นิพนธ์ต้นฉบับ

Interaction between environmental factors and maternal genes polymorphisms of folate metabolisms association with the risk of Down syndrome

Pattaraporn Wisajun* Junya Pattaraarechachai**
Chaloem Varavithya*** Verayuth Praphanphoj****

Abstract

The purpose of this study was to study the interaction between environmental factors and maternal genes polymorphisms of folate metabolism in association with the risk of Down syndrome. The samples of the studied were 278 person, 101 cases and 177 controls. The 101 mothers of the case group have children with Down syndrome. The 65 children with Down syndrome are from the lab of Rachanukul Institute, and the 36 children with Down syndrome are from the King Chulalongkorn Memorial hospital. All children had karyotypically confirmed full trisomy 21. The 177 control mothers are from the King Chulalongkorn Memorial hospital and they do not have children with Down syndrome. Data were consists of two parts. The first parts are MTHFR, MTRR and MTR genotype of samples. This part is abstract from the record in the study of "Association between Polymorphisms in Maternal Genes of Folate Metabolisms and Down Syndrome" (Thivaratana Sinthuwiwat, 2004). The Second part, environmental factors of mothers, data are from interviews of a sample group of individuals in the first part. Statistical analysis was described in percentage, hypothesis testing by Chi-square test and Fisher's exact test while risk estimation is explain by Odd ratio.

The result of this study showed that most general characteristic of case and control were similar ($p > 0.05$). The results of study on interaction between environmental exposure before pregnancies and genes polymorphisms were not different with statistical significance in mothers having children with Down syndrome and control mothers. Except the interaction between drinking alcohol and MTR 2756 AG polymorphisms in mothers who having children with Down syndrome were statistically significant.

* Candidate for M.Sc. degree in Medical Sciences, Faculty of Medicine, Thammasat University
** Graduate Study Program, Faculty of Medicine, Thammasat University
*** Faculty of Medicine, Thammasat University
**** Rachanukul Institute

Introduction

Down syndrome is also known, as Trisomy 21 is the most prevalence chromosomal disorders and most frequently recognized cause of intellectual disabilities.[1] The incidence rate of Down syndrome is approximately 1 per 800 live births.[2] In Thailand, an incidence rate is approximately 1.4 per 1,000 live births.[3] The only well established risk factor for Down syndrome is advance maternal age.[4]

Although advanced maternal age is a major risk factor, however, most children of Down syndrome are born to younger mothers. Because of the total population, older mothers have fewer babies, only about nine percent of total pregnancies occur in women 35 years or older each year. About 95 percent of babies with Down syndrome are born to mothers less than 35 year of age. Approximately 4 and 1 percent of babies with Down syndrome are born to mothers 35 to 39 and older than 39 year of age, respectively. Prenatal testing is available to detect fetuses with Down syndrome; nevertheless, many specialists recommend that only women who become pregnant at age 35 or older undergo prenatal testing for Down syndrome. But using maternal age alone will not detect over 95 percent of pregnancies that will result in Down syndrome, because of younger mothers are not recommended to undergo prenatal testing for Down syndrome. Due to the risk of having a miscarriage in younger mothers from undergo prenatal testing is greater than the risk of having a baby with Down syndrome.[5]

In the part, there are environmental studies have shown that external factors of mother were associated with increased risk of Down syndrome births such as advance paternal age[6]; socio-economic level[7]; parity[8]; diabetic mother[9]; drinking caffeine and alcohol; smoking; oral contraceptive use before pregnancy[10] and others. Although the association between environmental factors and risk of having a child with Down syndrome was studied, it was in different population. The environmental factors and the risk of having a child with Down syndrome among Thai population have not been studied before.

For the genetic aspect, S. Jill James and others had been interesting to study the gene polymorphisms of methylene tetrahydrofolate reductase (MTHFR) before they hypothesized that polymorphism of MTHFR might increase risk of chromosome nondisjunction, a cause of Down syndrome.[11] In 2004, Thivaratana[12] studied the association between polymorphisms in maternal genes of folate metabolism and Down syndrome.

Therefore, this study aims to study interaction between environmental factors and maternal genes polymorphisms of folate metabolism in association with the risk of Down's syndrome. This project is a continuous study. The researcher is going to use the result of genetic factors, is polymorphisms of in maternal genes of folate and homocysteinemetabolism, of Thivarattana S.'s study.

