Novel causal insights into idiopathic pregnancy loss

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Background/Aim. The definition of recurrent pregnancy loss (RPL) or recurrent miscarriage (RM) is the loss of two or more pregnancies before 24 weeks of gestation or at any point during pregnancy. The susceptibility to infections can alter the risk of RM/RPL in individuals. Our study utilized a Mendelian Randomisation approach to examine the causal relationship between ten infectious diseases — chickenpox, shingles, mononucleosis, mumps, measles, scarlet fever, bacterial meningitis, hepatitis B, hepatitis A, and COVID-19 — and the subsequent risk of pregnancy loss. **Methods.** We utilized two datasets for the outcome: (1) The LUCAR (Lviv Ukrainian Cohort for Advancing Reproductive Health) study, which comprises 350 women diagnosed with idiopathic recurrent pregnancy loss and 454 control women who have at least one healthy child. (2) The UK Biobank (UKBB) dataset, which includes 556 women with recurrent miscarriage and 2,928 control women who have at least one self-reported healthy-born child. The LUCAR and UKBB genome-wide array datasets underwent quality control and were imputed to the TopMED and HRC reference panels' density. PLINK1.9 was employed for clumping (using parameters: P-value = 1×10^{-5}, $r^2 = 0.5$, window size = 1000kb) of infection GWAS summary statistics. We conducted two-sample Mendelian randomization (MR) analysis using the TwoSampleMR 0.5.2 package. Summary statistics from genome-wide association studies (GWAS), specifically from PMID:28928442 and the 7th release of the COVID19 Host Genetics Initiative, served as instruments for infections in our analysis [1]. **Results.** Using 210/20 independent SNPs associated with shingles/mononucleosis as instruments, Mendelian randomization indicated a protective causal effect of shingles/mononucleosis on the risk of recurrent pregnancy loss (RPL) (OR[95%CI] = 0.40[0.32–0.50], P-value = 6.81×10^{-17} / OR[95%CI] = 0.34[0.14–0.80], P-value = 0.014). Subsequently, MR analyses were conducted for the UK Biobank dataset, and meta-analysis of the results revealed a significant protective causal effect of shingles against RPL/RM (OR[95%CI] = 0.98[0.96–0.995], P-value = 0.013). No other infections demonstrated causality (P-value > 0.5) in relation to RPL/RM risk. **Conclusions.** Our findings indicate that prior exposure to herpes zoster infections may provide protective effects against idiopathic pregnancy loss. **Grants/Fundings.** EMBO SLG5423–2023.

K e y w o r d s: GWAS (Genome-Wide Association Study), miscarriage, recurrent pregnancy loss, infections, shingles.

REFERENCES

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