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[Intervention Review]

Immunotherapy for recurrent miscarriage

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ABSTRACT

Background

Because immunological aberrations might be the cause of miscarriage in some women, several immunotherapies have been used to treat women with otherwise unexplained recurrent pregnancy loss.

Objectives

The objective of this review was to assess the effects of any immunotherapy, including paternal leukocyte immunization and intravenous immunoglobulin on the live birth rate in women with previous unexplained recurrent miscarriages.

Search methods

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (11 February 2014) and reference lists of retrieved studies.

Selection criteria

Randomized trials of immunotherapies used to treat women with three or more prior miscarriages and no more than one live birth after, in whom all recognized non-immunologic causes of recurrent miscarriage had been ruled out and no simultaneous treatment was given.

Data collection and analysis

The review author and the two co-authors independently extracted data and assessed study quality for all studies considered for this review.

Main results

Twenty trials of high quality were included. The various forms of immunotherapy did not show significant differences between treatment and control groups in terms of subsequent live births: paternal cell immunization (12 trials, 641 women), Peto odds ratio (Peto OR) 1.23, 95% confidence interval (CI) 0.89 to 1.70; third-party donor cell immunization (three trials, 156 women), Peto OR 1.39, 95% CI 0.68 to 2.82; trophoblast membrane infusion (one trial, 37 women), Peto OR 0.40, 95% CI 0.11 to 1.45; or intravenous immunoglobulin, (eight trials, 303 women), Peto OR 0.98, 95% CI 0.61 to 1.58.

Authors' conclusions

Paternal cell immunization, third-party donor leukocytes, trophoblast membranes, and intravenous immunoglobulin provide no significant beneficial effect over placebo in improving the live birth rate.

PLAIN LANGUAGE SUMMARY

Immunotherapy for recurrent miscarriage

Immunotherapy does not lower the risk of future miscarriage in women who repeatedly miscarry.

Background
Recurrent miscarriage is three or more consecutive early miscarriages. One theory is that for some women, this might be caused by an immune system response to the embryo or fetus. Therapies that try to immunize the woman against the 'foreign' cells of a future pregnancy have been tried. Immunotherapies have included white blood cells (leukocytes) from the woman's partner or a donor, products derived from early embryos (trophoblast membranes), or antibodies derived from blood (immunoglobulin).

Review question
We sought to determine whether immunological treatments would improve the chance of live births in women with a history of recurrent miscarriage.

Study characteristics
We included 20 randomized controlled trials involving 1137 women, which took place from 1985 and 2004 in 11 countries. The trials examined four different forms of immunotherapy: immunization using white blood cells from the woman's partner (12 trials, 641 women), white blood cells from a third-party donor (three trials, 156 women), products derived from early embryos (one trial, 37 women), or antibodies derived from blood (intravenous immunoglobulin) (eight trials 303 women).

Quality of the evidence and conclusions
Overall, we considered the risk of bias for the majority of included studies to be low.

The review of trials found that none of these treatments provided a significant beneficial effect over placebo in improving the live birth rate or lowered the risk of future miscarriage in women who have recurrent miscarriages.

BACKGROUND

Description of the condition

Approximately one to two per cent of couples experience recurrent pregnancy loss during the first trimester (Coulam 1991). Commonly defined as three or more consecutive miscarriages, recurrent miscarriage usually refers to those pregnancy losses occurring in the first trimester. This time limit is arbitrary and does not consider a variety of potential underlying causes of fetal death during the first half of pregnancy. Some couples who present for evaluation of recurrent miscarriage are found to have a disorder which is thought to be responsible for their pregnancy losses. However, the etiology of recurrent miscarriage remains elusive in the majority of women. It has been postulated that immunologic aberrations may be responsible for otherwise unexplained recurrent miscarriage.

The physiological mechanisms that allow a mother to tolerate her semi-allogeneic baby are unclear. Early reports proposed that human leukocyte (white blood cell) antigens compatibility of couples, the absence of maternal leukocytotoxic antibodies, or the absence of maternal blocking antibodies were related to recurrent miscarriage. Defects in molecular immunosuppressive factors (cytokines and growth factors) at the local decidual/trophoblast level have been implicated (Hill 1990; Johnson 1992). Elevated serum levels of systemic natural killer (NK) cells have also been found in women having miscarriages of karyotypically normal pregnancies (Clark 1995), and the presence of increased levels of NK cells in non-pregnant women was associated with a higher probability of miscarriage in a subsequent pregnancy (Aoki 1995; Yamada 2003). Most recently, experimental models of miscarriage have focused on the placental milieu showing that pregnancy survival depends on inhibition of local inflammatory mediators (Salmon 2004). Complement-inhibitory proteins, maternal regulatory T-cells, tryptophan catabolizing enzymes, and immunoregulatory cytokines may play a role in immunotolerance at the maternal-fetal interface (Aluvihare 2004; Mellor 2001; Xu 2000).

Not all studies favor an alloimmune cause of recurrent miscarriage. Several studies have found little correlation between pregnancy outcome and histocompatibility, the presence of antipaternal leukocytotoxic or blocking antibodies (Coulam 1992; Scott 1987; Smith 1988). Authorities point out that extrapolation from animal models may not be relevant in humans because of interspecies endocrine, immunologic, and reproductive differences, and the beneficial effect of pre-transplant blood transfusions to ameliorate rejection has been questioned (Scott 1995). The relationship of NK cell activity to pregnancy outcome has also been questioned (Morikawa 2001a).

Description of the intervention

Several immunologic treatments have been advocated by some investigators, based on evidence that pre-transplant blood transfusions decreased rejection of organ allografts. The most popular attempts at maternal immunomodulation have employed transfusion of paternal leukocytes (white blood cells - lymphocytes) prior to conception or passive immunization with intravenous immunoglobulin (IVIG) during pregnancy. Other interventions include third-party donor white cells or trophoblast membranes transfusions, although these have been largely abandoned because of doubts about efficacy.

How the intervention might work

The rationale for using IVIG to treat women with recurrent miscarriage is based on reports that it down regulates systemic NK cells (Kwak 1996; Ruiz 1996) and abrogates NK cell activity at the implantation site (Aoki 1995; Morikawa 2001b). Immunization with paternal white cells or third-party donor white cells has been postulated to prevent miscarriage in a similar manner as pre-transplant blood transfusions to improve kidney graft survival.

Why it is important to do this review

This is an update of a Cochrane review first published in 2003, and previously updated in 2006.

OBJECTIVES

To determine whether immunologic treatments improve the chance of live births in women with a history of recurrent miscarriage.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials that assessed the effect of immunologic treatments in women with recurrent miscarriages. Quasi-randomized and cross-over trials were excluded.

Types of participants

Women with recurrent miscarriages who met the following criteria:

1. three or more prior miscarriages and/or;
2. no more than one prior live birth and/or;
3. negative evaluations for non-immunologic causes recurrent miscarriage that included:
   a. normal parental karyotypes;
   b. antiphospholipid antibodies (lupus anticoagulant, anticardiolipin antibodies);
   c. abnormal uterine anatomy;
   d. luteal phase defect (as determined by endometrial biopsy or serum progesterone) and/or;
4. no simultaneous treatment or co-intervention.

Types of interventions

Immunization with leukocytes (paternal or third-party donor) or trophoblast membrane, or intravenous immunoglobulin versus placebo or no treatment.

Types of outcome measures

The primary outcome measure was a dichotomous variable defined as a live birth after 28 weeks' gestation in women receiving immunotherapy versus placebo/no treatment. In order to include the highest number of studies possible, this was expanded to include pregnancies alive after 20 weeks of gestation.

Primary outcomes

A live birth after 20 weeks' gestation in women receiving immunotherapy.

Secondary outcomes

None.

Search methods for identification of studies

The following methods section of this review is based on a standard template used by the Cochrane Pregnancy and Childbirth Group.

Electronic searches

We searched the Cochrane Pregnancy and Childbirth Group trials register by contacting the Trials Search Co-ordinator (11 February 2014).

The Cochrane Pregnancy and Childbirth Group's Trials Register is maintained by the Trials Search Co-ordinator and contains trials identified from:

1. monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
2. weekly searches of MEDLINE;
3. weekly searches of Embase;
4. handsearches of 30 journals and the proceedings of major conferences;
5. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

Details of the search strategies for CENTRAL, MEDLINE and Embase, the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service can be found in the 'Specialized Register' section within the editorial information about the Cochrane Pregnancy and Childbirth Group.

Trials identified through the searching activities described above are each assigned to a review topic (or topics). The Trials Search Co-ordinator searches the register for each review using the topic list rather than keywords.

[For details of additional searching carried out in an earlier version of the review (Porter 2006), please see Appendix 1.]

Searching other resources

We searched the reference lists of retrieved studies.

We did not apply any language restrictions.

Data collection and analysis

For the methods used when assessing the trials identified in the previous version of this review, *see* Porter 2006.

No new trials were included for this 2014 update. The following methods will be used in future updates.

The following methods section of this review is based on a standard template used by the Cochrane Pregnancy and Childbirth Group.

Selection of studies

Two review authors will independently assess for inclusion all the potential studies we identify as a result of the search strategy. We will resolve any disagreement through discussion or, if required, we will consult a third person.

Data extraction and management

We will design a form to extract data. For eligible studies, at least two review authors will extract the data using the agreed form. We will resolve discrepancies through discussion or, if required, we will consult a third person. We will enter data into Review Manager software (RevMan 2014) and check for accuracy.

When information regarding any of the above is unclear, we will attempt to contact authors of the original reports to provide further details.

Assessment of risk of bias in included studies

Two review authors will independently assess risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We will resolve any disagreement by discussion or by involving a third assessor.

(1) Random sequence generation (checking for possible selection bias)

We will describe for each included study the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.

We will assess the method as:

- low risk of bias (any truly random process, e.g. random number table; computer random number generator);
- high risk of bias (any non-random process, e.g. odd or even date of birth; hospital or clinic record number);
- unclear risk of bias.

(2) Allocation concealment (checking for possible selection bias)

We will describe for each included study the method used to conceal allocation to interventions prior to assignment and will assess whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment.

We will assess the methods as:

- low risk of bias (e.g. telephone or central randomization; consecutively numbered sealed opaque envelopes);
- high risk of bias (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth);
- unclear risk of bias.

(3.1) Blinding of participants and personnel (checking for possible performance bias)

We will describe for each included study the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. We will consider that studies are at low risk of bias if they were blinded, or if we judge that the lack of blinding would be unlikely to affect results. We will assess blinding separately for different outcomes or classes of outcomes.

We will assess the methods as:

- low, high or unclear risk of bias for participants;
- low, high or unclear risk of bias for personnel.