About environmental factors, researcher has determined the scope of factor into three aspects; each aspect is related with folate deficiencies.[13]

1. Beyond a nutriment, substances were taken into a body before pregnancy namely oral contraceptives use; smoking; and drinking of caffeine and alcohol.

2. Poor food intake. Adequate folate intake is essential before pregnancy for the growth of the fetus.

3. Chronic illness and medication such as diabetes, hypertension, and others.

Result from this study can suggest younger women who will be pregnant. If they were possessed from genetic and environmental risk factors, they should undergo prenatal testing. There is an advantage of knowledge about risk factors for disease prevention.

Materials and Methods

This study was case control. Cases consisted of 108 women who have children with Down syndrome presenting to King Chulalongkorn Memorial hospital and Rachanukul Institute. Selection criteria of study population, their children with Down syndrome had to have karyotypically confirmed full trisomy 21. They domicile in Bangkok and used to participate in Sinthuwiwat study. In addition, they consent to participate in this study. The 101 woman who have children with Down syndrome were selected and referred to case groups.

For each case mother, one or two age-matched control mothers were recruited. The control populations were 187 women who have children without Down syndrome used to delivery at King Chulalongkorn Memorial hospital. Selection criteria of control population, they were Thai (They described themselves as "Thai" and could speak Thai clearly and fluently). They consent participation in this study. The 177 woman were used in this study and referred to control groups.

Data were consists of two parts. The first parts are MTHFR, MTRR and MTR genotype of samples. This part is an abstract from the record in the study of "Association between Polymorphisms in Maternal Genes of Folate Metabolisms and Down Syndrome".[12] The Second part, environmental factors of mothers, data are from interviews of a sample group of individuals in the first part.

Data analysis

Descriptive statistics was used to describe general characteristics of study samples. This are age, gender, the number of children, educational level etc. Chi-square Test was used to test interaction between environmental factors and maternal genes polymorphisms of folate metabolism confidence level of 95%.

Results

In this study, there are two parts of information. The first part is information about MTHFR, MTRR and MTR genotype of samples. The second part is from interviews. There are 278 subjects which are 101 mothers of Down syndrome children. Down syndrome children had karyotypically confirmed full trisomy 21. The 177 control mothers are not having children with Down syndrome. The results of the study are presented as follows:

1. Higher percentages are found in younger age of mother at conceptions in both groups, as contrast to father at maternal conception. Only abortion and economic status are significantly different in proportion between cases and controls (p-value = 0.003 and 0.02) as shown in Table 1.

2. Interaction between the substances (besides food) was taken into a body of mothers before pregnancies and genes polymorphisms in mothers having children with Down syndrome and control mothers. Thus four types of substances that went into body of mothers were determined including hazardous matter (insecticide, radioactivity, heavy metal, and general anesthetic), contraceptive, smoking, and drinking. The results of study were shown in the below:

2.1 No statistication significant association was found between cases and MTHFR 677 CT in both substrata confident interval of odd ratio is very large because of few cases in the cells.

2.2 About the exposure of radioactivity together with mutation of genes of 4 positions, it was found that the odd ratio between exposed radioactivity and polymorphism of genes cannot be calculated. Because of there was only one mother of case group who was once exposing such matter. Therefore, when working on stratified on polymorphisms of gene, certain space of table was equal to zero, it cannot be applied statistical test (Table 3).

Table 1 General characteristic of responding control mothers and mothers of children with Down syndrome

General Characteristics	Case (%) n = 101	Control (%) n = 177	chi square	P-value
Age of mother at conception				
< 35 years	53 (52.5)	119 (67.2)	5.94	0.15
≥ 35 years	48 (47.5)	58 (32.8)		
Age of father at maternal conception				
< 35 years	40 (39.6)	80 (45.2)	0.82	0.36
≥ 35 years	61 (60.4)	97 (54.8)		
Abortion				
– yes	43 (42.57)	45 (25.42)	8.74	0.003*
– no	58 (57.43)	132 (74.58)		
Economic status				
– sufficient with saving	40 (39.6)	45 (25.42)		
– sufficient but without saving	46 (45.55)	86 (48.59)	7.99	0.02*
– insufficient level	15 (14.85)	46 (25.99)		

Table 2 Interaction between exposure of insecticide and MTHFR 677 CT polymorphisms in mothers who having children with Down syndrome and control mothers.

