INPLASY PROTOCOL

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Corresponding author:
Qian Zeng

zqian969d@126.com

Author Affiliation:
Chengdu University of Traditional Chinese Medicine.

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None declared.

Association of HLA-G and HLA-F with recurrent miscarriage and implantation failure: a systematic review and meta-analysis

Han, NN[1]; Xia, WT[2]; Zhu, C[3]; Zhang, X[4]; Wang, F[5]; Yin, ZX[6]; Zeng, Q[7].

Review question / Objective: **The objectives of this systematic review and meta-analysis on the polymorphism of HLA-G and HLA-F genes and the level of the two proteins expression are to elucidate whether they are involved in the pathogenesis of some cases of recurrent miscarriage (RM) or recurrent implantation failure (RIF).**
Condition being studied: **The unique HLA expression profile of two human leukocyte antigen (HLA) Class Ib molecules, HLA-F and HLA-G, at the feto-maternal interface is now recognized. Because of the apparent immunoregulatory functions of these proteins, they may also have a role in embryo implantation and pregnancy success. However, inappropriate HLA-F or HLA-G function has been implicated in reproductive failure, such as recurrent miscarriage (RM) or recurrent implantation failure (RIF).**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 27 December 2022 and was last updated on 27 December 2022 (registration number INPLASY2022120104).

INTRODUCTION

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METHODS

Search strategy: We will search the following databases for relevant English language literature: PubMed (MEDLINE), EMBASE, Web of Science and Cochrane Trials Registry from inception up to December 2022. The search string will be built as follows: Literature search strategies will be developed using medical subject headings (MeSH) and text words related to recurrent miscarriage, recurrent implantation failure, the human leucocyte antigen (HLA) class Ib molecules, HLA-G and HLA-F.

Participant or population: We will include studies examining all patients with two or more recurrent miscarriages and patients with two or more implantation failures after IVF.

Intervention: We will only include studies where NO interventions are given to the patients.

Comparator: We will only include studies where there are healthy fertile controls with a history of </= 1 previous miscarriage and infertile/fertile healthy controls with </= 1 previous implantation failure.

Study designs to be included: We included all observational studies on humans published as a full article. Cohort studies, case-control studies, or cross-sectional studies were included in the analysis. Case-reports were not considered.

Eligibility criteria: Inclusion criteria were studies with measurement of the expression levels of HLA-G and HLA-F genes and proteins. RM was defined as loss of two or more previous pregnancies occurring during the first and/or second trimester and RIF was defined as inability to achieve clinical pregnancy after two or more fresh or frozen transfers of high-quality embryos, both regardless of whether they were primary or secondary. The control group included women with no history of reproductive problems, including those undergoing ART because of male factor infertility that resulted in successful pregnancy outcome. In addition, concrete genotypic or allelic distribution data for patients and controls were provided or could be calculated and the full text was available. Case reports and studies without adequate information were excluded. If identical study populations were evaluated in different studies, only thestudy with a larger sample size and complete information was selected.

Information sources: Information comes from the following databases for relevant English language literature: PubMed (MEDLINE), EMBASE, Web of Science and Cochrane Trials Registry . We will seek further information from study authors where necessary to resolve questions about eligibility.

Main outcome(s): Primary outcome measure is the expression levels of HLA-G and HLA-F genes and proteins in women with RM or RIF at different stages versus fertile control.

Quality assessment / Risk of bias analysis: We will use the Risk Of Bias In Non-randomised Studies - of Interventions (ROBINS-I) tool to evaluate risk of bias and risk will be allocated as low, unclear or high risk. To reduce bias two authors will independently rate each study and any differences will be resolved by consensus or referring to a third reviewer.

Strategy of data synthesis: Studies were pooled for meta-analysis using the Stata software (StataCorp.2015. Stata Statistical Software, Release 14.0, College Station, TX, USA). Heterogeneity will be measured by considering variability of patient characteristics and trial factors. the fixed effects model is adopted if there is no heterogeneity, and the random effects

model is adopted if there is heterogeneity, and the heterogeneity is analyzed.

Subgroup analysis: If significant heterogeneity >50% is found, subgroup analyses into possible sources of heterogeneity will be performed for :
- Primary vs secondary RIF/RM
-Different types of test samples (e.g. peripheral blood, abortion tissue, placental samples, decidual tissue) and different periods of obtaining samples.
-Protein expression level and different kinds of gene polymorphism.

Sensitivity analysis: If individual studies are scored with a moderate to serious risk of bias, we will perform sensitivity analysis to exclude studies with serious risk of bias. sensitivity analyses will be performed for studies with mean values derived from median, graph extraction, critical or serious risk of bias, sampling from abortion tissue or placental samples, conference abstract, not completely fertile controls, or male infertility as controls.

Country(ies) involved: China.

Keywords: human leukocyte antigen; HLA Class Ib; HLA-G; HLA-F; recurrent miscarriage; recurrent implantation failure; reproductive immunology.

Contributions of each author:
Author 1 - Nana Han.
Author 2 - Wanting Xia.
Author 3 - Can Zhu.
Author 4 - Xuan Zhang.
Author 5 - Fan Wang.
Author 6 - Zhixing Yin.
Author 7 - Qian Zeng.

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