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**RESEARCH**

## Differences of Acid Levels of Folate Serums With Spontant Abortus With Normal Pregnancy

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**Abstract**

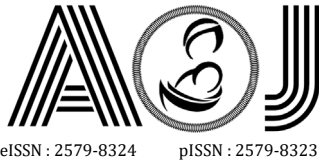
Abortion is the termination of pregnancy before fetus can survive in the outside world, regardless of the cause. One cause of spontaneous abortion due to maternal nutritional factors, such as folic acid deficiency, lead to disruption of cell function and ends with apoptosis as well as continuing with fetal death. The study was conducted to determine differences in the levels of folic acid serum between patients with normal pregnancy and spontaneous abortion in some hospitals in West Sumatra. The study was conducted by the method of analytic observational comparative cross-sectional design. This research was carried out on pregnant women who come to the clinic and emergency obstetric Dr.M.Djamil hospital Padang, Batusangkar Hospital, Reksodiwiryo Hospital Padang and examinations conducted in biomedical laboratory medical faculty Andalas University the period August-December 2014. The total number of women included in the statistical calculation after the inclusion and exclusion criteria are met is 54 people, statistical analysis was done afterwards. The mean levels of serum folic acid is lower in spontaneous abortion patients compared with average levels of folic acid in normal. Results of statistical analysis using t-test found significant differences in the mean serum levels of folic acid group of spontaneous abortion patients with normal pregnancy group, it can be seen from p-value 0.001 ( $p < 0.05$ ).

**Keywords:** Spontaneous abortion, folic acid, fetus death

**INTRODUCTION**

Abortion is the end of pregnancy before the fetus can live in the outside world, without questioning the cause. A new baby may live in the outside world if the weight has reached more than 500 grams or the gestational age is more than 20 weeks. Abortion can be divided into two groups, namely spontaneous abortion and provoke abortion. Spontaneous abortions are abortions that occur without mechanical action and are caused by natural factors. Provokatus abortion is an abortion that occurs as a result of an act or deliberate, either by using drugs or tools.<sup>1,2</sup>

Spontaneous abortion in Indonesia is estimated to be around 10-15% of 6 million pregnancies every year or around 600-900 thousand, while artificial abortion is around 750,000-1.5 million per year. In the United States spontaneous abortion, which is estimated to be 10-15% of pregnancies, increases the incidence to 50% when biochemical examination of hCG in blood is 7-10 days after conception are taken into account.<sup>3</sup> The risk of abortion



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decreases with increasing gestational age and decreases dramatically after 8 weeks' gestation.<sup>2</sup>

Pregnancy is a period of rapid cell growth and differentiation, both for mother and fetus. Therefore, it is a time when both are very vulnerable to changes in food intake, especially nutrients that are below normal limits. Nutritional mismatches cause not only an increased risk of death in utero, but also changes in birth weight and changes in neonatal organs. This change has a big effect. Among them, folic acid is very important for fetal development. Once absorbed, folic acid as a cofactor for cellular reactions includes the transfer of a single carbon unit. Folic acid is needed for cell division because of its role in DNA synthesis. Folic acid is a substrate for various reactions that affect the metabolism of several amino acids, including the transmethylation and transsulfuration pathways. In addition, associations between maternal folic acid concentrations and pathological changes in the placenta have been reported such as placental abruption, placental infarction and spontaneous abortion. This is because during pregnancy, increasing folate intake is needed for the speed of cell proliferation and growth of uterine and placental tissue, fetal growth and expansion of maternal blood volume. The need for folic acid is 5-10 times higher in pregnant women compared to non-pregnant women, so pregnant women may be at risk of folate deficiency.<sup>4,5</sup>