Insecticide	MTHFR 677 genotype	Case n = 101 (%)	Control n = 177 (%)		Odd ratio (95% CI)
Exposed	CT+TT	1 (0.99)	1 (0.56)	3	(0.00-228.45)
	CC	2 (1.98)	6 (3.39)	1	
Unexposed	CT+TT	23 (22.77)	48 (27.12)	0.78	(0.42-1.44)
	CC	75 (74.26)	122 (68.93)	1	

Table 3 Interaction between exposure of radioactivity and genes polymorphisms in mothers who have children with Down syndrome and control mothers.

Radioactivity	Genes of folate metabolism	Case n = 101 (%)	Control n = 177 (%)		Odd ratio (95% CI)
Exposed	polymorphisms ≥ 1 position	1 (0.99)	2 (1.12)		na
	normal all 4 positions	0 0			
Unexposed	polymorphisms ≥ 1 position	87 (86.14)	160 (90.4)	0.627	(0.286-1.379)
	normal all 4 positions	13 (12.87)	15 (8.48)		1

na = not applicable

Table 4 Interaction between exposure of heavy metal and MTRR 66 AG polymorphisms in mothers who having children with Down syndrome and control mothers.

Heavy metal	MTRR 66 genotype	Case n = 101 (%)	Control n = 177 (%)	Odd ratio (95% CI)
Exposed	AG+GG	3 (2.97)	1 (0.56)	3 (0.0-197.11)
	AA	2 (1.98)	2 (1.13)	1
Unexposed	AG+GG	51 (50.49)	90 (50.85)	1.06 (0.62-1.8)
	AA	45 (44.56)	84 (47.46)	1

Table 5 Interaction between exposure of general anesthetic and MTRR 66 AG polymorphisms in mothers who having children with Down syndrome and control mothers.

General anesthetic	MTRR 66 genotype	Case n = 101 (%)	Control n = 177 (%)	Odd ratio (95% CI)
Exposed	AG+GG	3 (2.97)	2 (1.13)	3 (0.0-197.11)
	AA	1 (0.99)	2 (1.13)	1
Unexposed	AG+GG	51 (50.49)	89 (50.28)	1.05 (0.62-1.77)
	AA	46 (45.55)	84 (47.46)	1

Table 6 Interaction between oral contraceptive used and genes polymorphisms in mothers who having children with Down syndrome and control mothers.

Contraceptive used	Genes of folate metabolism	Case n = 101 (%)	Control n = 177 (%)	Odd ratio (95% CI)
Oral contraceptive (OCs)	polymorphisms ≥ 1 position	35 (34.65)	59 (33.33)	0.791 (0.253-2.468)
	normal all 4 positions	6 (5.94)	8 (4.52)	1
Never	polymorphisms ≥ 1 position	50 (49.5)	92 (51.98)	0.634 (0.202-1.99)
	normal all 4 positions	6 (5.94)	7 (3.95)	1

2.3 No statistically significant association was found between exposure heavy metal and MTRR 66 AG in both substrata. Confident interval of odd ratio is very large because of few cases in the cells (Table 4).

2.4 No statistically significant association was found between exposure general anesthetic and MTRR 66 AG in both substrata. Confident interval of odd ratio is very large because of few cases in the cells (Table 5).

2.5 Interaction between oral contraceptive used and genes polymorphisms in mothers who have children with Down syndrome and control mothers. When calculating by statistics, it shows that the interaction between taking contraceptive and the polymorphism of genes in folate metabolism process is not related to giving birth of Down syndrome children.

Table 7 Interaction between factors of having toxin from cigarette and genes polymorphisms in mothers who have children with Down syndrome and control mothers.

