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Efficacy of Immunotherapy in Recurrent Pregnancy Loss and Recurrent Implantation Failure: Systematic Review and Meta analysis

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Abstract

Recurrent pregnancy loss (RPL) and recurrent implantation failure (RIF) are major challenges in reproductive medicine, often associated with immune dysregulation. Immunotherapy has emerged as a potential strategy to improve reproductive outcomes in these populations. This systematic review and meta-analysis aimed to evaluate the efficacy of immunotherapy in enhancing live birth rates (LBR), clinical pregnancy rates (CPR), and reducing miscarriage rates (MR) in women with RPL and RIF. A comprehensive search of PubMed, EMBASE, Cochrane Library, and ClinicalTrials.gov was conducted up to 31st January 2025 to identify randomized controlled trials (RCTs) assessing immunotherapy interventions such as intravenous immunoglobulin (IVIG), corticosteroids, lymphocyte immunotherapy (LIT), tumor necrosis factor (TNF) inhibitors, and granulocyte-colony stimulating factor (G-CSF). Thirty-six RCTs involving 3,614 women were included. Immunotherapy significantly improved LBR in women with RPL (OR = 1.15, 95% CI: 1.01–1.32, I^2=0%) and showed a stronger, though more variable, effect in RIF (OR = 1.52, 95% CI: 0.88–2.67, I^2=72.4%). Overall, immunotherapy was associated with a significant increase in LBR (OR = 1.26, 95% CI: 1.09–1.47, I^2=18.2%). A modest improvement in CPR was observed (OR = 1.12, 95% CI: 1.10–1.27, I^2=0%), particularly in RIF (OR = 1.33). The reduction in MR was not statistically significant, though a borderline effect was seen in RPL. These findings suggest immunotherapy may be beneficial, especially for women with RIF. However, due to heterogeneity and variability across studies, further high-quality RCTs are needed to confirm efficacy and guide clinical practice.

Keywords: Immunotherapy, Recurrent Pregnancy Loss, Recurrent Implantation Failure, Live Birth Rate, Clinical Pregnancy Rate, Meta-analysis

Abbreviations: RPL: Recurrent pregnancy loss; RIF: Recurrent Implantation Failure; LBR: Live Birth Rates; CPR: Clinical Pregnancy Rates; RCT: Randomized Controlled Trials; IVIG: Intravenous Immunoglobulin; LIT: Lymphocyte Immunotherapy; TNF: Tumor Necrosis Factor; G-CSF: Granulocyte-Colony Stimulating factor

Plain Language Summary

Recurrent pregnancy loss (RPL) and recurrent implantation failure (RIF) are emotionally distressing conditions faced by many women undergoing fertility treatments. These issues are often linked to problems in the immune system, prompting researchers to explore whether immunotherapy could improve pregnancy outcomes. This systematic review and meta-analysis examined 36 randomized controlled trials involving 3,614 women with RPL or RIF who received various immunotherapies, including intravenous immunoglobulin (IVIG), corticosteroids, lymphocyte immunotherapy (LIT), tumor necrosis factor (TNF) inhibitors, and granulocyte-colony stimulating factor (G-CSF). The results showed that immunotherapy significantly improved the chances of having

a live birth. Women with RIF appeared to benefit more from these treatments, while the improvement in women with RPL was more modest. Similarly, clinical pregnancy rates—an early sign of successful pregnancy—were higher among those who received immunotherapy, again with a more noticeable benefit in the RIF group. Although the risk of miscarriage was slightly reduced, the evidence was not strong enough to confirm a clear protective effect, especially in women with RIF. Overall, this study suggests that immunotherapy could be a helpful option for improving pregnancy outcomes, particularly in women with RIF. However, the results varied across studies, especially in the RIF subgroup, indicating that not all women may benefit equally. More high-quality, large-scale studies are needed to better understand which patients are most likely to benefit and to develop standardized treatment guidelines. Until then, immunotherapy remains a promising but still emerging approach in the management of RPL and RIF.