(3.2) Blinding of outcome assessment (checking for possible detection bias)

We will describe for each included study the methods used, if any, to blind outcome assessors from knowledge of which intervention a participant received. We will assess blinding separately for different outcomes or classes of outcomes.

We will assess methods used to blind outcome assessment as:

- low, high or unclear risk of bias.

(4) Incomplete outcome data (checking for possible attrition bias due to the amount, nature and handling of incomplete outcome data)

We will describe for each included study, and for each outcome or class of outcomes, the completeness of data including attrition and exclusions from the analysis. We will state whether attrition and exclusions were reported and the numbers included in the analysis at each stage (compared with the total randomized participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information is reported, or can be supplied by the trial authors, we will re-include missing data in the analyses which we undertake.

We will assess methods as:

- low risk of bias (e.g. no missing outcome data; missing outcome data balanced across groups);
- high risk of bias (e.g. numbers or reasons for missing data imbalanced across groups; 'as treated' analysis done with substantial departure of intervention received from that assigned at randomization);
- unclear risk of bias.

(5) Selective reporting (checking for reporting bias)

We will describe for each included study how we investigated the possibility of selective outcome reporting bias and what we found.

We will assess the methods as:

- low risk of bias (where it is clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review have been reported);
- high risk of bias (where not all the study's pre-specified outcomes have been reported; one or more reported primary outcomes were not pre-specified; outcomes of interest are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported);
- unclear risk of bias.

(6) Other bias (checking for bias due to problems not covered by (1) to (5) above)

We will describe for each included study any important concerns we have about other possible sources of bias.

We will assess whether each study was free of other problems that could put it at risk of bias:

- low risk of other bias;
- high risk of other bias;
- unclear whether there is risk of other bias.

(7) Overall risk of bias

We will make explicit judgements about whether studies are at high risk of bias, according to the criteria given in the *Handbook* (Higgins 2011). With reference to (1) to (6) above, we will assess the likely magnitude and direction of the bias and whether we consider it is likely to impact on the findings. We will explore the impact of the level of bias through undertaking sensitivity analyses - *see* Sensitivity analysis.

Measures of treatment effect

Dichotomous data

For dichotomous data, we will present results as Peto odds ratio with 95% confidence intervals.

Continuous data

Not applicable to the scope of our study.

Unit of analysis issues

Not applicable to the scope of our study.

Cluster-randomized trials

We will include cluster-randomized trials in the analyses along with individually-randomized trials. We will adjust their sample sizes using the methods described in the *Handbook* using an estimate of the intracluster correlation co-efficient (ICC) derived from the trial (if possible), from a similar trial or from a study of a similar population. If we use ICCs from other sources, we will report this and conduct sensitivity analyses to investigate the effect of variation in the ICC. If we identify both cluster-randomized trials and individually-randomized trials, we plan to synthesize the relevant information. We will consider it reasonable to combine the results from both if there is little heterogeneity between the study designs and the interaction between the effect of intervention and the choice of randomization unit is considered to be unlikely.

We will also acknowledge heterogeneity in the randomization unit and perform a sensitivity analysis to investigate the effects of the randomization unit.

Cross-over trials

One included study (Stephenson 1998) had a cross-over arm which was also double-blinded that was not included in this review.

Other unit of analysis issues

Not applicable.

Dealing with missing data

For included studies, we will note levels of attrition. We will explore the impact of including studies with high levels of missing data in the overall assessment of treatment effect by using sensitivity analysis.

For all outcomes, we will carry out analyses, as far as possible, on an intention-to-treat basis, i.e. we will attempt to include all participants randomized to each group in the analyses, and all participants will be analyzed in the group to which they were

allocated, regardless of whether or not they received the allocated intervention. The denominator for each outcome in each trial will be the number randomized minus any participants whose outcomes are known to be missing.

Assessment of heterogeneity

We will assess statistical heterogeneity in each meta-analysis using the Tau^2, I^2 and Chi^2 statistics. We will regard heterogeneity as substantial if an I^2 is greater than 30% and either a Tau^2 is greater than zero, or there is a low P value (less than 0.10) in the Chi^2 test for heterogeneity.

Assessment of reporting biases

If there are 10 or more studies in the meta-analysis, we will investigate reporting biases (such as publication bias) using funnel plots. We will assess funnel plot asymmetry visually. If asymmetry is suggested by a visual assessment, we will perform exploratory analyses to investigate it.

Data synthesis

We will carry out statistical analysis using the Review Manager software (RevMan 2014). We will use fixed-effect meta-analysis for combining data where it is reasonable to assume that studies are estimating the same underlying treatment effect: i.e. where trials are examining the same intervention, and the trials' populations and methods are judged sufficiently similar. If there is clinical heterogeneity sufficient to expect that the underlying treatment effects differ between trials, or if substantial statistical heterogeneity is detected, we will use random-effects meta-analysis to produce an overall summary, if an average treatment effect across trials is considered clinically meaningful. The random-effects summary will be treated as the average of the range of possible treatment effects and we will discuss the clinical implications of treatment effects differing between trials. If the average treatment effect is not clinically meaningful, we will not combine trials.

If we use random-effects analyses, the results will be presented as the average treatment effect with 95% confidence intervals, and the estimates of Tau^2 and I^2.

Subgroup analysis and investigation of heterogeneity

If we identify substantial heterogeneity, we will investigate it using subgroup analyses and sensitivity analyses. We will consider whether an overall summary is meaningful, and if it is, use random-effects analysis to produce it.

We plan to carry out the following subgroup analyses.

- Trials reporting data with intention-to-treat analysis.

The following outcomes will be used in subgroup analysis.

- A live birth after 20 weeks' gestation in women receiving immunotherapy.

We will assess subgroup differences by interaction tests available within RevMan (RevMan 2014). We will report the results of subgroup analyses quoting the Chi^2 statistic and P value, and the interaction test I^2 value.

Sensitivity analysis

Sensitivity analyses will be performed for aspects of the review that might affect the results, such as high risk of bias for allocation concealment. Sensitivity analysis will be conducted by excluding studies at high risk of bias for allocation concealment from the analysis, to see if this makes any difference to the overall result.

RESULTS

Description of studies

A total of 15 studies were assessed for this update.

Results of the search

The updated search in February 2014 retrieved seven new studies. Eight studies were awaiting classification at the time of the last review (Kilpatrick 1993; Li 1998; Mahmoud 2004; Quenby 2007; Sagot 1993; Scarpellini 2009; Stephenson 2001; Tang 2009). Fourteen studies were excluded (Kilpatrick 1993; Kim 2012; Kwon 2012; Li 1998; Mahmoud 2004; Quenby 2007; Sagot 1993; Scarpellini 2009; Scarpellini 2011; Stephenson 2001; Stephenson 2010; Tang 2009; Tang 2011; Tang 2013) and one is awaiting translation (Sun 2010).

Included studies

Twenty randomized controlled trials were included.

The included studies were categorized according to the type of intervention, as listed below.

(A) Paternal cell immunization

Published trials

1. Cauchi 1991*
2. Gatenby 1993*
3. Ho 1991*
4. Mowbray 1985
5. Illeni 1994*
6. Ober 1999
7. Pandey 2004

Unpublished trials

1. Christiansen 1994*
2. Kilpatrick 1994*
3. Reznikoff 1994*
4. Stray-Pederson 1994
5. Scott 1994*

(B) Third-party donor cell immunization

Published trials

1. Christiansen 1994*
2. Ho 1991*

Unpublished trials

1. Scott 1994*

(C) Trophoblast membrane immunization

Published trials

1. Johnson 1991

(D) Intravenous immunoglobulin

Published trials

1. Christiansen 1995*
2. Coulam 1995*
3. German RSA/IVIG 1994*
4. Stephenson 1998*
5. Perino 1997
6. Jablonowska 1999
7. Christiansen 2002

* Individual patient data sheets also reviewed

Settings

These studies were reported between 1985 and 2004 in 11 countries: Australia (Cauchi 1991, Gatenby 1993); Canada (Ober 1999; Stephenson 1998); Denmark (Christiansen 1994,Christiansen 1995, Christiansen 2002); France (Reznikoff 1994); Germany (German RSA/IVIG 1994); Italy (Illeni 1994; Perino 1997); Norway (Stray-Pederson 1994); Sweden (Jablonowska 1999); Taiwan (Ho 1991); United Kingdom (Johnson 1991; Kilpatrick 1994; Mowbray 1985); and USA (Coulam 1995; Ober 1999; Pandey 2004; Scott 1994).

Participants

All of the included studies recruited women with at least three or more prior miscarriages, no more than one prior live birth, a negative evaluation for non-immunologic causes of recurrent miscarriage (normal parental chromosomes, normal maternal uterine anatomy), and not known to have antiphospholipid antibodies. Only four trials included women with only primary recurrent miscarriages and excluded women with secondary recurrent miscarriage (German RSA/IVIG 1994; Illeni 1994; Perino 1997; Reznikoff 1994).

Interventions

Interventions studied include immunization with leukocytes (paternal or third-party donor) or trophoblast membrane, or intravenous immunoglobulin versus placebo or no treatment. Any trials in which there was simultaneous treatment or co-intervention were excluded.

There was no consistency among the trials with regards to timing of treatment initiation, duration, or dose. Among trials examining paternal cell immunization, treatment was administered prior to pregnancy in all trials except Kilpatrick 1994, where treatment was given prior to pregnancy with an additional treatment dose given after conception, and Cauchi 1991, where treatment was administered once pregnancy was established. With regards to trials of third-party cell immunization, both Christiansen 1994, Ho 1991, and Scott 1994 administered treatment prior to pregnancy. Johnson 1991 examined the utility of trophoblast membrane immunization prior to pregnancy. The majority of trials investigating the utility of intravenous immunoglobulin were performed once pregnancy had been established. The exception are Stephenson 1998, which studied intravenous immunoglobulin treatment prior to pregnancy and Coulam 1995 which initiated intravenous immunoglobulin treatment prior to pregnancy and continued its use throughout pregnancy.

Like treatment timing and duration, there was great heterogeneity in the mode of treatment administration. The majority of trials administered intervention intravenously, although some also administered treatment intramuscularly and subcutaneously.

Outcomes

The primary outcome measure was a dichotomous variable defined as a live birth after 28 weeks' gestation in women receiving immunotherapy versus placebo/no treatment (Christiansen 1994; Christiansen 1995; Christiansen 2002; Coulam 1995; Gatenby 1993; German RSA/IVIG 1994; Ho 1991; Illeni 1994; Jablonowska 1999; Johnson 1991; Kilpatrick 1994; Mowbray 1985; Ober 1999; Pandey 2004; Perino 1997; Reznikoff 1994; Scott 1994; Stephenson 1998; Stray-Pederson 1994). In order to include the highest number of studies possible, this was expanded to include pregnancies alive after 20 weeks of gestation (Cauchi 1991; Stephenson 1998).