Smoking cigarette	Genes of folate metabolism	Case n = 101 (%)	Control n = 177 (%)	Odd ratio (95% CI)
Secondary smoker	polymorphisms ≥ 1 position	27 (26.72)	43 (24.29)	1.465 (0.349-6.157)
	normal all 4 positions	3 (2.97)	7 (3.95)	1
Never	polymorphisms ≥ 1 position	60 (59.41)	116 (65.54)	0.414 (0.155-1.103)
	normal all 4 positions	10 (9.91)	8 (4.53)	1

Table 8 Interaction between drinking alcohol and MTR 2756 AG polymorphisms in mothers who having children with Down syndrome and control mothers.

Drinking alcohol	MTR 2756 genotype	Case n = 101 (%)	Control n = 177 (%)	Odd ratio (95% CI)
Yes	AG+GG	7 (6.93)	2 (1.13)	9.92 (1.27-97.18)
	AA	6 (5.94)	17 (9.6)	1
No	AG+GG	20 (19.8)	48 (27.12)	0.67 (0.35-1.28)
	AA	68 (67.33)	110 (62.15)	1

2.6 Interaction between factors of having toxin from cigarette and genes polymorphisms of folate metabolism in mothers who having children with Down syndrome and control mothers. The analysis of those who were secondary smokers together with polymorphisms of genes was done. When calculating by statistics, it shows that the interaction between factors of having toxin from smoke together with polymorphisms of gene in folate metabolism process is not related to the birth giving of Down syndrome children.

2.7 Interaction between drinking alcohol and genes polymorphisms of folate metabolism in mothers who having children with Down syndrome and control. Statistically significant association was found between drinking alcohol and MTRR 66 AG (OR=9.92, CI=1.27-97.18). However, confident interval of odd ratio is very large because of few cases in the cells (Table 8).

3. Interaction between having nutrient with insufficient folate in foods of mothers before pregnancies and genes polymorphisms in mothers who having children with Down syndrome and control mothers. In this study, the researcher selected 10 kinds of foods that to have folate rating of 3 levels (good, very good, and excellent) referred form World's Healthiest Foods. The foods were including chicken's liver, pig's liver, soya bean, green bean, ground-nut, asparagus, ivy gourd, cabbage, corn, and tomato. When evaluation of interaction between factors of nutrient and genes of 4 positions were neither show significant by stratified analysis.

4. Interaction between chronic illness of mothers before pregnancies and genes polymorphisms in mothers having children with Down syndrome and control mothers.

Table 9 Interaction between hypertension before pregnancy and MTHFR 1298 AC polymorphisms in mothers who having children with Down syndrome and control mothers.

Hypertension	MTHFR 1298 genotype	Case n = 101 (%)	Control n = 177 (%)	Odd ratio (95% CI)
Before pregnancy	AC+CC	2 (1.98)	1 (0.56)	2 (0.05-78.25)
	AA	1 (0.99)	1 (0.56)	1
During pregnancy	AC+CC	5 (4.95)	6 (3.39)	5 (0.33-153.19)
	AA	1 (0.99)	6 (3.39)	1
Never	AC+CC	45 (44.55)	80 (45.2)	0.99 (0.58-1.71)
	AA	47 (46.54)	83 (46.9)	1

The Odd Ratio (95% CI) of mothers with high-blood pressure before pregnant together with polymorphism of MTHFR 1298 AC was 2 (0.05-78.25). While, the Odd Ratio (95% CI) of mothers who never have high-blood pressure before pregnant together with mutation of MTHFR 1298 AC was 0.99 (0.58-1.71). After working on statistical test for interaction between hypertension before pregnancy and the polymorphisms of genes in the process of folate metabolism, it is not related to giving birth of Down syndrome children, and no significance was found (Table 9).

Discussion

Comparison odd ratio (95% CI) of mothers who had been exposed to potential teratogens including insecticide, radioactivity, heavy metal, and general anesthetic and mothers who had no such factor. It was found that there was no significant interaction between potential teratogens exposed and materal genes polymorphisms of folate metabolism in association with the risk of Down's syndrome; this was consistent with that Blaasaas[14] reported no association between down syndrome risk and maternal or paternal occupational exposure to electromagnetic fields; however, exposure was based on linkage to census data and exposure assessments by an expert panel. There is a controversy study by Sperling[15] which studied the chernobyl reactor accident. It was presented as an explanation for a cluster of trisomy 21 cases in Berlin. Alberman[16] explained the increased risk with maternal age and irradiation, such as from x-rays, accumulating over a lifetime.