Introduction

Recurrent pregnancy loss (RPL) and recurrent implantation failure (RIF) present significant challenges in reproductive medicine, often leading to considerable emotional and psychological distress for affected couples[1,2]. RPL is typically defined as two or more consecutive pregnancy losses before 20 weeks of gestation, affecting approximately 3–5% of women attempting to conceive. RIF, on the other hand, refers to the failure to achieve a clinical pregnancy after multiple in vitro fertilization (IVF) cycles, despite the transfer of good-quality embryos[3,4]. Emerging evidence suggests that immune dysregulation may play a pivotal role in the pathogenesis of both RPL and RIF[5–7]. Alterations in immune cell populations, such as uterine natural killer (NK) cells, macrophages, and T-helper cell subsets, have been implicated in these conditions. Specifically, an increased Th1/Th2 ratio and a decreased Treg/Th17 ratio have been observed, indicating a pro-inflammatory state that may be detrimental to implantation and pregnancy maintenance[8,9].

In response to these findings, various immunotherapeutic interventions have been explored to modulate the immune environment and improve pregnancy outcomes. These therapies include intravenous immunoglobulins (IVIG), corticosteroids, tumor necrosis factor (TNF) inhibitors, granulocyte colony-stimulating factor (G-CSF), intralipid infusions, and lymphocyte immunotherapy[10]. The efficacy of these treatments remains a subject of ongoing debate. For instance, a systematic review and meta-analysis evaluating immunotherapy in women with RPL or RIF found no significant improvement in live birth rates, suggesting that such interventions should currently be confined to research settings rather than routine clinical practice[11]. Conversely, another meta-analysis focusing on patients with abnormal NK cell levels reported that certain immunotherapies, such as IVIG, may enhance live birth rates, although the quality of evidence was limited, and further research is warranted[12].

Given these conflicting findings, it is imperative to conduct a comprehensive systematic review and meta-analysis of randomized controlled trials (RCTs) to elucidate the effectiveness of immunotherapy in improving live birth rates and clinical pregnancy rates among women with RPL and RIF. Such an analysis would provide valuable insights into the potential benefits and limitations of immunotherapeutic interventions, thereby informing clinical decision-making and guiding future research endeavours.

Methods

Study Design

This study is a systematic review and meta-analysis conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines. The protocol was registered in PROSPERO (Registration ID: [CRD42025628961]).

Eligibility Criteria

Inclusion Criteria

- Randomized controlled trials (RCTs) evaluating immunotherapy in women with recurrent pregnancy loss (RPL) or recurrent implantation failure (RIF).
- Studies assessing interventions such as intravenous immunoglobulin (IVIG), corticosteroids, lymphocyte immunotherapy (LIT), tumor necrosis factor (TNF) inhibitors, and granulocyte colony-stimulating factor (G-CSF).
- Studies reporting at least one of the following outcomes:
- Primary Outcome: Live Birth Rate (LBR)
- Secondary Outcomes: Clinical Pregnancy Rate (CPR) and Miscarriage Rate (MR)
- Studies published in peer-reviewed journals with full-text availability.

Exclusion Criteria

- Non-randomized studies, observational studies, case reports, or reviews.
- Studies lacking sufficient data for statistical analysis.
- Trials with duplicate data sets.

Search Strategy

A comprehensive literature search was conducted up to January 31, 2025, across four major electronic databases: PubMed, EMBASE, Cochrane Library, and ClinicalTrials.gov. The search strategy was designed to capture all relevant RCTs evaluating the efficacy of immunotherapy in women with RPL and RIF. The search utilized a combination of Medical Subject Headings (MeSH) terms and free-text keywords to maximize sensitivity and specificity. The primary search terms included: "Recurrent Pregnancy Loss,"

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"Recurrent Implantation Failure," "Immunotherapy," "Intravenous Immunoglobulin (IVIG)," "Lymphocyte Immunotherapy (LIT)," "Granulocyte-Colony Stimulating Factor (G-CSF)," "Corticosteroids," "Tumor Necrosis Factor (TNF) Inhibitors," "Live Birth Rate (LBR)," "Clinical Pregnancy Rate (CPR)," and "Miscarriage Rate (MR)." To minimize selection bias, additional manual searches were performed by screening the reference lists of key articles, systematic reviews, and meta-analyses. Grey literature and conference abstracts were also reviewed, where available, to identify any unpublished or ongoing studies. No language restrictions were applied to ensure the inclusion of all relevant studies. The retrieved articles were then screened for eligibility based on predefined inclusion and exclusion criteria.

