentetrahydrofolate reductase (*MTHFR*) gene.[4]

MTHFR enzyme plays role in homocystein metabolism by catalyzing the conversion of 5,10 methylenetetrahydrofolate to 5 methylentetrahydrofolat, the methyl group donor in B12 dependent remethylation of homocystein to methionine. Polymorphism of *MTHFR* gene (677 C->T) is the most common polymorphism which can reduced enzyme activity.[5]

A significant association between *MTHFR* gene polymorphism with RPL has been confirmed by some studies. Nelen et all found there was a significant OR (x2) of 3.3 (95% Cl 1.3-10.1) in women with REPL comparing the prevalence of the homozygous genotype versus the other two genotype which is mean that

homozygosity for the 677 C-T mutation in *MTHFR* gene is associated with a two to three fold risk of REPL.[6] Whereas other deprived of this association.[7,8] Since data related to trombophilia due to *MTHFR* C677T gene polymorphism to RPL among Indonesian women are relatively lacking, we proposed this study to determine this association.

1.2 Research Question

1.2.1 General Research Question

How are the presence and gene distribution of *MTHFR* C677T gene polymorphism in Indonesian women with RPL?

1.2.2 Research question in detail

1. How is genotype distribution of *MTHFR* C677T gene polymorphism in Indonesian women with RPL?
2. How is allele distribution of *MTHFR* C677T gene polymorphism in Indonesian women with RPL?

1.3 Research objectives

1.3.1 General objective

To search for the presence and gene distribution of *MTHFR* C677T gene polymorphism in Indonesian women with RPL.

1.3.2 Specific objectives

1. To identify genotype distribution of *MTHFR* C677T gene polymorphism in Indonesian women with RPL.

2. To identify allele distribution of *MTHFR* C677T gene polymorphism in Indonesian women with RPL.

1.4 Research advantages

1. To know the underlying of RPL related to genetic defect, in order to search for *MTHFR* C677T gene polymorphism in Indonesian women with RPL.
2. To encourage public awareness of genetic diseases, especially for the women with RPL in Indonesia.
3. To give more attentions about the importance of genetic counseling related to folic acid supplementation therapy and correlation with RPL especially for the women who still want to have pregnancy, also for Indonesian society.

1.5 Research originality

This is the first study to identify *MTHFR* C677T Polymorphism in RPL patients. The characteristic of this study compare to others are that the study only identify one polymorphism which is *MTHFR* C677T polymorphism, and secondly the study will be conducted to the RPL patients in Indonesia.

Table 1. Research originality

No.	Author	Title of Publication	Method	Result
1.	Tehrani MJ, Torabi R, Zarnani A H, et all (2011, American Journal of Reproductive Imunology)	Analysis of Plasminogen activator Inhibitor-1, Integrin Beta3, Beta Fibrinogen, and Methylenetetrahydrofolate Reductase Polymorphisms in Iranian Women with RPL	PCR-RFLP to assess the frequency of 5 candidate genetic risk factor for RPL, case and control groups	*MTHFR* 677 C/T and 1298 A/C polymorphism were found to be positively associated with RPL. The presence of both mutations of *MTHFR*

				genes highly increased the risk of RPL.
2.	Settin A, Elshazli R, Salama A, Elbaz R (2011, Genetic Testing and Molecular Biomarkers)	Methylenetetrahydofolate Reductase Gene Polymorphisms in Egyptian Women with Unexplained RPL	Detection of *MTHFR* C677T and A1298C polymorphisms was done by PCR-RFLP	Unexplained pregnancy loss showed higher frequency of the homozygous mutant MTHFR 677 TT, 1298 CC genotypes and the mutant haplotype 677T/1298C, although not reaching statistical

				significance
3.	Nelen WLDM, Steegers EAP, Eskes TKAB, Blom HJ (The Lancet, 1997)	Genetic risk factor for unexplained recurrent early pregnancy loss	All participant were screened for the 677 C-T mutation by PCR and RFLP with HinF1	There was significant OR (x_2) of 3.3 (95% CI 1.3 – 10.1) in the women with recurrent unexplained pregnancy loss comparing the prevalence of the homozygous genotype versus the other two genotype.