Due to the limitation on the number of participants in this research, certain space was 0; this means that there was no one who had both factors together, so the calculation of statistics cannot be done. In interviewing on data concerning occupation and condition of house of sample, it was found that most of them had worked in the office or were housewives, so there was little chance of exposing to insecticide. Besides, the location of houses was in the city and perimeter that was in allocated village separated from industrial plant, so there is little chance of being exposed to heavy metal and radioactivity since there was no participant in the research who was in the incidence of leakage or explosion of radioactivity or heavy metal and there was recall bias from the interview in that many of participants did not remember or were not sure that whether they had once been exposed to these hazardous matters or not.

No significant interaction between oral contraceptive used and maternal genes polymorphisms of folate metabolism in association with the risk

of Down's syndrome; this was contrary to the research of Martinez-Frias[10] who studied periconceptional exposure to contraceptive pill and risk for Down syndrome. The results showed an increased risk of 2.8-fold for infants with Down syndrome in woman younger than 35 years of age if the mother become pregnant while she was taking oral contraceptive pills. Read[17] postulated that the OCs activity is associated with the androgenic activity increasing the androgen/estrogen index, which is associated with the occurrence of Down syndrome in older mother. Thus, if the androgenic activity produced by OCs in younger woman acts near the time of conception; it may increase the risk of Down syndrome. Glauden[18] proposed that hormonal imbalance might cause a less-than-optimal microvascular to develop around the maturing oocytes. The resulting decrease in the size of perifollicular bed would reduce the volume of blood flow through the area and lead to oxygen deficit in egg. Moreover, Van Blerkom[19] observed a relationship between perifollicular blood flow traits and the behavior of chromosomes within developing oocytes. They found that oocytes from severely hypoxic follicle had high frequencies of abnormalities in chromosome organization on the metaphase spindle, possibly leading to an increases susceptibility to non-disjunction. However, the result study of Maria-Luisa Martinez-Frias[10] in older mothers did not show an increase risk for Down syndrome in woman who became pregnant when they were taking OCs.

Yang[20] studied the effect of OCs and maternal smoking on the risk of Down syndrome, separated the mothers in younger than the age of 35 and older than the age of 34, an observed a positive association only in younger mothers who used OCs and smoked. They concluded that the effect of environmental exposures may only be evident among younger mother because in older woman, the effect of time alone may be sufficient to disrupt meiotic events, and maternal age may obsure the effect of any added environmental exposure. Their results were obserced only for meternal meiosis II– what is conceivable for environmental factors that act periconcertionally.

Since this study did not separate mothers who were more than 35 years, this might make the result of having contraceptive of mothers who were more than 35 years old affect the analysis of data. However, the interesting point was that according to the in-depth interview concerning period of time in having contraceptive and stopping contraceptive before pregnant, it was found that most mothers with down syndrome had taken contraceptives for many years and mothers with down syndrome children for 3 persons stopped having contraceptive after being pregnant, and 14 mothers stopped having contraceptive before pregnant for less than 3 months, most of the mothers of control group stopped taking contraceptive before pregnant for more than 3 months.

No significant interaction between smoking and materal genes polymorphisms of folate metabolism in association with the risk of Down's syndrome. This result conform to study of Torfs[7] found that maternal smoking during the periconceptional period was not associated with risk of recognized Down syndrome (OR = 1.04; 95% CI: 0.79, 1.37). Rudnicka[21] determine the influence of maternal smoking on the birth prevalence of Down syndrome and on second trimester screening performance. They found that no evidence of an association between the birth prevalence of Down syndrome and maternal smoking.

Both primary and secondary smoker inhale the gas carbon monoxide. This gas hitches a ride on red blood cells and takes the place of some of the oxygen in blood stream. This means that the amount of oxygen is reduced when smoke. Nicotine chokes off oxygen by narrowing the blood vessels throughout a body. This reason is concordance with that observed by Van Blerkom.[22]

They observed a relationship between perifollicular blood flow traits and the behavior of chromosomes within developing oocytes. They found that oocytes from severely hypoxic follicle had high frequencies of abnormalities in chromosome organization on the metaphase spindle, possibly leading to an increases susceptibility to non-disjunction.