Data Extraction

Two independent reviewers screened the titles, abstracts, and full texts of eligible studies, with discrepancies resolved through discussion or consultation with a third reviewer. Data were extracted using a standardized form, capturing study design, patient population (RPL/RIF), type and dosage of immunotherapy (IVIG, LIT, G-CSF, corticosteroids, TNF inhibitors), presence of a placebo or control group, sample size, and outcome measures (LBR, CPR, MR). Additional details included study setting, follow-up duration, risk of bias assessment, and any reported adverse events. Missing data were sought by contacting study authors, ensuring completeness and accuracy for meta-analysis.

Quality Assessment

The methodological quality of included studies was evaluated using the Cochrane Risk of Bias tool [13], assessing randomization, allocation concealment, blinding, incomplete data, selective reporting, and other biases. Studies were categorized as low, unclear, or high risk of bias.

Statistical Analysis

A random-effects meta-analysis was conducted using STATA (Version 16.1) to account for potential variability across studies. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated for primary and secondary outcomes, including live birth rate (LBR), clinical pregnancy rate (CPR), and miscarriage rate (MR). Heterogeneity among studies was assessed using the I^2 statistic, where <25% indicated low, 25-50% moderate, and >50% high heterogeneity. Publication bias was evaluated using Egger's test and funnel plot analysis to detect asymmetry. To explore potential differences in treatment effects, subgroup analyses were performed based on population type (RPL vs. RIF) and type of immunotherapy, including IVIG, corticosteroids, LIT, TNF inhibitors, and G-CSF.

Results

Literature Search

A total of 1,011 articles were identified through the database search. After removing 487 duplicates and 455 studies were irrelevant studies leading to the exclusion by screening title and abstract. The remaining 69 studies underwent full-text assessment, resulting in the exclusion of 28 studies due to insufficient data, review articles, previous meta-analyses, missing or incomplete data, or lack of appropriate control groups. Ultimately, 36 studies met the inclusion criteria and were included in the final meta-analysis. The study selection process, conducted in accordance with PRISMA 2020 guidelines, is illustrated in (Figure 1).

Characteristics of included studies

The 36 included studies were published between 1991 and 2022, with study populations spanning multiple countries, including Australia, Italy, Germany, Denmark, the USA, Canada, Korea, Sweden, India, and China. The sample sizes varied significantly, ranging from 7 to 428 participants per study. The studies primarily investigated the efficacy of immunotherapy for RPL and RIF. Various interventions were assessed, including IVIG, leukocyte immunization, and other immune-based treatments, with control groups receiving placebo or standard care. The outcomes measured included LBR, MR and CPR (Table 1).

Live Birth Rate (LBR)

Overall, immunotherapy was associated with a significant improvement in LBR (OR = 1.26, 95% CI: 1.09–1.47, I^2=18.2%), suggesting a beneficial effect on successful pregnancy outcomes (Figure 2a). In subgroup analysis, the RPL group showed a moderate yet statistically significant improvement (OR = 1.15, 95% CI: 1.01–1.32, I^2=0%), indicating a potential benefit for individuals with recurrent pregnancy loss. The RIF group, however, showed a stronger effect (OR = 1.52, 95% CI: 0.88–2.67, I^2=72.4%), though with high heterogeneity and a P-value of 0.01, suggesting variability in study outcomes (Table 2). A second analysis of LBR across 25 studies reaffirmed a modest overall improvement (OR = 1.12, 95% CI: 1.10–1.27, I^2=0%). In the RPL subgroup, the effect size was minimal (OR = 1.05, 95% CI: 0.91–1.21, I^2=0%), whereas the RIF group showed a stronger association (OR = 1.33, 95% CI: 1.09–1.67, I^2=40.6%), suggesting that immunotherapy may be more effective for patients with recurrent implantation failure.

