Genetically determined lipoprotein(a) levels do not cause an increased risk of preeclampsia - a two-sample Mendelian randomization study

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Introduction: High blood levels of lipoprotein(a) [Lp(a)] were suggested to increase the risk of preeclampsia. Because excessive coagulation is involved in preeclampsia and Lp(a) is a known pro-coagulative protein, the hypothesis that Lp(a) is causally involved in preeclampsia seems to be consistent. Nevertheless, the exact impact and causal role of Lp(a) on preeclampsia was not well elucidated. Because the levels of Lp(a) are widely recognized to be highly genetics-dependent, we chose Mendelian Randomization [MR] as a tool to determine the impact of Lp(a) on the incidence of preeclampsia.

Purpose: To determine whether Lp(a) levels have impact on incidence of preeclampsia.

Methods: A two-sample MR study was conducted. Summary statistics were extracted from publicly available datasets. UK Biobank was the source of correlations for Lp(a) levels and FinnGen was used as the source of genetic correlations for preeclampsia. We restricted the variants used to LPA gene region. Inverse-variance-weighted mean was used as a primary analysis. Secondary analyses were performed using weighted median, mode, and MR-Egger methods. Sensitivity analysis was performed by leaving out random 30% of the variants as well as by using previously published variants correlated with Lp(a) levels.

Results: Summary statistics regarding genetic determinants of Lp(a) levels were retrieved for 318922 participants, while data regarding pre-eclampsia were available for 5922 cases and 176113 controls. Genetic associations of included variants with Lp(a) levels (horizontal axis) and with preeclampsia (vertical axis) are presented in Figure. Primary \( p = 0.562 \) and secondary analyses \( [\text{median} \ p = 0.825; \text{mode} \ p = 0.717; \text{MR-Egger} \ p = 0.785] \) indicated that Lp(a) levels have no impact on the incidence of preeclampsia. Selected variants did not show appreciable pleiotropy as indicated by MR-Egger intercept test \( [p = 0.898] \). Sensitivity analysis did not yield statistically significant results \( [\text{leave-30\%-out analysis IVM p-values: } 0.313-0.964] \).

Conclusions: Genetically determined Lp(a) levels were not correlated with and do not appear to have a causal role in preeclampsia. Therefore, Lp(a) screening provides no information as to patients’ risk of preeclampsia and Lp(a) reduction is not a promising strategy aimed at preeclampsia prevention. It is nevertheless possible that Lp(a) is involved in the pathogenesis of preeclampsia without a causal, level-dependent role. Irrespective, the effect of Lp(a) in recurrent pregnancy loss or intrauterine growth restriction needs to be further investigated.