Most mothers who had smoke from cigarettes were secondary or passive smoker from the smoking of the persons at house and at work. According to the interview of mothers who were primary smoker of case group and control group, there were few numbers; this made it impossible to analyze data by statistics. This might be due to 3 key causes that were female smokers have lower fertility levels, because nicotine reduces a woman's fertility by affecting the production of hormones that are necessary for pregnancy; secondly, smoking increases the risk of miscarriage or stillbirth, premature birth and, therefore, less chance of baby surviving; and thirdly, the hiding of information of real smoking since Thai culture considers it is unacceptable for women to smoke. There was recall bias as well that made it impossible to identify amount and frequency of having smoke accurately. The participants told only that they had smoke regularly, rarely, or never.

Folate helps produce and maintain new cells. This is especially important during periods of rapid cell division and growth such as infancy and pregnancy. Folate is needed to make DNA and RNA, the building blocks of cells. Folate is also essential for the metabolism of homocysteine, and helps maintain normal levels of this amino acid. Adequate folate intake during the periconceptual period, the time just before and just after a woman becomes pregnant, protects against neural tube defects. Barkai[23] proposed that a neural tube defect's and Down's syndrome are both associated with disturbances in the folate pathway, at least some cases of neutal tube defects and Down syndrome could be expected to have a common aetiology. Marcia[24] have shown that children born to families with a high risk of neural tube defects could also beat an increased risk of Down's syndrome and vice versa, suggesting there is a link between the two conditions.

In this research, the researcher created questionnaire by choosing food that is consistent with culture of having food of Thais that were food with folate of good level. However, this study found no statistically significant interaction between poor dietary folate and materal genes polymorphisms of folate metabolism in association with the risk of Down's syndrome. Since food used in questionnaire is food in local of Thailand, there were many who had once have such food. Therefore, OR could not be calculated for those who had never had such food. The result of research was consistent with previous study that failed to observe a decline the occurrence of trisomy 21 following folic acid food fortification.

There were no significant interaction between chronic illness and maternal genes polymorphisms of folate metabolism in association with the risk of Down's syndrome. These results were consistent with previous studies. In this study, analysis controlling onset of diseased showed that there is not an increased risk for Down syndrome in infants of mothers with chronic illness and genetic polymorphisms of folate metabolism.

There is interesting data, from in depth interview, some mothers who have Down's syndrome child disclose that they were treated for thyroid disorders. Furthermore, they were taking medicines for the disease for many years before conception. These interesting data were conformed to some evidence suggests that thyroid disorders in the mother may increase risk of bearing a Down syndrome child. However, other studies found neither hypothyroidism nor hyperthyroidism to influence risk of Down syndrome.

