

# Hubungan kadar serum asam folat selama kehamilan dengan status asam folat tiga tahun pasca melahirkan dan metilasi DNA insulin-like growth factor pada anak = Relationship of maternal serum folic acid levels with their three-year post-partum folic acid metabolisms and children's insulin-like growth factor 2 gene methylation

Lestari Octavia, examiner

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## Abstrak

**Background:** Methylenetetrahydrofolate reductase, (MTHFR) enzyme is involved in folic acid metabolism, and their allele types affected its activity. Providing folic acid supplementation to pregnant mothers may influence the change in methylation level in specific genes that affect the susceptibility of disease of their offspring. Although folic acid's role as a donor in the epigenetic mechanism has been investigated, a longitudinal study exploring the influence of iron-folic acid supplementation on maternal dan birth outcome by the nutrient-gene interaction approach is lacking. Therefore, we investigated the relationship of serum folic acid level among the mothers and the children, and the imprinted insulin-like growth factor 2 (IGF2) methylation level that is known actively involved in growth and development in children and possibly utilized as a surrogate marker for the disease **Methods:** In 2018, the follow-up study conducted by re-visited 67 subjects and put the mother and their children included in the study. For each group, sixty-seven serums were collected for folic acid measurement for mothers during gestation and three-year post-partum. Furthermore, forty-four serums for children were gathered for biomarker measurement. Serum folics were measured by using liquid chromatography-mass spectrometry/mass spectrometry. Determining the genotype of the MTHFR enzyme in position 677C>T and 1298 A>C was used Taqman Polymerase Chain Reaction (PCR) method. The pyrosequencing method was utilized to quantify the methylation level of the IGF-2 of the children. The relationship analysis between variables using multivariate linear regression. **Results:** There was no relationship between the folic acid intake during gestation and serum folic acid of the mothers during pregnancy, three-year post-partum, and the children ( $p>0.05$ ). There was no relationship between the allele type of MTHFR 677C>T and 1298A>C and serum folic acid status of the mother ( $p>0.05$ ). The serum folic acid during pregnancy had a significant relationship to the serum folic acid three-year post-partum ( $p<0.05$ ) as well as the serum folic acid of the children ( $p<0.05$ ). There was no significant relationship between the serum folic acid of the children, serum homocysteine, and the methylation status of IGF2 of the children ( $p>0.05$ ). **Conclusion:** The serum folic acid during pregnancy contributed to the serum folic acid three-year post-partum of mother and the children. The genotype of the MTHFR gene at 677C>T and 1298 A>C was possibly not involved in folic acid metabolism in the mother. Serum folic acid during pregnancy could not have an effect on the methylation status of the IGF2 in the differentially methylated region (DMR) area of the children. However, this conclusion needs to be taken in caution due to lack of study power **Recommendation:** Further cohorts studies with a large sample size and more advanced methods in determining the MTHFR enzyme and DNA methylation. **Keyword:** serum folic acid, genotyping MTHFR 677 C>T, MTHFR 1298 A>C, DNA methylation, IGF2

.....Latar belakang: Enzim metylenetetrahydrofolate reductase (MTHFR) terlibat dalam metabolisme asam folat dan tipe allele mempengaruhi aktivitas enzim. Memberikan suplementasi asam folat kepada ibu hamil

dapat mempengaruhi perubahan dalam derajat metilasi gen tertentu yang mempengaruhi kesehatan janin. Walaupun sudah banyak penelitian yang mempelajari peran asam folat sebagai donor dalam mekanisme epigenetik, namun penelitian pengaruh suplementasi besi-asam folat pada luaran kehamilan melalui pendekatan interaksi zat gizi-gen dalam desain penelitian longitudinal masih jarang. Penelitian ini bertujuan untuk mengetahui hubungan antara kadar serum asam folat pada ibu dan anak, dan derajat metilasi pada gen pencetak insulin-like growth factor (IGF2) yang dikenal terlibat dalam tumbuh kembang anak dan dapat digunakan sebagai penanda kemunculan penyakit Metode: Di tahun 2018, penelitian longitudinal dilakukan dengan mengunjungi 127 subyek termasuk anak yang dilahirkan dan mengikutsertakannya dalam penelitian. Enam puluh tujuh serum asam folat ibu selama hamil dan pasca melahirkan diperiksa, sementara serum asam folat anak dikumpulkan sebanyak 44 spesimen untuk pemeriksaan penanda darah. Pemeriksaan serum asam folat dengan menggunakan the liquid chromatography-mass spectrometry/mass spectrometry. Untuk pemeriksaan biomolekuler, tipe allele enzim MTHFR 677C>T and 1298A>C menggunakan Taqman polymerase chain reaction. Sementara metode pyrosequencing digunakan untuk menghitung DNA metilasi pada IGF2 pada anak. Hubungan antar variabel dianalisis menggunakan analisis regresi linier multivariat. Hasil: Tidak ada hubungan yang signifikan antara asupan asam folat dan serum asam folat ibu selama hamil, tiga tahun pasca melahirkan dan anak yang dilahirkan ( $p>0.05$ ). Penelitian ini tidak dapat menunjukkan hubungan antara tipe allele dari MTHFR 677 C>T dan 1298 A>C dan serum asam folat ( $p>0.05$ ). Serum asam folat selama hamil juga mempengaruhi status serum asam folat tiga tahun pasca melahirkan ( $p<0.05$ ) dan status serum asam folat anak ( $p<0.05$ ). Namun penelitian ini tidak dapat menunjukkan pengaruh status serum asam folat anak dengan DNA metilasi IGF2 pada anak ( $p>0.05$ ). Simpulan: Serum asam folat selama hamil berkontribusi pada serum asam folat tiga tahun pasca melahirkan dan anak. Genotipe dari MTHFR gene at 677C>T and 1298 A>C kemungkinan tidak terlibat dalam metabolisme asam folat pada ibu. Serum asam folat selama kehamilan tidak memiliki dampak pada status metilasi dari IGF2 pada wilayah differentially methylated region (DMR) untuk subyek anak. Namun, beberapa hal harus menjadi perhatian karena, secara statistik, jumlah subyek penelitian tidak memadai. Saran: Perlu dilakukan penelitian lanjutan yang melibatkan subyek lebih banyak dan metode yang lebih canggih dalam menentukan MTHFR dan metilasi DNA.