Excluded studies

See Excluded studies.

In total, 19 studies were excluded. Eight studies were outside the scope of our review (Check 1995; Cowchock 1995; Quenby 2007; Scarpellini 2009; Scarpellini 2011; Tang 2009; Tang 2011; Tang 2013). Three studies included participants that do not meet our inclusion criteria: Christiansen 1992 included patients who had anticardiolipin antibodies, Mahmoud 2004 included women who were antiphospholipid syndrome positive, and Stephenson 2010 included women with at least one ongoing gestation beyond 20 weeks without clarifying the number of prior live births. Three studies (Aoki 1993; Kim 2012; Li 1998) did not have a placebo and instead randomized to two different treatments. Two studies (Redman 1996; Stephenson 2001) did not report any data and two other studies (Kilpatrick 1993; Kwon 2012) did not report our outcome of interest (live birth). One study was not a randomized controlled trial (Sagot 1993).

Risk of bias in included studies

Overall risk of bias for the majority of included studies was judged to be low. Assessment of the methodological quality of the included studies was based on the following 'Risk of bias' domains: selection bias (method of randomization and allocation concealment), performance bias, detection bias, attrition bias (loss of participants from the analyses) and reporting bias. A summary of 'Risk of bias' assessments for each study, and for included trials overall, are set out in Figure 1 and Figure 2.

Figure 1. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

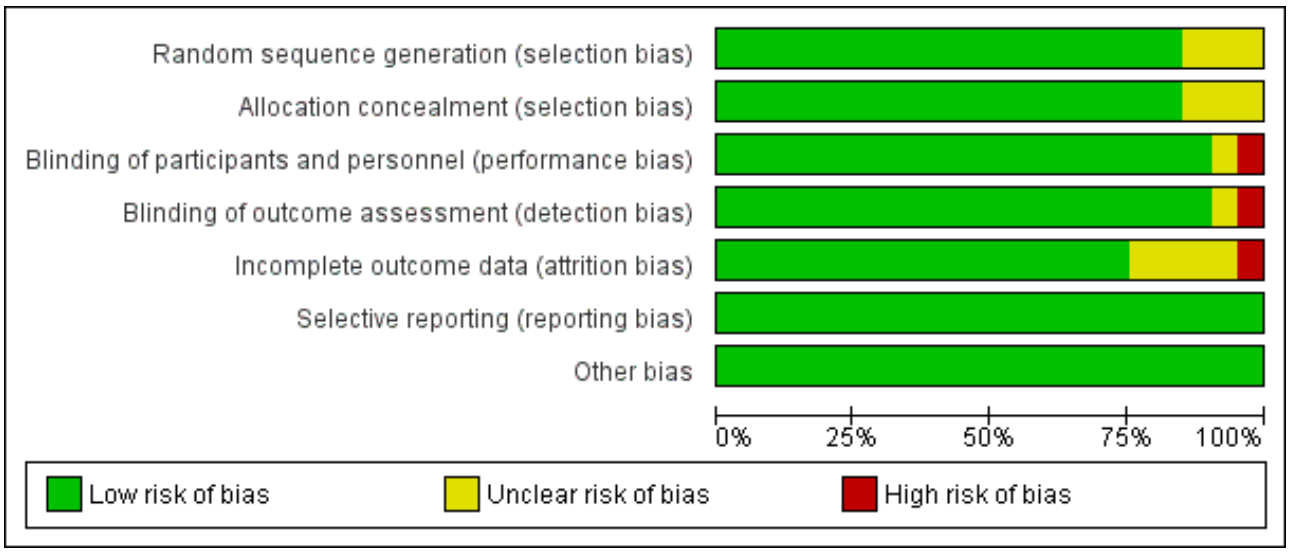


Figure 2. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.

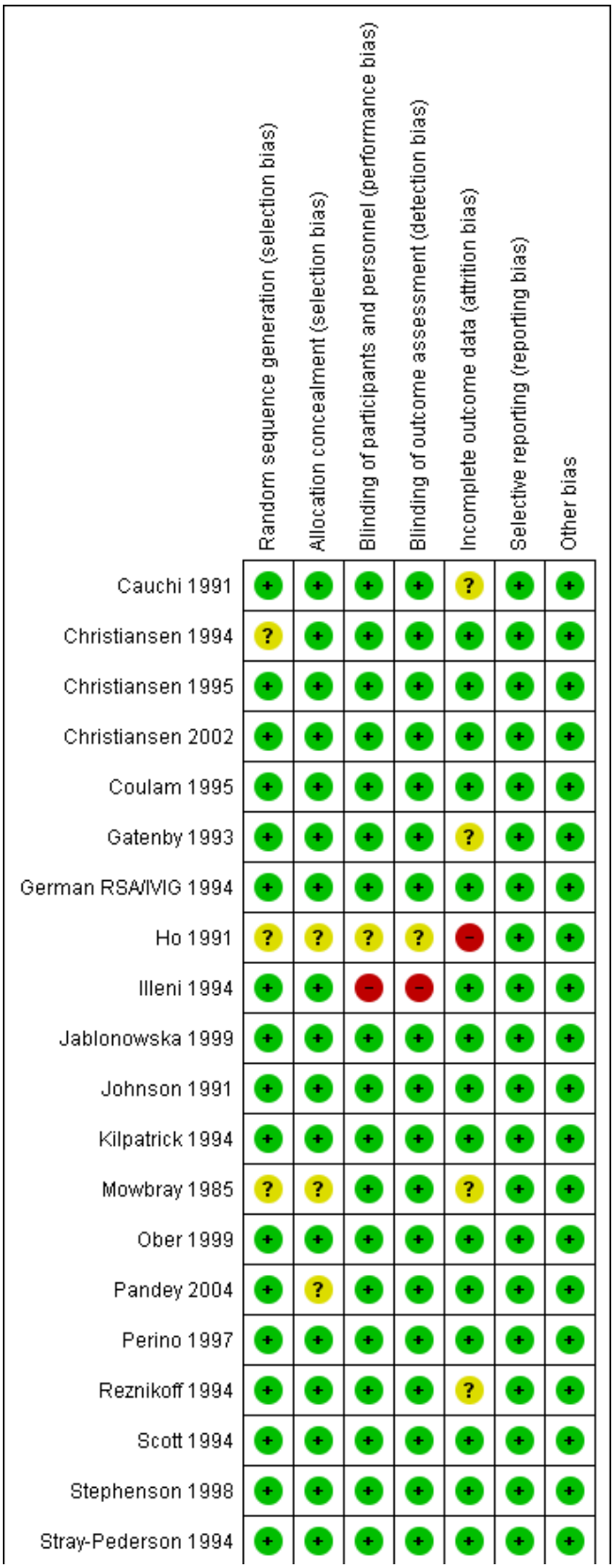
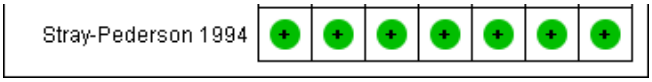


Figure 2. (Continued)



Allocation

In the majority of included studies selection bias was assessed as being low with adequate methods of both sequence generation and allocation concealment. Only three trials provided insufficient information to permit evaluation of selection bias.

Blinding

Performance bias was minimized because all studies with co-interventions were excluded, and the majority of included trials provided adequate documentation of blinding of both provider and participant. One trial did not provide sufficient information to permit evaluation of performance and detection bias (Ho 1991). Another trial (Illeni 1994) did not blind the treatment or control groups to patients, physicians, or investigators.

Incomplete outcome data

Attrition bias was limited because included studies accounted for participants who withdrew from the trial. Only one study (Ho 1991) had an attrition of approximately 20%. Four other studies had missing data, but these were either similar for both treatment and control groups and/or were a small portion and not likely to have a relevant impact on the effect estimates.

Selective reporting

Reporting bias was minimal since inclusion of a study for this review requires that the outcome be reported in a pre-specified manner.

Other potential sources of bias

The majority of studies included were free of other sources of bias.

Effects of interventions

Twenty randomized controlled trials of high quality were included involving total of 1137 women.

Paternal white cell immunization versus placebo

Twelve randomized controlled trials comparing paternal white cell immunization versus placebo involving a total of 641 women were included.

Primary outcomes

Women who were treated with paternal cell immunization were not at increased odds for live birth as compared to placebo, Peto odds ratio (OR) 1.23, 95% confidence interval (CI) 0.89 to 1.70 (Analysis 1.1). The use of intention-to-treat analysis did not result in significant differences between paternal cell immunization treatment and control groups in terms of subsequent live births (four trials, 350 women) OR 1.38, 95% CI 0.90 to 2.12 (Analysis 1.2).

We investigated for reporting biases using a funnel plot which appeared symmetric on visual assessment. Thus no further exploratory analyses to investigate reporting biases were pursued.

Secondary outcomes

Not within the scope of this review.

Donor white cell immunization versus placebo

Third-party donor white cell immunization (three trials, 156 women) did not result in increased odds for live birth as compared to placebo, Peto OR 1.39, 95% CI 0.68 to 2.82 (Analysis 2.1).

Trophoblast membrane immunization versus placebo

Trophoblast membrane infusion (one trial, 37 women) did not result in increased odds of live birth as compared to placebo, Peto OR 0.40, 95% CI 0.11 to 1.45 (Analysis 3.1).

Intravenous immunoglobulin versus placebo

Intravenous immunoglobulin (IVIG) (eight trials, 303 women) did not result in increased odds of live birth as compared to placebo, Peto OR 0.98, 95% CI 0.61 to 1.58 (Analysis 4.1). The earlier published trials tended to give higher estimates of treatment effect, although these were not statistically significant. Thus the possibility of publication bias is low. The use of intention-to-treat analysis did not result in significant differences between IVIG treatment and control groups in terms of subsequent live births: IVIG (four trials, 279 women), OR 1.18, 95% CI 0.72 to 1.93 (Analysis 4.1).

DISCUSSION

Summary of main results

In this updated version of the review, we assessed a total of 15 studies (seven new studies identified from an updated search; and eight studies that were awaiting assessment at the time of the last review). Fourteen of these studies were excluded as they did not meet inclusion criteria for our review and one of these studies is awaiting translation into the English language to allow classification. In total, 20 randomized controlled trials of high quality were included involving a total of 1137 women. The results of this review indicate no improvement in live births with paternal cell immunization, third-party donor cell immunization, trophoblast membrane immunization, or intravenous immunoglobulin (IVIG) immunotherapy regimens.