Miscarriage Rate (MR)

A significant reduction in MR was observed overall (OR=0.85, 95% CI: 0.73–1.00, I^2=0%), indicating that immunotherapy may reduce pregnancy loss (Figure 2b). Among specific interventions, prednisolone showed a significant reduction in MR (OR=0.59, 95% CI:0.35–0.93, I^2=28%), while IVIG (OR=0.88, 95% CI:0.69–1.12, I^2=0%) and LIT (OR=0.88, 95% CI: 0.47–1.65, I^2=38.9%) demonstrated a protective trend but did not reach statistical significance. Dydrogesterone (OR=0.90, 95% CI:0.69–1.17, I^2=60.6%) showed moderate heterogeneity, and aspirin (OR=1.29, 95% CI:0.43–3.86) did not show a significant benefit in reducing miscarriage risk.

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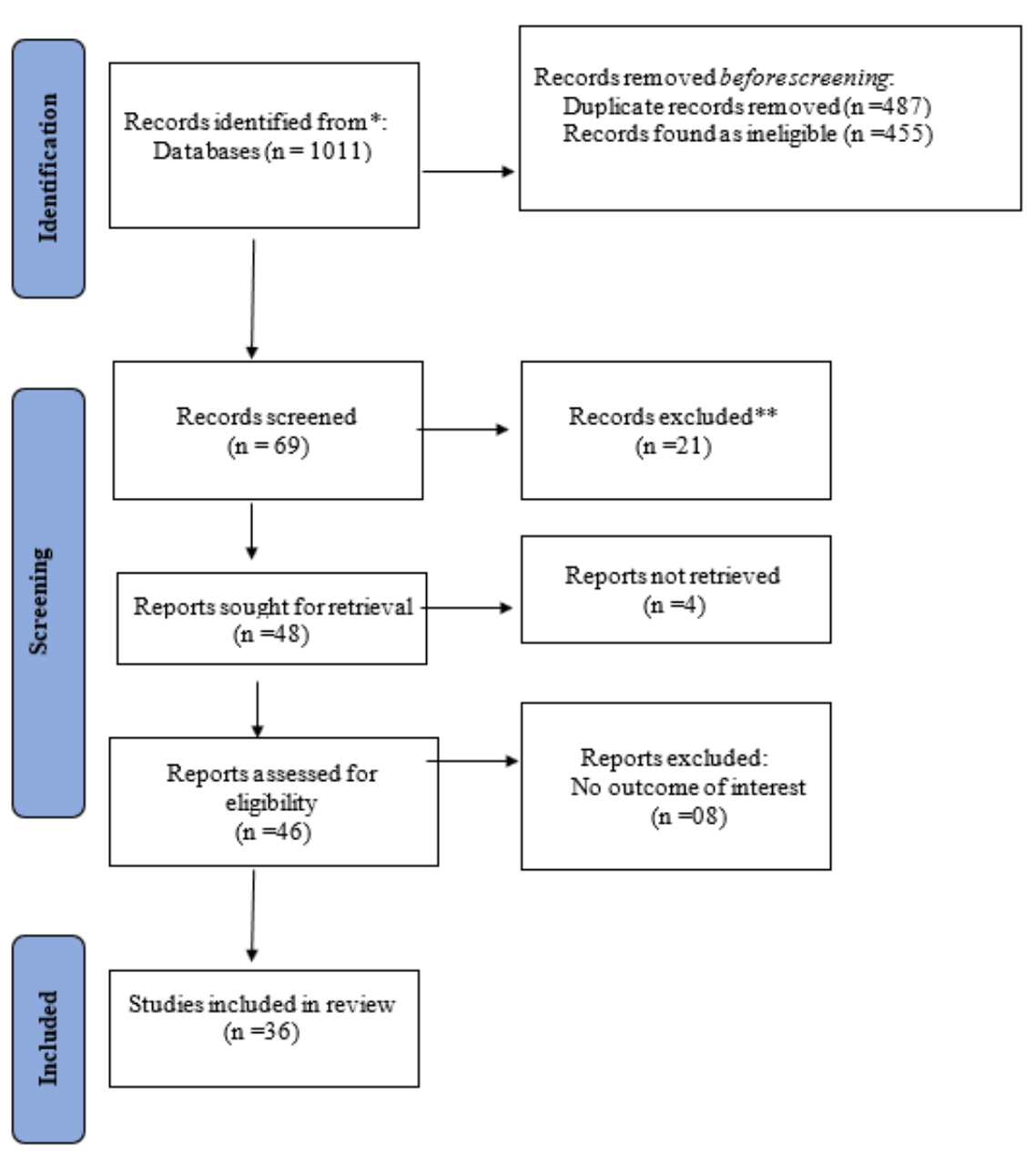


