

CHAPTER 5

DISCUSSION, SUMMARY AND RECOMMENDATION

5.1 Discussion

Trisomy 21 is a major public health concern. It is leading of genetic cause of mental retardation and specific major congenital malformations. Despite advanced maternal age is a major risk factor, however, most children of Down syndrome is born to younger mothers. 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 (Chanane Wanapirak, 1993). Therefore, there should other factors besides ages of mothers that are the causes of birth giving of Down syndrome child. Both environmental and genetic studies make me interesting in topic about factors which association with having Down syndrome child.

Hypothesis tests 1 “Mothers who exposed the substance, beyond a nutriment, into a body before pregnancies additionally possess the genetic polymorphisms of folate metabolism have association with the risk for having Down’s syndrome child.”

1. Hazardous Matters: 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 maternal genes polymorphisms of folate metabolism in association with the risk of Down’s syndrome (Table 3); this was consistent with that Blaasaas et al. (2002) 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. Louik et al. (1987) failed to find any

link between parental occupational exposure to lead and Down syndrome risk.

There is controversy studies of Bound et al (1995) found that low-dose ionizing radiation from atomic weapon testing correlated with increased occurrence of Down syndrome in a time-series study in England. Ionizing radiation is the only known lifestyle/environmental agent to induce nondisjunction in experimental animals (Hook, 1984). Sperling et al. (1994) studied the chernobyl reactor accident was presented as an explanation for a cluster of trisomy 21 cases in Berlin. Alberman et al. (1972) explanation presented for the increased risk with maternal age is irradiation, such as from x-rays, accumulating over a lifetime. Vrijheid et al. study (2002) found a significant association between proximity to hazardous waste landfill sites and risk of chromosomal abnormalities; when the analysis was restricted to Down syndrome, the risk was still elevated, although not statistically significant.

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 incident 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.

2. Oral contraceptive (OCs) used : No significant interaction between oral contraceptive used and maternal genes polymorphisms of folate metabolism in association with the risk of Down's syndrome (Table 4); this was contrary to the research of Maria-Luisa Martinez-Frias et al. (2001) who studied periconceptional exposure to contraceptive pill and risk for Down syndrome. The results shown 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. In 1982, Read 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 (1992) proposed that hormonal imbalance might cause a less-than-optimal microvascular to develop around the maturing oocytes. The resulting decrease in the size of perfollicular bed would reduce the volume of blood flow through the area and lead to oxygen deficit in egg. Moreover, Van Blerkom et al. (1997) observed a relationship between perfollicular 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 et al. (2001) in older mothers did not show an increase risk for Down syndrome in woman who became pregnant when they were taking OCs.

Yang et al. (1999) 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 positivw 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 obscure the effect of any added environmental exposure. Their results were obserced only for meternal meiosis II -- what is conceivable for environmental factors that act periconcentionally.

Since this study did not separate mothers who were more than 35 years, this might make the results 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 ending having contraceptive before being pregnant, it was found that most mothers with down syndrome had had 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 being pregnant for less than 3 months, most of the mothers of control group stopped having contraceptive before being pregnant for more than 3 months and over.

3. Smoking cigarettes: No significant interaction between smoking and maternal

genes polymorphisms of folate metabolism in association with the risk of Down's syndrome (Table 5). This result conform to study of Torfs et al. (2000) 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 et al. (2002) 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 et al. (1997). 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 unaccpetable 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.

Hypothesis tests 2“Mothers who having nutrient with insufficient folate in foods before pregnancies additionally possess the genetic polymorphisms of folate metabolism are association with the risk for having Down's syndrome child.”

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 et al (2003) 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 neural tube defects and Down syndrome could be expected to have a common aetiology. Marcia RA. et al. (2004) have shown that children born to families with a high risk of neural tube defects could also bear an increased risk of Down's syndrome and vice versa, suggesting there is a link between the two condition.

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 maternal 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

Hypothesis tests 3 “Mothers who were having chronic illness additionally possess the genetic polymorphisms of folate metabolism are association with the risk for having Down's syndrome child.”

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 having Down's syndrome disclose that they were threatening by thyroid disorders. Furthermore, they were taking medicines to be curing the disease for many years before conception. These interesting data were conform 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

Cautiously, this research is continued from Reasearch on association between polymorphism in maternal genes of folate metabolism and Down syndrome and used same sample and used result of genetic polymorphism from such research. The results of Thivaratana (2004) found no difference in the allele and genotype frequencies of MTHFR 677 CT, MTHFR 1298 AC, MTRR 66 AG and MTR 2756 AG between mothers of Down syndrome and control. Such results may affect the analysis of interaction between environment and gene by this study.

Additionally, case mothers are not homogeneous. The extra chromosome 21 can be resulted from both maternal and paternal origin but researcher did not determine this. The researcher was gathering only maternal genotype and environment exposure. Because of trisomy 21 is of origin in 95 percent of cases and of paternal origin in 5 percent of cases (Antonarakis et al., 1991; Sherman et al., 1991), the genotype and environment exposure of the mothers are the major determinants of Down syndrome.

5.2 Conclusion

Conclusion of this study as follow:

1. General characteristic of mothers who having children with Down syndrome and control mothers.

Cases and controls are similar in age of mother at conception, age of father at maternal conception, sex of child, order of birth, number of time of pregnancy, educational level, and marital status. Only abortion and economic status are significantly difference in proportion between cases and controls ($p < 0.05$).

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.

In this Study, 4 types of substances that went into body of mothers were determined including hazardous matter, contraceptive, smoking, and drinking.

When calculating by statistics, the interaction between exposure the substances (besides food) was taken into a body of mothers before pregnancies and the polymorphisms of genes in folate metabolism process shows that the interaction between both factors is not related to the birth giving of down-syndrome children. Such results were contrary to the hypothesis of research item 1.

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 ranked as quality sources of folate (2006). The foods were including chicken's liver, pig's liver, soya bean, green bean, ground-nut, asparagus, ivy gourd, cabbage, corn, and tomato.

It shows that the interaction between the factor of having food with insufficient folate and the mutation of gene in the process of folate metabolism is not related to the birth giving of down-syndrome children. Such results were contrary to the hypothesis of Research Item 2.

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

In this study, 2 kinds of disease or chronic illness are specified that are diabetes and high-blood pressure.

The interaction between chronic illness of mothers before pregnancies and the mutation of gene in the process of folate metabolism is not related to the birth giving of down-syndrome children. Such results were contrary to the hypothesis of research item 3.

5.3 Recommendation

1. Recall bias occurred in this study. Because of the design study is case control. Collected environmental factors by interviewing events of subjects that happened in the past. From this problem can be correct by interview an intimate of subject such as her husband. This method for confirm and stimulate remembrance.
2. A sample size had few. This problem can be correct by increase the number of hospital or institute that Down syndrome child comes to take health service

5.4 Suggestion for further Study

1. Comparative study of contraceptive used. Should study in aspect of type of hormone, use period, monthly period in case and control mothers.
2. Comparative study of age of grandmother in case and control mothers.
3. Study of paternal factors such as occupation, smoking, and drinking alcohol etc.