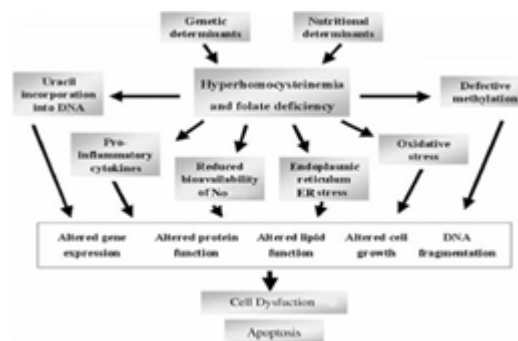
As for the influence of folate and homocysteine metabolism on human reproduction as follows, first, it has been shown that homocysteine induces vascular inflammation by encouraging the expression of proinflammatory cytokines, such as monocyte chemoattractant protein 1 (MCP-1), which regulates the migration and activation of monocytes / macrophages, and interleukin 8 (IL-8), which is an important chemoattractant for neutrophils and T. lymphocytes

Second, homocysteine decreases the bioavailability of nitric oxide (NO), one of the endothelial-dependent vasodilators produced by endothelial isoforms of nitric oxide synthase (eNOS). This effect is caused either by accelerating oxidative inactivity of NO and / or eNOS or by increasing serum asymmetric dimethylarginine, an endogenous inhibitor of eNOS. Third, there is ample evidence that hyperhomocysteinemia is associated with the production of reactive oxygen species (ROS) in endothelial cells and smooth muscle. This oxidative stress mechanism depends either on the auto-oxidation of the highly reactive homocysteine thiol group or on the formation of intracellular superoxide and peroxy radicals together with inhibition of cellular antioxidant enzymes, such as superoxide dismutase and glutathione peroxidase.

Stress ER induces the expression of several chaperone molecules and proteins that respond to other stresses, which aim at correct folding protein repair or retranslocation of defective proteins back to the cytosol to be degraded on proteasomes. In cases of prolonged ER stress, UPR extends to the activation of apoptosis by various signaling pathways. This is

what happens to human endothelial cells after exposure to homocysteine in vitro: While inducing misfolding in ER by changing local redox potential and interfering with disulfide bond formation, homocysteine activates UPR and, after that, retained growth and apoptosis.

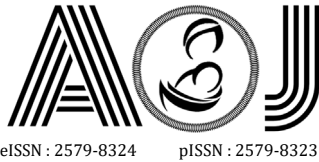
Homocysteine-induced endothelial apoptosis may also involve other mechanisms such as the classic p53 pathway. Furthermore, folic acid deficiency and genetically determined low MTHFR activity causes inadequate remetilation of homocysteine to methionine and decreased SAM production and SAM / SAH ratio. Inadequate SAM will cause disruption of the methylation reaction, with various consequences, especially to the extent that DNA methylation is linked. In homozygous MTHFR 677 TT patients, the deficit in 5-methylTHF has been associated with hypomethylation of DNA in peripheral blood mononuclear cells. Thus, defective methylation will cause the expression of aberrant genes resulting in abnormal fetal development and malignant disease.



**Figure 1.** Cellular and Molecular Mechanisms of Hyperhomocysteinemia

Finally, deficiency of folate intake and due to lack of cellular synthesis of 5,10-methylene THF, as well as a decrease in MTHFR activity leads to accumulation of dUMP and also excessive incorporation of uracil into DNA, with further repair mechanisms increasing the risk of chromosomal damage. Whether all or some of the pathogenetic mechanisms of endothelial dysfunction are also involved in changes induced by folate deficiency is currently unknown. However, all these mechanisms cause disruption of cell protein function, cell fat function, cell growth, gene expression and DNA fragmentation, causing cell dysfunction and ending in cell death (apoptosis).<sup>6</sup>