Figure 1: PRISMA 2020 Flow diagram for the selection of studies and specific reasons for exclusion from the present meta-analysis

Clinical Pregnancy Rate (CPR)

The overall analysis showed a modest improvement in CPR (OR=1.12, 95% CI:1.00–1.27, $I^2=0\%$), indicating that immunotherapy may contribute to higher conception rates (Figure 2c). Among individual therapies, LIT demonstrated a significant increase in CPR (OR=1.40, 95% CI:1.07–1.84, $I^2=59.9\%$, P=0.005), while IVIG (OR =1.09, 95% CI:0.88–1.34, $I^2=0\%$), prednisolone (OR=1.14, 95% CI: 0.84–1.54, $I^2=0\%$), and Dydrogesterone (OR = 1.04, 95% CI:0.83–1.29, $I^2=0\%$) showed no significant impact. Aspirin (OR=0.94, 95% CI:0.54–1.63, $I^2=0\%$) did not demonstrate any benefit in improving CPR.

Publication Bias

Funnel plot analysis showed no clear signs of asymmetry, indicating an even distribution of studies around the estimated effect. This suggests the absence of significant publication bias that could influence the results. The funnel plots for LBR (p=0.26), MR (p=0.86) and CPR (p=0.73). are presented in (Figure 3a–c). For outcomes reported in fewer than 10 studies, funnel plots were not generated due to the limited number of data points, which could affect the reliability of asymmetry assessment.

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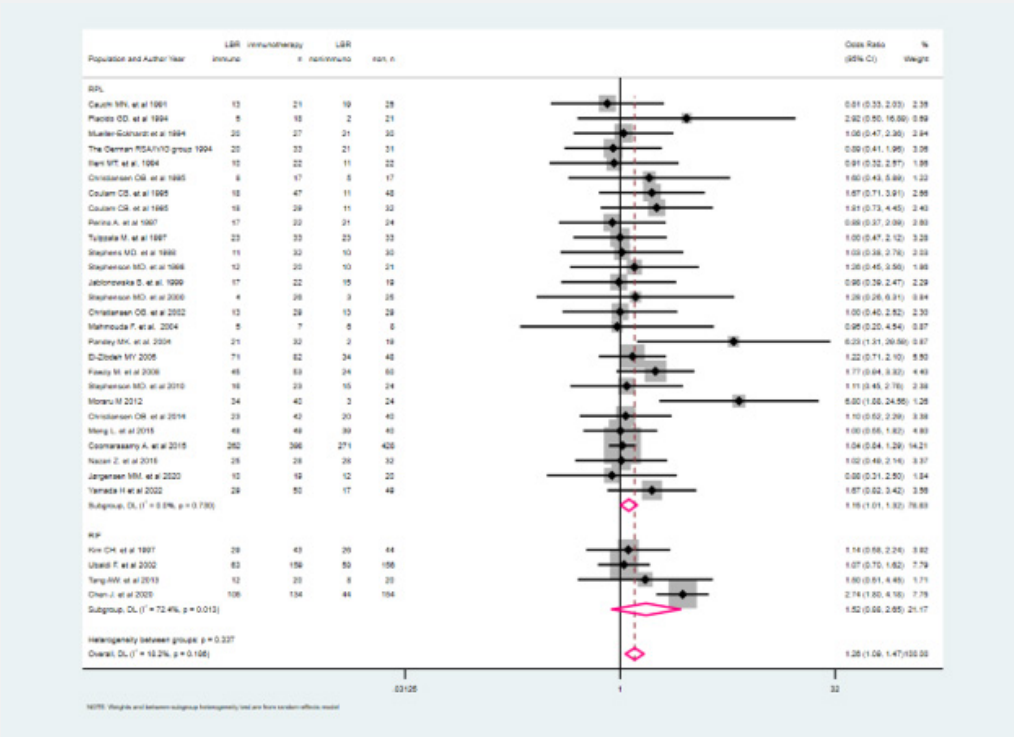