References

1. Selikowitz M, Down Syndrome: the facts. 2nd edition. New York: Oxford University Press Inc. 1999.
2. Aitken DA, Crossley JA, and Spencer K. Prenatal screening for neural tube defects and aneuploidy. Emery and Rimoin's principles and practices of medical genetics. 4th edition. New York: Churchill Livingstone; 2002.
3. ศักนัน มะโนทัย และ สุชิต เผ่าสวัสดิ์. กลุ่มอาการดาวน์: ขอบเขตปัญหาและแนวทางแก้ไข. การประชุมเสวนาโต๊ะกลม. ภาควิชาสูติศาสตร์-นรีเวชวิทยา คณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย, 2540.
4. Hecht CA, Hook EB. Rates of Down syndrome at livebirth by one-year maternal age intervals in studies with apparent close to complete ascertainment in populations of European origin: A proposed revised rate schedule for use in genetic and prenatal screening. Am J Med Genet 1996;62:376-85.
5. Len Leshin. Prenatal Screening for Down Syndrome. <http://www.ds-health.com/prenatal.htm.> June 2005.
6. Fisch H, Hyun G, Golden R, Hensle TW, Olsson CA, and Liberson GL. The influence of paternal age on down syndrome. J Urol 2003;169:2275-8.
7. Torfs CP. and Christianson RE. Socioeconomic effects on the risk of having a recognized pregnancy with Down syndrome. Birth Defect Research (Part A) 2003;67:522-8.
8. Doria-Rose VP, Kim HS, Augustine ETJ. and Edwards KL. Parity and the Risk of Down's Syndrome. Am J Epidemiol 2003;158:503-8.
9. Narchi H. and Kulaylat N. High incidence of Down's syndrome in infants of diabetic mothers. Arch Dis Child 1997;77:242-4.
10. Martinez-Frias ML, Bermejo E, Rodriguez-Pinilla E, and Prieto L. Periconceptional Exposure to Contraceptive Pills and Risk for Down Syndrome. Perinatol 2001;21:288-92.
11. James SJ, Pogribna M, Pogribny IP, Melnyk S, Hine RJ, Gibson JB, Yi P, Tafoya DL, Swenson DH, Wilson VL, and Gaylor DW. Abnormal folate metabolism and mutation in the methylenetetrahydrofolate reductase (MTHFR) gene may be maternal risk factors for Down syndrome. Am J Clini Nutrit 1999; 70:495-501.
12. ทิวารัตน์ สินธุวิวัฒน์. ความสัมพันธ์ระหว่างโพลิมอร์ฟิซึมในยีนของมารดาในกระบวนการเมแทบอลิซึมของกรดโฟลิกกับกลุ่มอาการดาวน์. วิทยาศาสตรมหาบัณฑิต สาขาวิทยาศาสตร์การแพทย์ คณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย, 2547.
13. Elizabeth S. Hands. Nutrients in Food. U.S.A.: Lippincott Williams & Wilkins; 2000.
14. Blaasaas KG, Tynes T, Irgens A, Lie RT. Risk of birth defects by parental occupational exposure to 50 Hz electromagnetic fields: a population based study. Occup Environ Med 2002;59:92-7.
15. Sperling K, Pelz J, Wegner RD, Dorries A, Gruters A, Mikkelsen M. Significant increase in trisomy 21 in Berlin nine months after the Chernobyl reactor accident: temporal correlation or causal relation? BMJ 1994;309:158-62.
16. Alberman E, Polani PE, Roberts JA, Spicer CC, Elliott M, Armstrong E. Parental exposure to x- irradiation and Down syndrome. Ann Hum Genet 1972;36:195-208.
17. Read SG. The distribution of Down syndrome. J Ment Defic Res 1982;26:215-27.
18. Glauden ME. Maternal age effect: the enigma of Down syndrome and other trisomic conditions. Mutat Res 1992;296:80-8.

19. Van Blerkom J, Antczak M, Schrader R. The developmental potential of the human oocyte is related to the dissolved oxygen content of follicular fluid: association with vascular endothelial growth factor levels and perifollicular blood flow characteristics. Hum Reprod 1997;12:1047-55.
20. Yang Q, Sherman SL, Hassold TJ, Allran K, Taft L, Pettay D, Khoury MJ, Erikson JD, and Freeman SB. Risk Factors for Trisomy 21: Maternal Cigarette Smoking and Oral Contraceptive Use in a Population-Based Case-Control Study. Genet Med 1999;55:447-52.
21. Rudnicka AR, Wald NJ, Huttly W, and Hackshaw AK. Influence of maternal smoking on the birth prevalence of Down syndrome and on second trimester screening performance. Prenat Diagn. 2002 October 22:893-7.
22. Van Blerkom J, Antczak M, Schrader R. The developmental potential of the human oocyte is related to the dissolved oxygen content of follicular fluid: association with vascular endothelial growth factor levels and perifollicular blood floe characteristics. Hum Reprod 1997;12:1047-55.
23. Barkai G, Arbuzova S, Brekenstadt M, Heifetz S, Cuckel H. Frequency of Down syndrome and neutral-tube defects in the same family. Lancet 2003;361:1331-5.
24. Marcia RA, Eduardo ES, Ieda MO. Is there a familial link between Down syndrome and neural tube defect? Population and familial survey. BMJ 2004 January 10;328(7431):84.