Overall completeness and applicability of evidence

There is considerable variation in reported subsequent live birth among studies examining immunotherapy for recurrent miscarriage. This may be attributed to significant variation in the participants included, methodology, intervention, and treatment regimen. Given the considerable costs for immunotherapy and potential for serious side effects (Clark 1991; Coulam 1994; Duhem 1994), it is important to establish the efficacy of immunotherapy for the treatment of recurrent miscarriage. While we performed individual analysis for paternal cell immunization, third-party donor cell immunization, trophoblast membrane immunization, and IVIG, our ability to reach conclusive findings is limited by heterogeneity in dose, duration, and timing of immunotherapy.

Subgroup analysis by these variables was not feasible due to the small number of included trials and participants. However, our review was inclusive of published and unpublished data as well as English and non-English data. Furthermore, our review was restricted to randomized controlled trials of moderate to high quality, increasing the level of confidence in our conclusion that immunotherapy does not improve the live birth rate in women with unexplained recurrent miscarriage. Moreover, women should be spared the pain and grief associated with false expectations that an ineffective treatment might work. These therapies should no longer be offered as treatment for unexplained recurrent pregnancy loss.

Quality of the evidence

The overall quality of the trials included in this review was moderate to high since only randomized controlled trials were included and all but one trial (Illeni 1994) was double-blinded. The overall risk for bias of the included trials is low. None of the studies assessed were at high risk of bias for the majority of the domains. Only two trials were noted to be at high risk for bias in one or two areas. Ho 1991 was noted to be at high risk for attrition bias, with outcomes not reported in approximately 20% of the participants due to early reporting for reasons unstated. Illeni 1994 was found to be at high risk for performance and detection bias because the treatment and control groups were not blinded to investigators, patients, or physicians. There were also several trials that did not provide clear information on methodology. Three trials (Christiansen 1994; Ho 1991; Mowbray 1985) were reported as randomized trials, but did not provide sufficient information to permit evaluation of their random sequence generation. The risk of selection bias was unclear for three trials (Ho 1991; Mowbray 1985; Pandey 2004) because their methods for allocation concealment were not described. One trial (Ho 1991), did not provide sufficient information to permit evaluation of performance and detection bias. Four studies (Cauchi 1991; Gatenby 1993; Mowbray 1985; Reznikoff 1994) reported missing data, although the risk for attrition bias is likely low given the similarly small proportion of missing data in treatment and control groups.

The use of so-called intention-to-treat analysis has been suggested as the best method of comparing the effects of any treatment on a given disease process versus those of placebo, because it more closely resembles actual patient care in everyday clinical practice. The validity of intention-to-treat studies evaluating the effects of preconceptional treatment on pregnancy outcome has been questioned since women who do not achieve pregnancy cannot have a primary outcome. Most studies of immunotherapy for recurrent miscarriage given prior to conception excluded women from analysis if pregnancy was not achieved. However, two recent studies of paternal cell immunization (Ober 1999; Pandey 2004) included outcome data from all treated women, regardless of whether or not conception occurred. In the present review, it was also possible to combine the results of four trials of each type of immunotherapy using an intention-to-treat analysis. No significant benefit was found.

Potential biases in the review process

We took steps to minimize introduction of bias at every stage of the review process. We were able to identify all relevant trials, including unpublished studies and published abstracts from conference proceedings, and those from English and non-English publications alike. At least two review authors independently assessed each trial, performed data extraction, and assessed quality for each of the included trials. A member of the review team was an author on one of the included trials (Scott 1994) but was not involved in assessing the quality and risk of bias for this trial or carrying out data extraction of this trial. No new unpublished trials have been identified since the initial review. Previously identified unpublished trials have remained unpublished and our assessment of their methodology and potential biases are limited to the records of the initial communication between our authors and the authors of the unpublished trials.

Agreements and disagreements with other studies or reviews

Conclusions about the value of paternal cell immunization in recurrent miscarriage have been conflicting and highly dependent on the methods used for meta-analysis. The earliest meta-analysis, which included only published trials, reported no improvement in live birth rates among women with recurrent miscarriage (Fraser 1993). Using a different data set and adjusting for maternal age and the number of prior miscarriages, paternal cell immunization appeared to slightly increase the live birth rate over placebo (Scott 1994). Another meta-analysis performed simultaneously using similar methodology also demonstrated a small but significant benefit (Collins 1994; Coulam 1994). This benefit disappeared when the largest published trial was included (Ober 1999). Even so, the most recent randomized controlled trial of paternal cell immunization trials reported a significant increase in live births among treated women (Pandey 2004).

In the current review, we were unable to identify a statistically significant improvement in live birth when paternal cell immunization was used to treat women with recurrent miscarriage. Our findings disagree from those of the most recent meta-analysis (for several reasons. Pandy et al. introduced bias by including control patients who received neither treatment nor placebo. They pooled study group pregnancy outcomes and control group (when available) outcomes in lieu of using the more statistically appropriate method of weighted averages in either a fixed-effect or random-effects model. The inclusion of non-randomized trials in a meta-analysis of randomized trials is likely to bias the results in favor of a significant difference.

Paternal cell immunization using viable mononuclear cells carries a risk for transmission of hepatitis and human immunodeficiency virus (HIV). Reactions are uncommon but include soreness and redness at the injection site, fever, maternal platelet alloimmunization, blood group sensitization, and cutaneous graft-versus-host-like reaction (Clark 1991; Coulam 1994). Rare adverse pregnancy outcomes have also been reported, including placental abruption, placenta accreta, oligohydramnios, pre-eclampsia, fetal growth retardation, preterm delivery, renal anomalies, trisomy 21 and 13, and an unusual case of undefined immunodeficiency disease. One trial (Ober 1999) indicated that women who have received lymphocyte immunotherapy may have a higher incidence of subsequent miscarriage than women who did not receive such cellular products. The Director of the Office of Therapeutics Research and Review, United States Food and Drug Administration (FDA), sent a letter on January 30, 2002 to physicians believed to be using lymphocyte immunotherapy to prevent miscarriages. He informed them that the injectable products used in lymphocyte immunotherapy do not have the required FDA approval and are considered investigational drugs that pose several safety concerns.

Administration of such cells or cellular products in humans can only be performed in the United States as part of clinical investigations, and then only if there is an Investigational New Drug application (IND) in effect. All institutions, reproductive centers, and physicians were reminded that they should not administer allogeneic cells or cellular products to miscarriage patients until an IND has been submitted and reviewed by the FDA's Center for Biologics Evaluation and Research.

Intravenous immunoglobulin has become a popular treatment for unexplained recurrent miscarriage in some centers. One meta-analysis of four randomized trials reported a treatment effect of 10% (Daya 1998). However, a more recent meta-analysis using both published data (MAL) and review of individual patient data (MAP) from six trials indicates that IVIG treatment has no clinically meaningful effect on the live birth rate (Daya 1999). The authors of the latest randomized trial (Christiansen 2002) suggested that IVIG may have a role in the treatment of women with secondary recurrent miscarriage. However, inclusion of their data with the six other trials shows no significant increase in the overall pregnancy success rate over placebo or no treatment. These data on the use of IVIG for recurrent miscarriage are important because of its expense, not to mention the serious and life-threatening reactions to IVIG, which have occasionally been reported (Duhem 1994).

AUTHORS' CONCLUSIONS

Implications for practice

Neither immunization with paternal leukocytes nor treatment with intravenous immunoglobulin (IVIG) improve the live birth rate in women with unexplained recurrent miscarriage. Both are expensive and have potential serious side effects. Moreover, women should be spared the pain and grief associated with false expectations that an ineffective treatment might work. These therapies should no longer be offered as treatment for unexplained recurrent pregnancy loss. Furthermore, immunological laboratory tests, which have been previously been advocated as justification for immunotherapies, have no predictive value for pregnancy success and should be abandoned.

Implications for research

Effective treatment of an alleged alloimmune cause of recurrent miscarriage awaits more complete knowledge of the underlying pathophysiology. A specific assay to diagnose immune-mediated early pregnancy loss and a reliable method to determine which women might benefit from manipulation of the maternal immune system are urgently needed. It is not presently known exactly how many recurrent early pregnancy losses are the result of anembryonic or chromosomally abnormal conceptuses, anatomic or structural abnormalities and how many are embryonic or fetal deaths. It is likely that some unexplained early losses are due to as yet undefined subchromosomal genetic abnormalities impairing early development of the conceptus (Copp 1995; Pegoraro 1997; Quenby 2002; Rossant 2001; Spandidos 1998; Tempfer 2001; Tsai 1998). New molecular techniques should be directed at understanding the factors responsible for successful pregnancy as well as pregnancy loss.

To establish definitively or to rule out the efficacy of any proposed treatment for recurrent pregnancy loss, randomized controlled trials with adequate numbers of participants are needed. These should be studies approved by institutional review boards in centers with research expertise and interest in this problem. New therapeutic modalities should be tested only under protocol with rigorous study designs. Finally, further studies on complications of treatment and long-term follow-up of offspring are necessary. The National Institutes of Health (NIH) in the United States and other funding agencies should be encouraged to support proposals that offer new and innovative approaches to this problem. The Agency of Health Care Policy and Research in the United States and similar funding agencies in other countries need to support proposals to evaluate outcome of treatments especially for large trials.

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Scott 2003

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Cauchi 1991

Methods	Women were allotted to 1 or the other treatment group using a computer-generated list of numbers. Neither the treating physician nor the women knew whether they were injected with cells or placebo.
Participants	3 or more consecutive first trimester miscarriages with the same partner, and after exclusion of other known causes of recurrent miscarriage. Assessment included full physical gynecological examination for evidence of fibroids, excluding other abnormalities of the uterus, by hysterosalpingogram and/or hysteroscopy, endocrinological tests including thyroid function tests, hemoglobin A1C, and chromosomal abnormalities. Standard coagulation tests (including aPTT, KCT), auto-antibody tests (including anti-nuclear antibody, anti-DNA antibody) as well as anti-cardiolipin antibody were performed, and women were excluded if the results were abnormal. Women were also excluded from this study if they were rhesus negative or had cytotoxic antibodies.
Interventions	Mononuclear cells (10-100 million) were prepared from 100-150 mL of heparinized blood taken from the partner, separated by density centrifugation and concentrated to 2 mL, half of which was injected intravenously and the rest injected into multiple sites intradermally and subcutaneously. Women in the control group were given 2 mL of normal saline, injected in the same manner.

Cauchi 1991 *(Continued)*

Outcomes	Live births after paternal white cell immunization or placebo.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were allotted to 1 or the other treatment group using a computer-generated list of numbers.
Allocation concealment (selection bias)	Low risk	Adequate.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Neither the treating obstetrician nor the patient knew whether they were injected with cells or saline.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Neither the treating obstetrician nor the patient knew whether they were injected with cells or saline.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear. A paired sequential trial was performed but it is unclear whether a portion of the women enrolled were later excluded if any participants were excluded.
Selective reporting (reporting bias)	Low risk	All expected outcome results reported.
Other bias	Low risk	Appears to be free of other sources of bias of bias.

