Homocysteine and the Risk of Intrauterine Growth Retardation

The association of inherited and acquired thrombophilias (which predispose to thrombotic vascular occlusions) with the risk of eclampsia, abruptio placentae, intrauterine growth restriction (IUGR), and stillbirth has been the object of many studies in the last few years (1). The rationale for these studies was based on the hypothesis that the formation of thrombi in the placental circulation of thrombophilic women could lead to impaired nutrition of the fetus. As a matter of fact, some studies have documented the presence of thrombotic lesions in the placentas of women with adverse pregnancy outcomes, although this has not been a consistent finding (2-4).

Early case-control studies of the prevalence of thrombophilia in women with adverse pregnancy outcomes gave contrasting results because each of them involved a relatively low number of participants (5-7). More recently, Infante-Rivard et al. (8) published a large study, which involved 493 women who gave birth to babies with IUGR and 472 women who had babies of normal size. The study, which had sufficient statistical power to detect odds ratios that had been estimated by previous reports, showed that there was no difference in the prevalence of the two most common thrombophilic polymorphisms (factor V Leiden and prothrombin G20210A) among cases and controls. In addition, the prevalence of placentas that had signs of infarction was low (5.9%), although it was higher among cases (10.5%) than controls (1.5%; odds ratio (OR), 7.6; 95% confidence interval (CI), 3.1-20.3). Overall, the results of the study by Infante-Rivard et al. (8) suggest that thrombosis of the placental vessels may account for only a small minority of cases of IUGR and that common polymorphisms that are associated with a heightened risk of (mostly venous) thrombosis do not predispose to IUGR.

In addition to giving these clear messages, the study by Infante-Rivard et al. (8) also raised the hypothesis that some association could exist between homocysteine metabolism and the risk of IUGR, although the picture that it gave was quite unclear. Two common variants of the gene encoding for methylene tetrahydrofolate reductase (MTHFR) were studied, 1298C and 677T, which predispose to hyperhomocysteinemia, especially in individuals whose dietary intake of folic acid is inadequate (9-11). Mothers who were homozygous carriers for the 1298C variant of MTHFR had a low risk of bearing a child with IUGR (OR, 0.49; 95% CI, 0.25-0.93). In contrast, mothers who were homozygous carriers for the 677T variant and were not taking vitamin supplements during the third trimester of pregnancy were at high risk of giving birth to babies with IUGR (OR, 12.3; 95% CI, 1.2-126.2). To complicate the picture further, babies who were homozygous carriers for the 1298C MTHFR variant had a normal risk of IUGR, whereas babies who were homozygous carriers for the 677T variant were protected from IUGR (OR, 0.52; 95% CI, 0.29-0.94). To summarize, MTHFR variants that may predispose to mild hyperhomocysteinemia were paradoxically associated with both high and low risks of IUGR. Measurements of the plasma concentrations of total homocysteine (tHcy), which would have helped in clarifying the issue, had not been done.

In this issue of Clinical Chemistry, Infante-Rivard et al. (12) filled the gap by measuring tHcy in the plasma of 468 control mothers, 483 case mothers, 438 control babies, and 409 case babies from the same study population. Their working hypothesis was that high concentrations of plasma tHcy would be associated with a greater risk of IUGR through a thrombotic placental effect, regardless of the relative contribution of MTHFR polymorphisms.

Homocysteine is a sulfhydryl amino acid derived from the metabolic conversion of methionine, which is dependent on several vitamins (riboflavin, folic acid, vitamin B12, and vitamin B6) as cofactors or cosubstrates (13). Several case-control, cross-sectional, and prospective studies showed that hyperhomocysteinemia is associated with heightened risk of arterial and venous thrombosis independent of other, established risk factors (13). The question still remains open of whether the association of hyperhomocysteinemia with thrombotic diseases is causal. Although hyperhomocysteinemia fulfills all the minor criteria for causality (14), including a demonstration of the association between cardiovascular risk and the mutant 677T allele of MTHFR (15, 16), the final word on this issue will be given by the results of ongoing randomized, placebo-controlled, double-blind trials of the effects of the administration of homocysteine-lowering vitamins on thrombotic risk.

The results of the new study by Infante-Rivard et al. (12) show that, contrary to the authors’ expectations, there was an inverse association between plasma tHcy and the risk of IUGR. For a 5 μmol/L increase in maternal plasma tHcy, the OR for IUGR was 0.37 (95% CI, 0.24-0.58), and the estimated increase in birth weight was 178.1 g (95% CI, 92.5-263.7 g). Similar results were obtained when newborns’ tHcy concentrations were considered. In conclusion, the new study by Infante-Rivard et al. (12) solves the controversy raised by their previous findings on the effects of MTHFR variants predisposing to hyperhomocysteinemia, favoring the view that these variants protect from IUGR.

Commenting on the results of this study is certainly not an easy task. The negation of the authors’ working hypothesis that high tHcy concentrations are associated with an increased risk of IUGR is not surprising. As already mentioned, the hypothesis was based on the assumption that IUGR is associated with thrombosis of the placental vessels and, as a consequence, with risk factors of thrombosis. However, we know that this assumption is most likely wrong, as Infante-Rivard and her collaborators showed in their previous study (8). In addition, it must be emphasized, as the authors correctly do, that the plasma tHcy values were largely lower than the threshold concentration often used to define hyperhomocysteinemia (15...
μmol/L) (13) in the vast majority of studied individuals (mean values were 5.11 and 4.99 among case mothers and babies, and 5.59 and 5.06 among control mothers and babies, respectively). A more difficult task is to try to explain the protective effect of high tHcy concentrations against IUGR. Plasma tHcy is influenced by many variables, including dietary habits (13). Dietary habits of the mother are also important for the development of the fetus (17–19). It is not unlikely that the most advantageous diet of a mother for the development of her fetus is the one that favors the accumulation of relatively high, albeit normal plasma tHcy concentrations.

The simple take-home message to draw from the studies by Infante-Rivard and her collaborators (8, 12) is that a search for thrombophilic states, including tHcy, in pregnant women is of no or very limited help for predicting the risk of IUGR.

References

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