Figure 2a: Live birth rate (LBR)

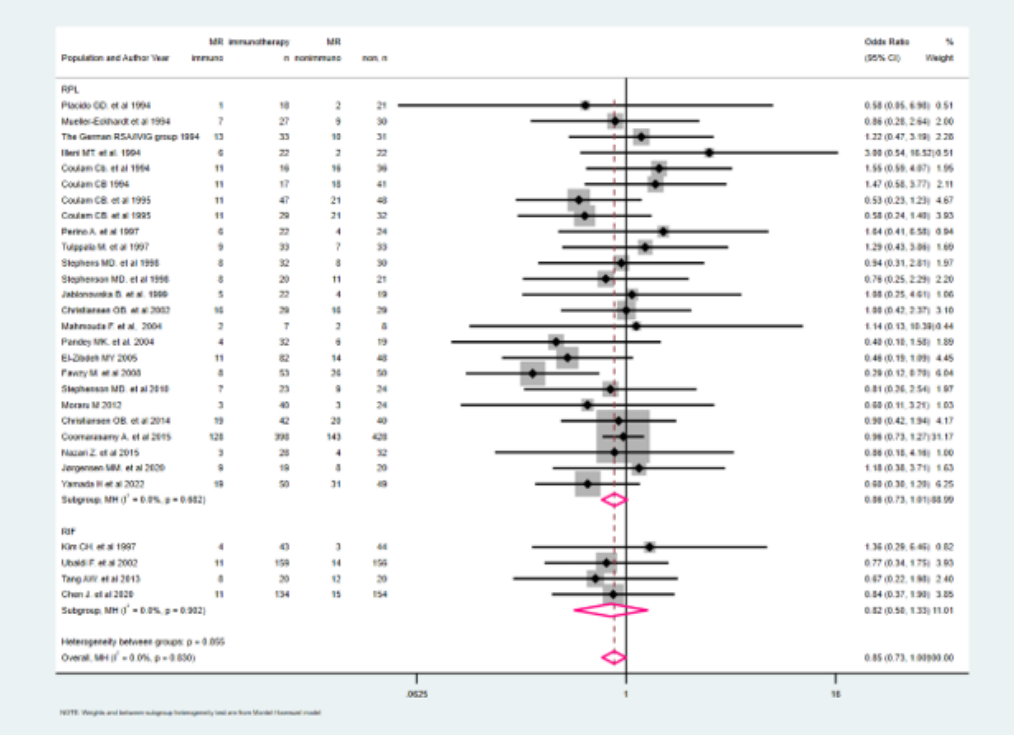


Figure 2b: Miscarriage Rate (MR)