Christiansen 1994

Methods	Women were randomly allocated to the treatment or control group in a 2:1 ratio. Neither the couple nor the woman's obstetrician knew whether active treatment or placebo was provided.
Participants	At least 3 consecutive miscarriages documented by pregnancy tests or ultrasound scans, a maximum of 1 pregnancy loss after 14th week of gestation, and not consanguineous with spouse; all known causes excluded.
Interventions	Immunization with intravenous infusions of 150 mL buffycoat (leukocyte enriched blood) from erythrocyte compatible third-party donors or 150 mL of the woman's autologous blood (control). The women were given 1 repeated infusion of third-party buffycoat (from 2 donors) or autologous blood every fifth month until conception.
Outcomes	Live births after donor leukocytes vs placebo.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Christiansen 1994 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Insufficient information about the sequence generation process to permit judgement.
Allocation concealment (selection bias)	Low risk	Adequate.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Neither the couple nor the women's obstetricians knew whether active treatment or placebo was provided.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Neither the couple nor the women's obstetricians knew whether active treatment or placebo was provided.
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 woman did not complete immunization procedure because of anaphylactic reaction.
Selective reporting (reporting bias)	Low risk	All expected outcome results reported.
Other bias	Low risk	Appears to be free of other sources of bias.

Christiansen 1995

Methods	Women were randomized to the treatment or control group.
Participants	3 or more miscarriages and no more than 1 live birth or 1 fetal death after 14 weeks' gestation. All had a negative evaluation for other causes of miscarriage including hysterosalpingography or hysteroscopy, parental karyotypes, luteal phase progesterone level, and systemic lupus erythematosus. Women were eligible if they had no IgA deficiency.
Interventions	IVIG or human albumin given at week 5-8, then every other week. IVIG was adjusted according to weight: (1) 60-80 kg: 35 g in week 5-6; 25 g weeks 7-26; 30 g weeks 28, 30 32 and 34. (2) > 80 kg: 5 g more at each infusion.
Outcomes	Live births after IVIG vs placebo.
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomizaton was performed using the sealed envelope method by computerized randomization. Each number on the randomization list corresponded to either treatment with IV Ig or placebo.
Allocation concealment (selection bias)	Low risk	Adequate.
Blinding of participants and personnel (performance bias)	Low risk	The packages of Nordimmun/placebo could not be distinguished between, and the codes were blinded for both the patients and hospital staff, including the authors.

Christiansen 1995 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The packages of Nordimmun/placebo could not be distinguished between, and the codes were blinded for both the patients and hospital staff, including the authors.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data.
Selective reporting (reporting bias)	Low risk	All expected outcome results reported.
Other bias	Low risk	Appears to be free of other sources of bias.

Christiansen 2002

Methods	Women were randomly allocated to the treatment or placebo group. Neither the patients, hospital staff nor physicians knew whether IVIG or placebo was provided.
Participants	1) History of 4 or more confirmed miscarriages before the end of the 26th gestational week, of which the last 3 had been consecutive. 2) No uterine or parental chromosome abnormality. 3) Regular menstruation with cycle length between 21 and 35 days. 4) Written, informed consent, and 5) A positive pregnancy test carried out in the hospital. Exclusion criteria were: 1) Total IgA deficiency. 2) Autoimmune rheumatic disease. 3) Insulin dependent diabetes mellitus. 4) Pregnancy obtained by IVF or controlled ovarian stimulation. 5) Application to participate in the trial later than 7 days after the expected menstruation.
Interventions	Weekly IVIG or human albumin given at week 5 until week 10. Infusions were subsequently carried out every second week until the 26th week of gestation. Until the 20th gestational week, a total of 0.8 g of study drug per kg body weight was administered. From gestational weeks 20 to 26, 1.0 g of study drug per kg bodyweight was given.
Outcomes	Primary effect: proportion of all randomized participants in the 2 allocation groups discharged from the birth clinic with at least 1 living child. Secondary effects: 1) LBR after exclusion of participants with S-P level < 35 nmol/L and a beta hCG level < 100 U/L at the time of exclusion before the first infusion. 2) LBR after exclusion of participants with ectopic pregnancies, miscarriages with a chromosome abnormal fetus or fetal losses immediately after invasive prenatal diagnostics. 3) LBR after exclusions of both. 4) LBR among participants with secondary recurrent miscarriage.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	When a serum or urine B-HCG test was positive, the patient was allocated a consecutive number of randomization.

Christiansen 2002 *(Continued)*

Allocation concealment (selection bias)	Low risk	Allocation to the treatment arms was made according to a computer-generated randomization list which was retained by HemaSure A/S, Copenhagen, during conduct of the trial.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The randomization code was blinded to the patients and hospital staff (including the authors) until after the last included patient had given birth and all data had been entered into a computer database. The placebo drug could not be distinguished visually from the active drug.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The randomization code was blinded to the patients and hospital staff (including the authors) until after the last included patient had given birth and all data had been entered into a computer database.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data.
Selective reporting (reporting bias)	Low risk	All expected outcome results reported.
Other bias	Low risk	Appears to be free of other sources of bias.

Coulam 1995

Methods	Women were randomized to the treatment or control group.
Participants	Between ages 18-45 with 2 or more miscarriages and a normal evaluation for other causes of miscarriage which included hysterosalpingography or hysteroscopy, parental karyotypes, luteal phase endometrial biopsy or progesterone level, anticardiolipin antibody, and aPTT. No history of IgA deficiency or hypersensitivity to immunoglobulin.
Interventions	500 mg/kg IVIG vs 0.5% albumin given in the follicular phase of the cycle and every 28 days until pregnancy was achieved and then continued until 28-32 weeks' gestation.
Outcomes	Live births after IVIG or placebo.
Notes	Only women with 3 or more miscarriages included in this review.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	A total of 95 women were randomized using computer-generated random number.
Allocation concealment (selection bias)	Low risk	Adequate.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded, placebo-controlled trial.
Blinding of outcome assessment (detection bias)	Low risk	Double-blinded, placebo-controlled trial.

Coulam 1995 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Low risk	Medication was discontinued in 34 women (18 receiving IVIG and 16 placebo) because of lack of conception. Otherwise no missing data for those who conceived.
Selective reporting (reporting bias)	Low risk	All expected outcome results reported.
Other bias	Low risk	Appears to be free of other sources of bias.

Gatenby 1993

Methods	Multicenter trial, randomized to paternal white cell immunization or autologous white cell immunization (control) using random number tables. Neither the women, the treating obstetrician, nor the staff were aware of the source of cells the women received.
Participants	3 or more consecutive miscarriages prior to 20 weeks' gestation with 1 sexual partner and no more than 1 previous live birth. All other known causes of miscarriage were excluded by gynecological examination, hysterogram, parental chromosome analysis, thyroid function tests, blood glucose, premenstrual endometrial biopsy, serum copper, TORCH titers, serum creatinine, anticardiolipin antibodies, lupus anticoagulant, and ANA. Women with lymphocytotoxic antibodies were also excluded.
Interventions	400 million paternal or maternal (placebo) peripheral blood mononuclear leukocytes injected IV, IM and subcutaneously.
Outcomes	Live births after paternal white cell immunization or placebo.
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomized in groups of 4 using random number tables.
Allocation concealment (selection bias)	Low risk	Adequate.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Neither the patient, the treating obstetrician, nor the staff in Clinical Immunology with whom the patients dealt were aware of the source of cells the patient received.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Neither the patient, the treating obstetrician, nor the staff in Clinical Immunology with whom the patients dealt were aware of the source of cells the patient received.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Incomplete reporting of missing data to permit judgement of level of risk. Perusal of the sequential trial chart indicates that the study was suspended 1 couple short of the stopping line. This was done because 3 women who received their own cells could not be paired with women who received their husband's cells because the latter had not yet conceived.

Gatenby 1993 *(Continued)*

Selective reporting (reporting bias)	Low risk	Appears to be free of other sources of bias.
Other bias	Low risk	Appears to be free of other sources of bias.

German RSA/IVIG 1994

Methods	Multicenter trial with randomization carried out centrally in blocks of 4 into treatment or control groups.
Participants	3 or more miscarriages < 16 weeks' gestation and no live children with the following inclusion criteria: age < 40 years, exclusion of known gynecological, genetic or endocrinologic causes, no history of leukocyte treatment or blood transfusion, no IgA deficiency, gestational age of present pregnancy not beyond 8 weeks' gestation.
Interventions	30 g of IVIG or 5% albumin (control) initiated at < 8 weeks' gestation and 20 g given thereafter every 3 weeks until 25 weeks' gestation.
Outcomes	Live births after IVIG or placebo.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization was carried out centrally in blocks of 4. Chronological sequence of code numbers was required (1 number per patient).
Allocation concealment (selection bias)	Low risk	Adequate.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind trial, with central randomization and distribution of treatment/placebo.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind trial, with central randomization and distribution of treatment/placebo.
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 case could not be evaluated because the woman left the study at an early stage. Her pregnancy was successful. Performed intention-to-treat analysis.
Selective reporting (reporting bias)	Low risk	All expected outcome results reported.
Other bias	Low risk	Appears to be free of other sources of bias.

Ho 1991

Methods	Women were randomly assigned to paternal white cell immunization or immunization with autologous white cells (control).
Participants	3 or more consecutive miscarriages with the same husband and no other cause found for miscarriage with the following tests: parental chromosome analysis, hysterosalpingography and hysteroscopy, serum prolactin, testosterone, T3, T4, TSH, fasting and postprandial blood glucose, midluteal phase progesterone levels x2, C3, C4, ANA, anti-ENA, anti-DNA, aPTT, anticardiolipin antibody.
Interventions	100-200 million paternal or autologous (control) peripheral blood lymphocytes injected intradermally. Women who did not seroconvert by lymphocytotoxic assays were given a further dose of lymphocytes prepared from 50 mL of blood. Women who did not conceive within 6 months and did not have lymphocytotoxic antibodies were re-immunized.
Outcomes	Live births after paternal cell immunization or placebo.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about the sequence generation to permit judgement on risk.
Allocation concealment (selection bias)	Unclear risk	Insufficient information about the sequence generation to permit judgement on risk.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	If a patient could not conceive within 6 months, she was re-examined, and if she did not have any antibodies against the immunizing lymphocytes, she was reimmunized. It is unclear how many patients in each arm were reimmunized, and if blinding was broken in these cases.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	If a patient could not conceive within 6 months, she was re-examined, and if she did not have any antibodies against the immunizing lymphocytes, she was reimmunized. It is unclear how many patients in each arm were reimmunized, and if blinding was broken in these cases.
Incomplete outcome data (attrition bias) All outcomes	High risk	Results reported while a portion had not yet delivered/completed the study (13 in treatment group and 9 in control group). The number of missing outcomes in the treatment arm is > 20% and may induce clinically relevant bias.
Selective reporting (reporting bias)	Low risk	All expected outcome results reported.
Other bias	Low risk	Appears to be free of other sources of bias.