บทคัดย่อ

ปฏิสัมพันธ์ระหว่างสิ่งแวดล้อมและโพลิมอร์ฟิซึมของยีนในกระบวนการเมแทบอลิซึมกรดโฟลิกของมารดาต่อการให้กำเนิดบุตรกลุ่มอาการดาวน์

ภัทรพร วิสาจันทร์* จรรยา ภัทรอาชาชัย** เฉลิม วราวิทย์*** วีรยุทธ ประพันธ์พจน์****

* นักศึกษาปริญญาโท สาขาวิทยาศาสตร์การแพทย์ คณะแพทยศาสตร์ มหาวิทยาลัยธรรมศาสตร์

** โครงการบัณฑิตศึกษา คณะแพทยศาสตร์ มหาวิทยาลัยธรรมศาสตร์

*** ที่ปรึกษาคณบดี คณะแพทยศาสตร์ มหาวิทยาลัยธรรมศาสตร์

**** สถาบันราชานุกูล

วัตถุประสงค์ของงานวิจัยครั้งนี้คือ เพื่อศึกษาปฏิสัมพันธ์ระหว่างสิ่งแวดล้อมและโพลิมอร์ฟิซึมของยีนในกระบวนการเมแทบอลิซึมกรดโฟลิกของมารดา ต่อการให้กำเนิดบุตรกลุ่มอาการดาวน์ กลุ่มตัวอย่างคือมารดาจำนวนทั้งหมด ๒๗๘ คน แบ่งออกเป็นกลุ่มศึกษาและกลุ่มควบคุมจำนวน ๑๐๑ และ ๑๗๗ คน ตามลำดับ กลุ่มศึกษาได้แก่มารดาที่ให้กำเนิดบุตรกลุ่มอาการดาวน์ และมารับบริการที่สถาบันราชานุกูลและโรงพยาบาลจุฬาลงกรณ์ ซึ่งบุตรทั้งหมดได้รับการตรวจทางพันธุกรรมยืนยันว่าเป็นแบบ trisomy 21 ส่วนกลุ่มควบคุมได้แก่มารดาที่ให้กำเนิดบุตรไม่ใช่กลุ่มอาการดาวน์ที่โรงพยาบาลจุฬาลงกรณ์ ข้อมูลที่ใช้ในการศึกษาประกอบด้วย ๒ ส่วน ส่วนแรกคือ ข้อมูลผลโพลิมอร์ฟิซึมของยีนในกระบวนการเมแทบอลิซึมกรดโฟลิก ได้แก่ MTHFR, MTRR and MTR genotype ของมารดา ข้อมูลส่วนนี้ผู้วิจัยได้ขออนุญาตใช้ผลงานวิจัยเรื่องความสัมพันธ์ระหว่างโพลิมอร์ฟิซึมในยีนของมารดาในกระบวนการเมแทบอลิซึมของกรดโฟลิกกับกลุ่มอาการดาวน์ของทิวารัตน์ สินทุวิวัฒน์[12] ส่วนที่สองเป็นข้อมูลด้านสิ่งแวดล้อมที่มารดาสัมผัสหรือได้รับก่อนการตั้งครรภ์ ๑ ปี ซึ่งได้จากการสัมภาษณ์กลุ่มตัวอย่างที่มีข้อมูลในส่วนแรก การวิเคราะห์ข้อมูลใช้สถิติพรรณนา อธิบายลักษณะทั่วไปของกลุ่มตัวอย่าง การทดสอบสมมติฐานใช้ Chi-square test และ Fisher's exact test และการประมาณค่าของปัจจัยเสี่ยงใช้ Odd ratio

ผลจากงานวิจัยแสดงให้เห็นว่าลักษณะทั่วไปของกลุ่มศึกษา และกลุ่มควบคุมมีความคล้ายคลึงกัน ($p>0.05$) ส่วนผลการศึกษาเกี่ยวกับปฏิสัมพันธ์ระหว่างสิ่งแวดล้อมและโพลิมอร์ฟิซึมของยีนในกระบวนการเมแทบอลิซึมกรดโฟลิกของมารดา ระหว่างกลุ่มที่มีบุตรกลุ่มอาการดาวน์และกลุ่มควบคุมไม่มีความแตกต่างกันอย่างมีนัยสำคัญ ยกเว้นปฏิสัมพันธ์ระหว่างการดื่มเครื่องดื่มที่มีส่วนผสมของแอลกอฮอล์และโพลิมอร์ฟิซึมของยีน MTR 2756 AG กลุ่มศึกษาและกลุ่มควบคุมมีความแตกต่างกันอย่างมีนัยสำคัญทางสถิติ