The relationship between folic acid levels and the occurrence of abortion was evaluated in a recent study in Sweden. Cases are spontaneous abortion women with 6-12 weeks gestational age and control. Women with low plasma folic acid concentrations ( $\leq 4.9$  nmol / L) are more likely to experience abortion than women with plasma folic acid concentrations between 5.0 and 8.9 nmol / L. The occurrence of abortion did not increase in women with higher plasma folic acid concentrations ( $\geq 14.0$  nmol / L) relative to women with plasma folic acid concentrations between 5.0 and 8.9 nmol / L. So they concluded that folic acid deficiency significantly increased the occurrence of abortion.<sup>7,8,9</sup>



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Pietzrik et al (1992) conducted a case control study of serum folic acid in women with spontaneous abortion in the first trimester (n = 37) or habitual abortion (n=46) compared to controls (n = 11). It was found that serum folic acid concentrations were lower in women with habitual abortion compared to the control group and spontaneous abortion in the first trimester compared to controls. While Neiger et al. (1993) conducted an Uncontrolled study of serum folic acid and spontaneous abortion in women with vaginal bleeding in the first trimester (n = 151). They conclude there is no significant difference in women with spontaneous abortion of high or low serum serum folic acid levels.<sup>4</sup>

**METHOD**

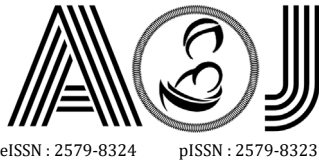
This research was conducted with an observational analytic method with a comparative cross-sectional design. This research was conducted on pregnant women who came to the clinic and obstetric emergency hospital Dr.M.Djamil Padang, Batusangkar Regional Hospital, RST Reksodiwiry Padang and examinations were carried out at the Faculty of Biology FK UNAND Laboratory in the period of August - December 2014. The study was conducted to determine differences in serum folic acid levels in spontaneous abortion patients with normal pregnancy in several hospitals in West Sumatra. The total number of women included in the statistical calculations after the inclusion and exclusion criteria were met was 54 people, divided into 2 groups: 27 in the spontaneous abortion group and 27 in the normal pregnancy group. Statistical analysis to assess the significance using the unpaired t test and chi square on SPSS 18.0 for windows.

**RESULTS****Basic Characteristics of Research Subjects**

The study was conducted from August 2014 to December 2014 with the number of research subjects as many as 54 people. The research subjects who were sampled in the study were divided into 2 groups, 27 patients with spontaneous abortion and 27 patients with normal pregnancy.

**Table 1.** Basic Characteristics of Research Subjects

Characteristics	Group		p-value
	Abortion (mean ± SD)	Normal Pregnancy (mean ± SD)	
Age	30,81 ± 5,82	31,15 ± 5,09	0,824
Parity	2,52 ± 1,40	2,89 ± 1,28	0,315
Gestasional Age	12,44 ± 2,45	14,63 ± 2,90	0,04



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Based on the characteristics of the age of the respondents in Table 1, it was found that the mean age of the spontaneous abortion group was lower than the mean value in the normal pregnant group ( $30 \pm 5.82$ :  $31.15 \pm 5.09$ ). This shows that the age difference in patients with spontaneous abortion is equivalent to a normal pregnancy, this can be seen from the p value of 0.824 ( $p > 0.05$ ).

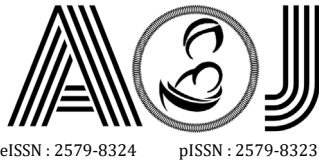
Based on the parity characteristics in Table 1, it was found that the mean age of the spontaneous abortion group was lower than the mean value in the normal pregnant group ( $2.52 \pm 1.40$  :  $2.89 \pm 1.28$ ). This shows that the parity difference in patients with spontaneous abortion is equivalent to normal pregnancy, this can be seen from the p value of 0.315 ( $p > 0.05$ ).

Based on the characteristics of gestational age, the mean value of gestational age in patients with spontaneous abortion was lower than the mean value in the normal pregnant group ( $12.44 \pm 2.45$  :  $14.63 \pm 2.90$ ). This shows that there is a significant difference based on gestational age in patients with spontaneous abortion with normal pregnancies, this can be seen from the p value of 0.04 ( $p < 0.05$ ).