Illeni 1994

Methods	Women were randomized by telephone to the physician (multicenter study) from a computer-generated randomization list to paternal cell or no treatment groups. The treatment and control groups were not blinded to investigators, patients or physicians.
Participants	At least 3 miscarriages and no live births who had all nonimmunologic causes ruled out. Women were also excluded if they had a positive test for lupus anticoagulant, anticardiolipin, or ANA test, a positive MLR, or she matched with her husband at the DR3 HLA locus.

Illeni 1994 *(Continued)*

Interventions	Paternal leukocytes from 400 mL blood (200 million cells) injected intravenously, intradermally, and subcutaneously or no treatment.
Outcomes	Live births after paternal white cell immunization or no treatment.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were allocated to 1 of the following treatments by phone according to a computer-generated randomization list.
Allocation concealment (selection bias)	Low risk	Patients were allocated to 1 of the following treatments by phone according to a computer-generated randomization list.
Blinding of participants and personnel (performance bias) All outcomes	High risk	The treatment and control groups were not blinded to investigators, patients or physicians.
Blinding of outcome assessment (detection bias) All outcomes	High risk	No placebo. No specific instructions were given for clinical management of pregnancy, but clinicians were asked to manage the 2 treatment groups similarly.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Compliance with the study protocol was complete.
Selective reporting (reporting bias)	Low risk	All expected outcome results reported.
Other bias	Low risk	Appears to be free of other sources of bias.

Jablonowska 1999

Methods	Multicenter; women were centrally randomized, double-blind.
Participants	3 miscarriages < 20 weeks' gestation and all other causes ruled out.
Interventions	20 g IVIG or saline (control) every 3 weeks X5 after ultrasound confirmation of viable pregnancy.
Outcomes	Live births after IVIG or placebo.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A double-blind, randomized, placebo-controlled study. Patients were classified as belonging to a primary or a secondary RSA group. Within each RSA group women were separately, centrally randomized by using sealed en-

Jablonowska 1999 *(Continued)*

		velopes at the hospital pharmacy to IVIG or placebo treatment as soon as a transvaginal ultrasound scan had identified fetal heart activity.
Allocation concealment (selection bias)	Low risk	Adequate.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	IVIG and saline (placebo) could not be distinguished, and the codes were blind for both the patients and the hospital staff. IVIG were distributed 2 h after request and in identical, nontransparent plastic bags.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Adequate.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data.
Selective reporting (reporting bias)	Low risk	All expected outcome results reported.
Other bias	Low risk	Appears to be free of other sources of bias.

Johnson 1991

Methods	Women were randomized 'by an individual without any knowledge of patients' names or history' into a group treated with trophoblast membrane infusion or a group given a 1:600 dilution of intralipid emulsion that was visually identical to the trophoblast membrane preparation (control).
Participants	At least 3 consecutive confirmed miscarriages by the same partner and no more than 1 live birth with other chromosomal, anatomic, microbiological, and hormonal causes of miscarriage ruled out. Women were also excluded if the following tests were positive or abnormal: lymphocytotoxic antibodies, anti-erythrocyte antibodies, tissue-reactive antibodies, antiphospholipid antibodies, blood coagulation times, and serum IgE.
Interventions	A slow intravenous infusion of a sterile preparation of isolated placental syncytiotrophoblast plasma membrane preparation suspended in 250 mL saline or 250 mL intravenous infusion of the intralipid (placebo) solution.
Outcomes	Live births after trophoblast membrane or placebo infusion.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization for the double-blind trial was performed by an individual without any knowledge of patients' names or history.
Allocation concealment (selection bias)	Low risk	Adequate.

Johnson 1991 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Patients were entirely unaware of whether they had received TMI or placebo until closure of the double-blind study.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome in the randomized double-blind study was monitored by a 'fourth party' who had no contact with either the patients or those staff members directly involved with this study.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data.
Selective reporting (reporting bias)	Low risk	All expected outcome results reported.
Other bias	Low risk	Early stopping: When it became apparent that there was much less than 5% probability that TMI could ever show any advantage over placebo without an impossible increase in patient numbers, the double-blind trial was stopped.

Kilpatrick 1994

Methods	This study was part of a multicentered trial, and randomization was organized centrally. A numbered envelope was obtained, and the blood bank technician prepared the appropriate cells, which were injected by the investigator. Neither investigators, women, nor physicians were aware of the treatment.
Participants	At least 3 miscarriages and no more than 1 live birth and all non-immunologic causes ruled out. Women were excluded if they has a positive test for lupus anticoagulant, anticardiolipin, ANA, or lymphocytotoxic antibodies.
Interventions	Paternal leukocytes from 100 mL blood or autologous leukocytes from 40-60 mL blood given intravenously, intradermally, and subcutaneously and boosted once in early pregnancy.
Outcomes	Live births after paternal white cell immunization or placebo.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization was done by giving a numbered envelope from Oxford along with blood samples from both the patent and partner to the technician preparing the vaccine.
Allocation concealment (selection bias)	Low risk	Adequate.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Neither investigators, patients, or physicians were aware of the treatment.
Blinding of outcome assessment (detection bias)	Low risk	Neither investigators, patients, or physicians were aware of the treatment.

Kilpatrick 1994 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Low risk	3 pregnant patients were excluded from analysis as they had not yet delivered.
Selective reporting (reporting bias)	Low risk	All expected outcome results reported.
Other bias	Low risk	Appears to be free of other sources of bias.

Mowbray 1985

Methods	A computer-generated list of pseudo-randomized numbers was used to allot the woman to receive either her husband's or her own lymphocytes. Neither the obstetrician nor the couple knew which cells were used until after completion of the next pregnancy.
Participants	At least 3 miscarriages with the same partner and no more than 1 live birth who had no detectable antibody against paternal lymphocytes and no cause found for miscarriages who were rhesus positive and were UK residents. The screening procedure to rule out other causes included antibodies for brucella and toxoplasmosis, cultures for cytomegalovirus, chlamydia, and herpes simplex, serum thyroxine, random blood sugar, 'evidence' for cervical incompetence, fibroids or septate uterus, parental chromosome analysis, and lymphocytoxic antibody.
Interventions	5 mL of buffycoat paternal or autologous (control) peripheral blood lymphocytes injected intravenously, intradermally, and subcutaneously.
Outcomes	Live births after paternal white cell immunization or placebo.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	A computer-generated list of pseudo-random numbers was used to allot the patient to receive either her own or her husband's lymphocytes. Insufficient information provided with regards to pseudo-random number generation to permit judgement of risk.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement of risk.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Neither the obstetrician nor the couple knew either which cells were used or the results of the antibody tests until after completion of the next pregnancy.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Adequate.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Use of a sequential trial chart. At the completion of the trial 53 of 105 women had become pregnant, and results were completed for 47 of them. 2 pairs had to be discarded—in 1 case the woman had an ectopic pregnancy and in the

Mowbray 1985 *(Continued)*

		other there was considerable doubt at the time of delivery as to whether the pregnancy had reached 28 weeks' gestation.
Selective reporting (reporting bias)	Low risk	All expected outcome results reported.
Other bias	Low risk	Appears to be free of other sources of bias.

Ober 1999

Methods	Computer randomization was stratified centrally with permuted blocks of size 8 and 10.
Participants	At least 3 miscarriages that were not of chromosomally abnormal fetuses or ectopic pregnancies; no more than 1 liveborn child; age 40 years or younger; not pregnant at time of immunization; no anti-HLA antibodies; no identifiable cause for previous miscarriages.
Interventions	5 mL paternal lymphocytes (200 million lymphocytes) injected ravenously, intramuscularly and subcutaneously or sterile saline (control).
Outcomes	Live births after paternal white cell immunization or placebo.
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer randomization was stratified centrally with permuted blocks of size 8 and 10.
Allocation concealment (selection bias)	Low risk	Opaque, sequentially numbered, sealed envelopes, prepared by the study biostatistician were kept at the Blood Bank (USA) or Transfusion Medicine Center (Canada) of each center.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Neither the patients nor the study personnel who had contact with the patients were aware of the treatment allocation.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Neither the patients nor the study personnel who had contact with the patients were aware of the treatment allocation.
Incomplete outcome data (attrition bias) All outcomes	Low risk	3 of 89 patients in the treatment arm were censored and 5 of 90 patients in the placebo arm were censored. The proportion of missing outcomes are not likely to have a relevant impact.
Selective reporting (reporting bias)	Low risk	All expected outcome results reported.
Other bias	Low risk	Appears free of other sources of bias.

Pandey 2004

Methods	Single center, double-blind, placebo-controlled RCT.
Participants	Inclusion criteria: 1) 3 or more pregnancy losses < 20 weeks' gestation, 2) normal karyotype, 3) negative serology for toxoplasmosis, antiphospholipid antibodies, antinuclear antibodies, antithyroid antibodies, and antiendothelial cell antibodies, 4) normal glucose tolerance, hysterosalpingogram, thyroid function tests, luteal phase plasma progesterone, pelvic ultrasound, and mixed lymphocyte reaction blocking antibodies. Exclusion criteria: 1) positive test for blocking antibody prior to paternal cell immunization.
Interventions	5 mL paternal, autologous (control), or third-party lymphocytes injected intravenously, intramuscularly, or subcutaneously at 4-week intervals to a maximum of 6 total injections. Women who developed a blocking antibody were advised to conceive.
Outcomes	Live birth.
Notes	Only women who received autologous lymphocytes, paternal lymphocytes, and normal saline, were included in this review. Original study used only intention-to-treat.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	All women participants with RSA were enrolled in double-blind randomized trial by randomization in groups of 4 using a computer-generated list of random numbers.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	This trial was carried out in which neither the patient, the treating doctors, nor the staff in Medical Genetics of SGPGIMS, Lucknow, with whom the patients dealt, where aware of the source of the therapy the patient received.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	This trial was carried out in which neither the patient, the treating doctors, nor the staff in Medical Genetics of SGPGIMS, Lucknow, with whom the patients dealt, where aware of the source of the therapy the patient received.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data.
Selective reporting (reporting bias)	Low risk	All expected outcome results reported.
Other bias	Low risk	Appears to be free of other sources of bias.

Perino 1997

Methods	Multicenter; computer-generated central allocated, randomized, double-blind trial.
Participants	At least 3 miscarriages and no live births < age 42 and all known causes excluded.
Interventions	IVIG 25 g/day on 2 consecutive days and 25 g 3 weeks later with ultrasound confirmation of viable pregnancy or saline solution with 5% human albumin (control).

