Citation

Ee Von Woon, Orene Greer, Nishel Shah. Natural Killer Cells in Recurrent Miscarriage and Recurrent Implantation Failure : Systematic Review and Meta Analysis. PROSPERO 2020 CRD42020175868 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020175868

Review question

1. What are the levels of pNK and uNK in recurrent miscarriage versus controls?

3. What are the levels of pNK and uNK in recurrent implantation failure versus fertile controls?

Searches

Literature search strategies will be developed using medical subject headings (MeSH) and text words related to recurrent miscarriage, recurrent implantationf failure and natural killer cells. We will search MEDLINE, EMBASE, Web of Science, Cochrane Central Register of Controlled Trials (CENTRAL) and Cochrane Database of Systematic Reviews (CDSR). This will be supplemented by searching for trial protocols via metaRegister. Grey literature will be searched in Google Scholar.

Types of study to be included

There are no restriction to the type of study to be included. Our only exclusion criteria is study that involve usage of immunotherapy.

Condition or domain being studied

Immunological factor as an aetiology in patients with recurrent miscarriage and recurrent implantation failure.

Participants/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(s), exposure(s)

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

Comparator(s)/control

We will only include studies where there are healthy fertile controls with a history of </= 1 previous miscarriage (for objectives 1 and 2); and infertile/fertile healthy controls with </= 1 previous implantation failure

Context

There are no restrictions in the setting for the studies.

Main outcome(s)

Primary outcome measure is level of NK cells (percentage/number) in women with RM or RIF versus fertile control.

Measures of effect

Standard mean difference (SMD) of NK cells levels (absolute number/percentage) in RM or RIF versus fertile controls

Additional outcome(s)

Peripheral and uterine natural killer cell cytotoxicity in RM/RIF versus fertile controls.

Measures of effect

As there is no absolute measure of this effect, we intend to report this as a narrative outcome.

Data extraction (selection and coding)

Two reviewers will screen titles and abstracts independently and a full report will be obtained for those that meet inclusion criteria. Full reports will be further screened to meet inclusion criteria. We will seek further information from study authors where necessary to resolve questions about eligibility. A data spreadsheet will be developed and agreed among all authors. The data will be extracted by two reviewers independently into Covidence. Any disagreements will be resolved by discussion or by a senior reviewer. Authors will be contacted to resolve any uncertainties.

Data extracted will include :

- Year of publication, country of study, author details

- study aim

- Sample size

- patient characteristics

- methodology

- inclusion and exclusion criteria,

- reason for reproductive failure (implantation failure or recurrent miscarriage),

- source (pNK or uNK) and method of measurement of NK cell levels/activity and reference range of the test, if applicable,

- Levels of NK cells (percentage and/or absolute number)

- Cytotoxicity of NK cells (percentage and/or absolute number)

Risk of bias (quality) assessment

The Risk Of Bias In Non-randomised Studies - of Interventions (ROBINS-I) tool will be used to evaluate risk of bias – this includes bias due to confounding, selection of participants into the study, classification of interventions, deviations from intended interventions, missing data, measurement of outcomes, selection of the reported result. Two reviewers will independently rate each study and risk will be allocated as low, unclear or high risk. Any differences will be resolved by consensus or referring to a third reviewer.

Strategy for data synthesis

If two or more studies within each group of RM or RIF is found, data will be synthesised.
Standard mean difference (SMD) of NK cells levels (number/percentage) in RM or RIF versus respective controls will be calculated, with a confidence interval of 95%. SMD will be plotted on a forest plot graph – RM/RIF will be plotted on the right side, and controls plotted on the left side.
Heterogeneity will be measured by considering variability of patient characteristics (e.g. age, BMI, pre-existing comorbidities, primary/secondary RIF or RM, fertile/infertile, previous number of RM or RIF, method of NK cell measurement) and trial factors (randomization concealment, blinding of outcome assessment, losses to follow up) – I^2>50% is considered as significant in which case a random effects model will be used. If I^2 <50%, a fixed effects model (Mantel-Haenszel) will be used.

Analysis of subgroups or subsets

If significant heterogeneity >50% is found, subgroup analyses into possible sources of heterogeneity will be performed for :

- Primary vs secondary RIF/RM

- Number of previous RM (2 vs >2) or RIF (2 vs >2)

- Fertile vs infertile patients

- uNK vs pNK

- Number vs percentage of NK cells

- Methodology of measurement of NK cells (e.g. flow cytometry versus immunohistochemistry)

Contact details for further information

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Organisational affiliation of the review

None

Review team members and their organisational affiliations

Dr Ee Von Woon. Imperial College London
Dr Orene Greer. Imperial College London
Dr Nishel Shah. Chelsea and Westminster Hospital

Type and method of review

Diagnostic, Meta-analysis, Systematic review

Anticipated or actual start date

30 March 2020

Anticipated completion date

06 July 2020

Funding sources/sponsors

No external funding has been sought for the purpose of the review.

Grant number(s)

State the funder, grant or award number and the date of award

Not applicable

Conflicts of interest

Language

English

Country

England

Stage of review

Review Ongoing

Subject index terms status

Subject indexing assigned by CRD

Subject index terms

MeSH headings have not been applied to this record

Date of registration in PROSPERO

28 April 2020

Date of first submission
22 March 2020

Stage of review at time of this submission
The review has not started

Stage	Started	Completed
Preliminary searches	No	No
Piloting of the study selection process	No	No
Formal screening of search results against eligibility criteria	No	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

The record owner confirms that the information they have supplied for this submission is accurate and complete and they understand that deliberate provision of inaccurate information or omission of data may be construed as scientific misconduct.
The record owner confirms that they will update the status of the review when it is completed and will add publication details in due course.

Versions
28 April 2020