**Table 2.** Characteristics of study sample frequencies

Characteristics	Group				p-value
	Abortion		Normal Pregnancy		
	f	%	f	%	
<b>Education</b>					
Elementary School	1	100	0	0	0,037
Junior High School	2	20	8	80	
Senior High School	14	45,2	17	54,8	
D3	5	83,3	1	16,7	
Bachelor	5	83,3	1	16,7	
<b>History of abortion</b>					
0	23	50	23	50	0,091
1	1	20	4	80	
$\geq 2$	3	100	0	0	

Based on the characteristics of abortion history, it was found that the most abortion history was in the group of abortion patients who had never had a history of abortion, the same as the normal pregnant group who never had a history of abortion, namely 23 people (50%). The results of further statistical analysis, the difference in history of abortion in patients with spontaneous abortion with normal pregnancy did not have a significant difference, this can be seen from the p value of 0.091 ( $p > 0.05$ ).



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## Differences in serum folic acid levels in patients with spontaneous abortion and normal pregnancy

**Table 3.** Differences in serum folic acid levels in patients with spontaneous abortion and normal pregnancy

	Abortion n = 27	Normal Pregnancy n = 27	p-value
Mean	16,97	23,42	0,001
SD	8,34	3,30	
Minimum	0,41	15,36	
Maximum	25,63	29,25	

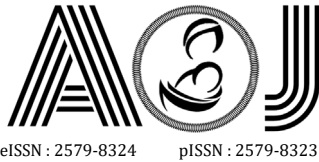
The mean serum level of folic acid in patients with spontaneous abortion was lower, namely 16.97 nmol / L compared to the mean level of folic acid in normal pregnancy, which was 23.42 nmol / L. The results of statistical analysis with t-test showed a significant difference in the mean serum folic acid levels in the group of spontaneous abortion patients with the normal pregnancy group, this can be seen from the p value of 0.001 ( $p < 0.05$ ).

## DISCUSSION

Maternal age and parity are widely observed risk factors. Sullivan et al found an increased risk of spontaneous abortion due to maternal age.<sup>10</sup> Hooge et al. Stated that maternal age over 37 years is significantly associated with the risk of spontaneous abortion. the mean value in the normal pregnant group was  $31.15 \pm 5.09$ . The results of further statistical analysis showed that the age difference between patients with spontaneous abortion and normal pregnancy did not have a significant difference, this can be seen from the p value of 0.824 ( $p > 0.05$ ). Cunningham FG et al stated that the risk of spontaneous abortion increases according to parity, which is related to maternal age.<sup>12</sup> In this study, based on parity characteristics, the mean value of parity in the group of patients with spontaneous abortion was lower, namely  $2.52 \pm 1.40$  compared to the mean value in the normal pregnant group, namely  $2.89 \pm 1.28$ . The results of further statistical analysis, the difference in parity in patients with spontaneous abortion with normal pregnancy did not have a significant difference, this can be seen from the p value of 0.315 ( $p > 0.05$ ).

The risk of abortion decreases with increasing gestational age and decreases dramatically after 8 weeks of gestation. in the normal pregnant group, namely  $14.63 \pm 2.90$ . The results of further statistical analysis showed that the parity difference between patients with spontaneous abortion and normal pregnancy had a significant difference, this can be seen from the p value of 0.04 ( $p < 0.05$ ).