Perino 1997 *(Continued)*

Outcomes	Live births after IVIG or placebo.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were randomized by a computer-generated random number list to receive either treatment or placebo.
Allocation concealment (selection bias)	Low risk	Each participating center received coded units continuing Ig or placebo which could not be identified by the center. The coded list was kept confidential by Sclavo Pharmaceutical Company. The key to the code was provided to the study managers at the end of the research.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinding of participants and key study personnel ensured.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of outcome assessment ensured.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients completed the treatment protocol.
Selective reporting (reporting bias)	Low risk	All expected outcome results reported.
Other bias	Low risk	Appears to be free of other sources of bias.

Reznikoff 1994

Methods	Sealed envelopes with paternal or autologous group were opened in the blood bank (laboratory) where the appropriate cells were prepared and administered. Physicians and women were unaware of which treatment was given.
Participants	At least 3 miscarriages with the same partner and no live births who were less than 36 years of age, had all other nonimmunologic causes ruled out, and had no lymphocytotoxic antibodies. Women were also excluded if they did not achieve a pregnancy within 6 months.
Interventions	Approximately 400 million (range 146-1075 million) paternal or autologous leukocytes were injected intravenously, intradermally, and subcutaneously.
Outcomes	Live births after paternal white cell immunization or placebo.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Reznikoff 1994 *(Continued)*

Random sequence generation (selection bias)	Low risk	Prospective, double-blind, randomized.
Allocation concealment (selection bias)	Low risk	Sealed envelopes with paternal or autologous group opened by the blood bank (laboratory) which then prepared the appropriate cells and administered the injection.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Physicians and patients were unaware of treatment.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Physicians and patients were unaware of treatment.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Ongoing trial. Do not have records on the total number of patients entered into the multicentered trial. Records available for 7 of the 12 participating centers. 8 patients were excluded from the treatment group (1 ectopic pregnancy, 5 not pregnant, 1 code broken because of a reaction, 1 eliminated because did not meet inclusion criteria). 6 patients were excluded in the placebo group (1 ectopic pregnancy and 5 not pregnant).
Selective reporting (reporting bias)	Low risk	All expected outcome results reported.
Other bias	Low risk	Appears to be free of other sources of bias.

Scott 1994

Methods	A computer-generated list was used to randomize women into paternal versus saline control groups. The allotted groups were obtained by the project nurse who informed the blood bank, gave the appropriate cells, and kept all records. Neither investigators, women nor physicians were aware of the treatment given.
Participants	At least 3 consecutive miscarriages and no more than 1 live birth who had all non-immunologic causes ruled out.
Interventions	Paternal leukocytes or donor leukocytes from 1 unit of blood (400-900 million cells) or saline were given intravenously in a blinded fashion.
Outcomes	Live births after paternal or donor white blood cell immunization or placebo.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Prospective, double-blind, randomization from computerized list.
Allocation concealment (selection bias)	Low risk	Randomization list and treatment was obtained by the nurse from the blood bank.

Scott 1994 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Neither investigators, patients, or physicians were aware of treatment.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Neither investigators, patients, or physicians were aware of treatment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Ongoing trial at the time of assessment.
Selective reporting (reporting bias)	Low risk	All expected outcome results reported.
Other bias	Low risk	Appears to be free of other sources of bias.

Stephenson 1998

Methods	Centrally randomized, double-blind trial.
Participants	At least 2 consecutive miscarriages < 20 weeks' gestation and all known causes excluded.
Interventions	IVIG 500 mg/kg pre-pregnancy or normal saline (control).
Outcomes	Live births after IVIG or placebo.
Notes	Only women with 3 or more miscarriages and no more than 1 live birth included in this review.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization was stratified for primary, secondary, and unclassified unexplained RSA, as previously defined. An individual code number assigned to each enrollee was not to be broken unless medically indicated.
Allocation concealment (selection bias)	Low risk	An individual code number assigned to each enrollee was not to be broken unless medically indicated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Neither investigators, patients, or physicians were aware of treatment.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Neither investigators, patients, or physicians were aware of treatment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Individual code number was broken for 2 patients during the trial. 2 patients developed generalized rashes after the administration of an infusion. 1 of the 2 was receiving saline, and the rash was diagnosed as contact dermatitis. Skin biopsies confirmed that the second patient had an allergic response to IVIG. Subsequent infusions were discontinued, The third patient had acute Graves

Stephenson 1998 *(Continued)*

		disease develop during the initial infusion. This patient was found to be receiving saline but was withdrawn from the trial.
Selective reporting (reporting bias)	Low risk	All expected outcome results reported.
Other bias	Low risk	Appears to be free of other sources of bias.

Stray-Pederson 1994

Methods	'Randomization was performed at the Institute of Transplantation Immunology.' Treatment was blinded to the investigator, physicians and women.
Participants	At least 3 verified first trimester miscarriages with the same partner who had all non-immunologic causes ruled out and who had a negative test for lymphocytotoxic antibodies.
Interventions	Immunization with 100-150 million paternal or autologous leukocytes injected intravenously, intradermally, and subcutaneously.
Outcomes	Live births after paternal or autologous white cell immunization.
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomization was performed at the Institute of Transplantation Immunology.
Allocation concealment (selection bias)	Low risk	Randomization was performed at the Institute of Transplantation Immunology.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Treatment was blinded to the investigator, physicians, and patients.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Treatment was blinded to the investigator, physicians, and patients. The code was broken 12 months after immunization or after the patient had achieved a pregnancy of 16 weeks' gestation. However, outcome measurement (live birth) is not likely to be influenced by incomplete blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Ongoing trial at the time of assessment. No missing data.
Selective reporting (reporting bias)	Low risk	All expected outcome results reported.
Other bias	Low risk	Appears to be free of other sources of bias.

anti-ENA: extractable nuclear antigen antibodies
aPTT: activated partial thromboplastin time
ANA: antinuclear antibody

hCG: human chorionic gonadotropin
HLA: human leukocyte antigens
IgA: immunoglobulin A
IM: intramuscular
IV: intravenous
IVF: intravenous fertilization
IVIG: intravenous immunoglobulin
KCT: Kaolin Clotting Time
LBR: live birth rate
MLR: mixed lymphocyte reaction
RCT: randomized controlled trial
RSA: recurrent spontaneous abortion
S-P: serum progesterone
TMI: trophoblast membrane immunization
TSH: thyroid stimulating hormone
vs: versus

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Aoki 1993	Randomized to 2 different doses of paternal cells.
Check 1995	Not relevant to scope of this review. The type of intervention (progesterone and paternal lymphocyte immunization vs. progesterone alone) does not meet eligibility criteria for our review.
Christiansen 1992	A study of women positive for anticardiolipin antibodies.
Cowchock 1995	Compares outcomes of paternal cell immunization before conception vs. after conception, without a placebo group.
Kilpatrick 1993	Type of comparison was not within the randomization arm. Live birth is not one of the study's outcomes measured.
Kim 2012	Type of intervention (Etanercept versus IVIG) does not meet eligibility criteria for our review.
Kwon 2012	Does not meet criteria for outcome measure (does not examine live birth).
Li 1998	Compares immunization of leukocyte from paternal donor versus immunization of leukocyte from third-party donor. No placebo or control.
Mahmoud 2004	Women included for treatment in the study were positive for antiphospholipid syndrome and a portion had a history of more than 1 prior live birth.
Quenby 2007	Not relevant to the scope of this review. The type of intervention (prednisolone vs placebo) does not meet eligibility criteria for our review.
Redman 1996	To our knowledge, the data from this multicentered trial were never analyzed or published.
Sagot 1993	This study is not a randomized controlled trial.
Scarpellini 2009	Not relevant to scope of this review. The type of intervention (recombinant G-CSF) does not meet eligibility criteria for our review.
Scarpellini 2011	Not relevant to the scope of this review. The type of intervention (recombinant G-CSF) does not meet eligibility criteria for our review.
Stephenson 2001	To our knowledge, the data from this trial were never analyzed or published.

Study	Reason for exclusion
Stephenson 2010	Does not meet our criteria for participants: a portion of women included had more than 1 ongoing pregnancy beyond 20 weeks (unclear what portion resulted in live births) and a portion had less than 3 miscarriages.
Tang 2009	Not relevant to the scope of this review. The type of intervention (prednisolone vs placebo) does not meet eligibility criteria for our review.
Tang 2011	Not relevant to the scope of this review. The type of intervention (prednisolone vs placebo) does not meet eligibility criteria for our review.
Tang 2013	Not relevant to the scope of this review. The type of intervention (prednisolone vs placebo) does not meet eligibility criteria for our review.

G-CSF: Granulocyte-colony stimulating factor
IVIG: intravenous immunoglobulin

Characteristics of studies awaiting assessment *[ordered by study ID]*

Sun 2010

Methods	Prospective trial (details not provided in English).
Participants	Women with unexplained recurrent spontaneous abortion (definition not provided in English).
Interventions	IVIG versus traditional Chinese medicine and/or progesterone initiated once pregnancy is confirmed and continued every 4 weeks until 20 weeks' gestation.
Outcomes	Live birth rate was 24/28 in the treatment group and 17/30 in the control group, P = 0.021.
Notes	Abstract is in English but the body of the publication is in Chinese. Awaiting translation.

IVIG: intravenous immunoglobulin

DATA AND ANALYSES

Comparison 1. Paternal white cell immunization versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Live birth rate	12	641	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.23 [0.89, 1.70]
2 Live birth rate - intention-to-treat	4	350	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.38 [0.90, 2.12]

Analysis 1.1. Comparison 1 Paternal white cell immunization versus placebo, Outcome 1 Live birth rate.

Study or subgroup	Paternal WBC immunization n/N	Placebo n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Cauchi 1991	13/20	16/22		6.26%	0.7[0.19,2.56]
Christiansen 1994	4/8	16/28		4.31%	0.75[0.16,3.59]
Gatenby 1993	13/19	12/20		6.28%	1.43[0.39,5.2]
Ho 1991	33/42	32/49		12.73%	1.9[0.77,4.71]
Illeni 1994	10/16	11/14		4.42%	0.48[0.1,2.22]
Kilpatrick 1994	8/12	6/10		3.61%	1.32[0.24,7.24]
Mowbray 1985	25/37	14/30		11.16%	2.33[0.88,6.14]
Ober 1999	31/68	41/63		22.25%	0.46[0.23,0.91]
Pandey 2004	21/25	6/20		7.44%	9.03[2.75,29.57]
Reznikoff 1994	17/26	14/26		8.7%	1.6[0.53,4.79]
Scott 1994	6/10	5/12		3.9%	2.01[0.39,10.38]
Stray-Pederson 1994	24/33	22/31		8.95%	1.09[0.37,3.21]
Total (95% CI)	**316**	**325**		**100%**	**1.23[0.89,1.7]**
Total events: 205 (Paternal WBC immunization), 195 (Placebo)					
Heterogeneity: $Tau^2=0$; $Chi^2=24.58$, df=11(P=0.01); $I^2=55.26\%$					
Test for overall effect: Z=1.26(P=0.21)					

Favours placebo — Favours Paternal WBC

Analysis 1.2. Comparison 1 Paternal white cell immunization versus placebo, Outcome 2 Live birth rate - intention-to-treat.

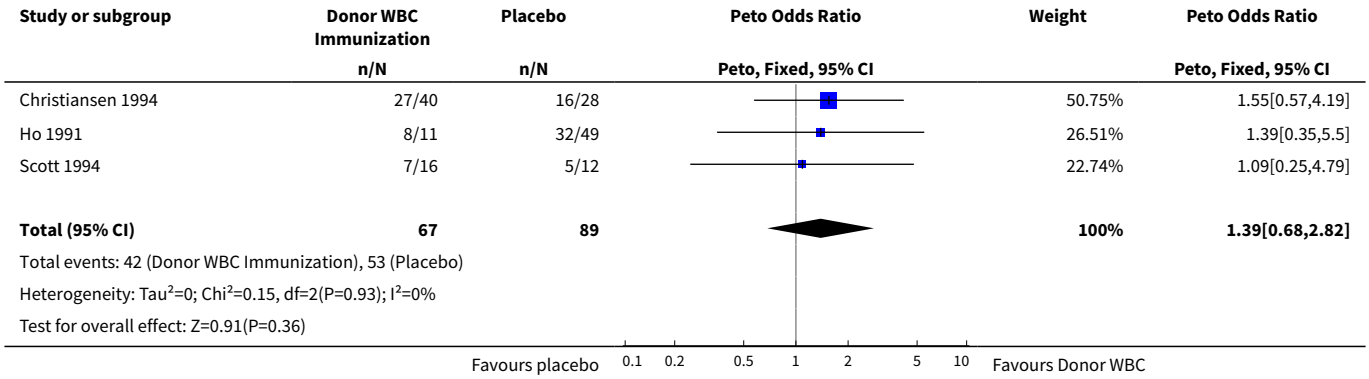
Study or subgroup	Paternal WBC immunization n/N	Placebo n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Gatenby 1993	13/22	9/22		13.44%	2.04[0.63,6.55]
Illeni 1994	10/22	11/22		13.41%	0.84[0.26,2.7]
Ober 1999	31/91	41/92		52.43%	0.65[0.36,1.17]
Pandey 2004	21/32	6/47		20.72%	10.17[3.97,26.08]
Total (95% CI)	**167**	**183**		**100%**	**1.38[0.9,2.12]**
Total events: 75 (Paternal WBC immunization), 67 (Placebo)					
Heterogeneity: $Tau^2=0$; $Chi^2=24.78$, df=3(P<0.0001); $I^2=87.89\%$					
Test for overall effect: Z=1.48(P=0.14)					

Favours placebo — Favours Paternal WBC

Comparison 2. Donor white cell immunization versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Live birth rate	3	156	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.39 [0.68, 2.82]

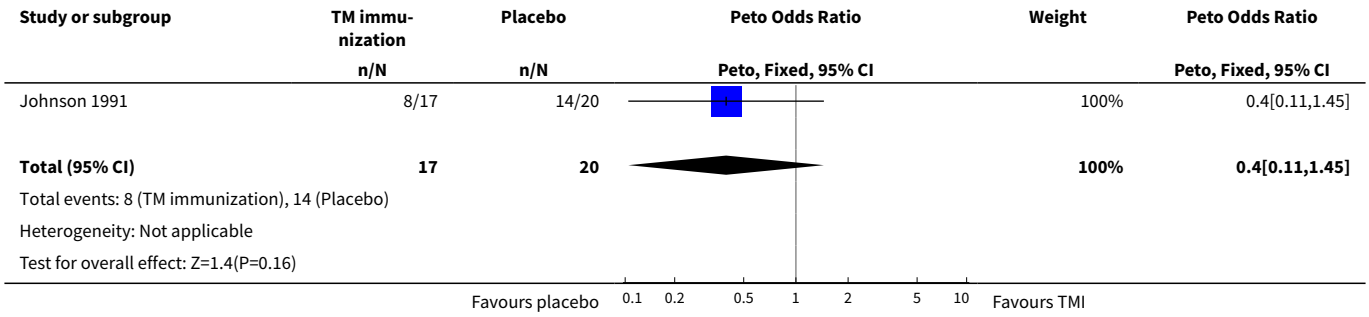
Analysis 2.1. Comparison 2 Donor white cell immunization versus placebo, Outcome 1 Live birth rate.



Comparison 3. Trophoblast membrane immunization versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Live birth rate	1	37	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.40 [0.11, 1.45]

Analysis 3.1. Comparison 3 Trophoblast membrane immunization versus placebo, Outcome 1 Live birth rate.



Comparison 4. Intravenous immunoglobulin versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Live birth rate	8	303	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.98 [0.61, 1.58]
2 Live birth rate - intention-to-treat	4	279	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.18 [0.72, 1.93]

Analysis 4.1. Comparison 4 Intravenous immunoglobulin versus placebo, Outcome 1 Live birth rate.

Study or subgroup	IVIG n/N	Placebo n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Cauchi 1991	0/1	0/1			Not estimable
Christiansen 1995	8/14	2/8		7.82%	3.45[0.63,18.95]
Christiansen 2002	13/29	13/29		21.59%	1[0.36,2.79]
Coulam 1995	10/21	7/19		14.79%	1.54[0.45,5.31]
German RSA/IVIG 1994	20/33	21/31		22.12%	0.74[0.27,2.03]
Jablonowska 1999	17/22	15/19		10.59%	0.91[0.21,3.93]
Perino 1997	16/22	20/24		11.81%	0.54[0.14,2.18]
Stephenson 1998	8/17	7/13		11.27%	0.77[0.19,3.18]
Total (95% CI)	**159**	**144**		**100%**	**0.98[0.61,1.58]**
Total events: 92 (IVIG), 85 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=3.72, df=6(P=0.71); I^2=0%					
Test for overall effect: Z=0.08(P=0.94)					

Analysis 4.2. Comparison 4 Intravenous immunoglobulin versus placebo, Outcome 2 Live birth rate - intention-to-treat.

Study or subgroup	IVIG n/N	Placebo n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Christiansen 2002	13/29	13/29		22.8%	1[0.36,2.79]
Coulam 1995	18/47	11/48		31.81%	2.05[0.86,4.89]
German RSA/IVIG 1994	20/33	21/31		23.36%	0.74[0.27,2.03]
Stephenson 1998	11/32	10/30		22.03%	1.05[0.37,2.97]
Total (95% CI)	**141**	**138**		**100%**	**1.18[0.72,1.93]**
Total events: 62 (IVIG), 55 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=2.53, df=3(P=0.47); I^2=0%					
Test for overall effect: Z=0.67(P=0.5)					

APPENDICES

Appendix 1. Search strategies

For Porter 2006, authors carried out the following additional searching:

The Cochrane Central Register of Controlled Trials (*The Cochrane Library* 2004, Issue 3) and MEDLINE (1966 to September 2004) using the following terms: (immunoglobulin, intravenous (MeSH) OR leukocytes [immunology] (MeSH) OR immunotherapy (MeSH)) AND (fetal death (MeSH) OR abortion, spontaneous (MeSH) OR abortion, habitual (MeSH) OR fetal loss (two) OR miscarriage$ (tw) OR recurrent abortion$ (tw) OR recurrent miscarriage$ (tw)).

The term MeSH refers to medical subject headings and tw to text word in the title or abstract. The $ is a truncation character which allows all possible suffix variations of the root word. In the search of CENTRAL we replaced the $ with *.

In MEDLINE, the result of this search was combined with the phase one and phase two search strategy developed by Carol Lefebvre of the UK Cochrane Centre (Higgins 2005).

We searched EMBASE (1980 to September 2004) using a sensitive strategy developed by the Cochrane Stroke Group (Stroke Group 2005) combined with the following terms: (immunoglobulin [drug therapy] (sh) OR leukocyte (sh) OR immunotherapy (sh) OR immunization (sh)) AND (fetus death (sh) OR spontaneous abortion (sh) OR recurrent abortion (sh) OR fetal loss (tw) OR miscarriage$ (tw) OR recurrent abortion$ (tw) OR recurrent miscarriage (tw)).

sh refers to subject headings in the EMBASE thesaurus.

FEEDBACK

Dratman, November 2002

Summary

Please comment on whether the trials reported genetic abnormalities in the miscarried fetuses, and whether allowing for these abnormalities changes the conclusions about immunotherapy. Also, several relevant studies are not mentioned in the review, including some from Japan, and it would be good to know why.

Reply

Genetic abnormalities in miscarriage specimens were noted in some studies but not all. Miscarriage specimens with abnormalities were excluded. Only randomized controlled trials were included in this review. While some studies from Japan were identified initially, none were randomized controlled trials.

[Summary of response from Flint Porter, February 2006.]

Contributors

Summary of comment received from Cathy Dratman, November 2002.

WHAT'S NEW

Date	Event	Description
11 February 2014	New citation required but conclusions have not changed	No new studies included.
11 February 2014	New search has been performed	Search updated. Fourteen studies excluded and one is awaiting classification. Methods updated.

HISTORY

Protocol first published: Issue 2, 1996
Review first published: Issue 2, 1996

Date	Event	Description
22 October 2012	Amended	Search updated. Seven new reports added to Studies awaiting classification (Quenby 2007a;Scarpellini 2009a; Scarpellini 2011a; Stephenson 2010a; Sun 2010; Tang 2009a; Tang 2011a).
3 September 2008	Amended	Converted to new review format.
3 January 2006	New citation required but conclusions have not changed	New authors joined the review team to prepare the update.
30 December 2005	New search has been performed	One additional trial has been added (Pandey 2004).

CONTRIBUTIONS OF AUTHORS

Luchin F Wong, MD, MPH: screened studies for inclusion/exclusion; statistical consultant.
T Flint Porter, MD, MPH: screened studies for inclusion.
James R Scott: screened studies for inclusion/exclusion; manuscript editor.

DECLARATIONS OF INTEREST

None known.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Methods updated to current Pregnancy and Childbirth Group standard text.

INDEX TERMS

Medical Subject Headings (MeSH)

Abortion, Habitual [*prevention & control]; Immunotherapy [*methods]; Randomized Controlled Trials as Topic

MeSH check words

Female; Humans; Pregnancy