Previous history of spontaneous abortion is a risk factor to consider. Women who have had a previous spontaneous abortion have a higher risk of spontaneous abortion in subsequent pregnancies than those who have never had a spontaneous abortion. The risk of



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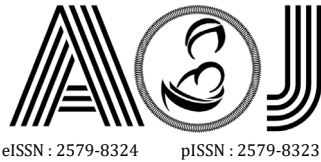
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abortion in women who have experienced abortion once, twice, and 3 times is 11.5-20%, 28-29.4% and 43%. abortion is the same as the normal pregnant group who never had a history of abortion, namely 23 people (50%). The results of further statistical analysis showed that the difference in history of abortion in patients with spontaneous abortion and normal pregnancy did not have a significant difference, this can be seen from the p value of 0.091 ( $p > 0.05$ ). However, in this study, there was one sample of the spontaneous abortion group (attachment 7 order no. 32) obtained folic acid levels of 0.41 nmol / L with a mean value of folic acid levels in the spontaneous abortion group was  $16.97 \pm 8.34$  nmol / L. This is in line with George L's study in 2002, it was found that there was a significant difference between a history of previous spontaneous abortion and the risk of abortion for subsequent pregnancies, this was seen at a p-value of 0.01 ( $p < 0.05$ ). This is in accordance with the literature as for the effect of folic acid deficiency which causes impaired cell protein function, cell fat function, cell growth, gene expression and DNA fragmentation, causing cell dysfunction and ending with cell death (apoptosis).<sup>6</sup>

After the t-test was carried out on the patients with spontaneous abortion and normal pregnancy, it showed that there was a significant difference ( $p < 0.05$ ) in the mean serum folic acid levels in the group of spontaneous abortion patients ( $16.97 \pm 8.34$  nmol / L) with the normal pregnancy group ( $23.42 \pm 3.30$  nmol / L), namely  $p = 0.001$ . Not many studies have compared serum folic acid levels in patients with spontaneous abortion with normal pregnancies. This is consistent with a study by George L et al. In 2002 in Sweden, where women with low plasma folic acid concentrations ( $\leq 4.9$  nmol / L) were more likely to experience abortion than women with plasma folate concentrations between 5.0 and 8.9 nmol / L. . The incidence of abortion was not increased in women with higher plasma folic acid concentrations ( $\geq 14.0$  nmol / L) relative to women with plasma folic acid concentrations between 5.0 and 8.9 nmol / L.9 Although overall serum folic acid levels were This study was higher than serum folic acid levels in the study of George L et al. in both the spontaneous abortion group and in the normal pregnant group, this may be due to differences in daily food consumption habits in the population.

This study is in accordance with the previous study by Pietzrik et al. (1992) conducted a case control study of serum folic acid in women with spontaneous abortion in the first trimester ( $n = 37$ ) or habitual abortion ( $n = 46$ ) compared to controls ( $n = 11$ ). It was found that serum folic acid concentrations were lower in women with habitual abortion compared to the control group and spontaneous abortion in the first trimester compared to controls but in several other studies showed the opposite where there was no significant difference in women with spontaneous abortion against high and low serum levels. Serum folic acid as in the study Neiger et al (1993) conducted a study on serum folic acid and spontaneous abortion in women with vaginal bleeding in the first trimester ( $n = 151$ ) and they concluded there was



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no significant difference in women with spontaneous abortion against high and low levels of serum folic acid.<sup>4</sup>

The strength of this study is the finding of a significant relationship between serum folic acid levels in patients with spontaneous abortion and normal pregnancy. This is consistent with the study by Goerge L et al. In 2002 in Sweden which concluded that low folic acid levels are associated with an increased risk of spontaneous abortion.

The weakness of this study is the absence of chromosomal analysis because 50% of young and early fetuses experience spontaneous abortion, chromosomal abnormalities are the main cause as the most common cause of spontaneous abortion.<sup>12</sup>

## CONCLUSION

The mean serum folic acid level in patients with spontaneous abortion was  $16.97 \pm 8.34$  nmol / L, while the mean serum folic acid level in normal pregnancy was  $23.42 \pm 3.30$  nmol / L. The mean serum folic acid level in patients with spontaneous abortion was lower than the mean serum folic acid level in normal pregnancy in RS.DR.M.Djamil Padang, RST Reksodiwiryo and RSUD Batusangkar.

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