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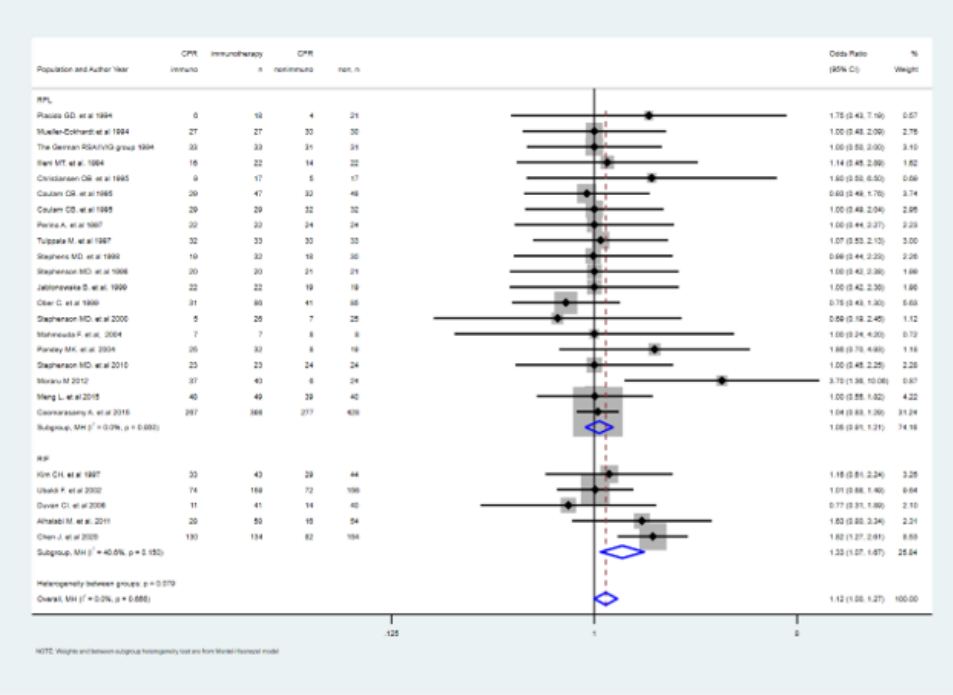


Figure 2c: Clinical Pregnancy rate (CPR)
Figure 2 (a-c): Forest plot for a. live birth rate (LBR) b. Miscarriage Rate (MR) and c. Clinical Pregnancy rate (CPR) in women with recurrent pregnancy loss (RPL) and recurrent implantation failure (RIF) receiving immunotherapy versus control.

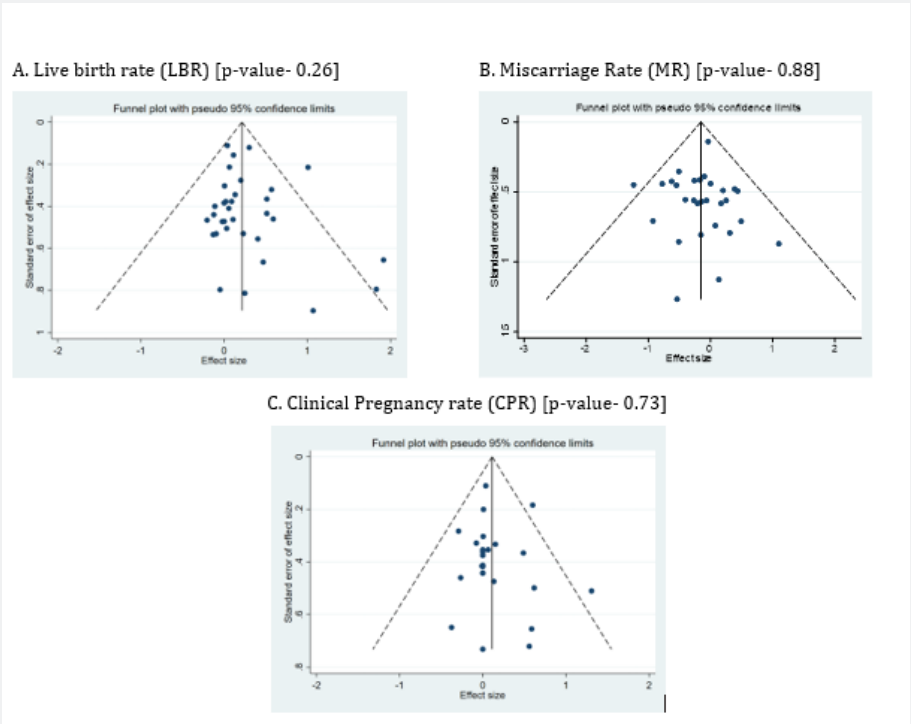


Figure 3 (a-c): Funnel plot for A. live birth rate (LBR) B. Miscarriage Rate (MR) and C. Clinical Pregnancy rate (CPR) in women with recurrent pregnancy loss (RPL) and recurrent implantation failure (RIF) receiving immunotherapy versus control.

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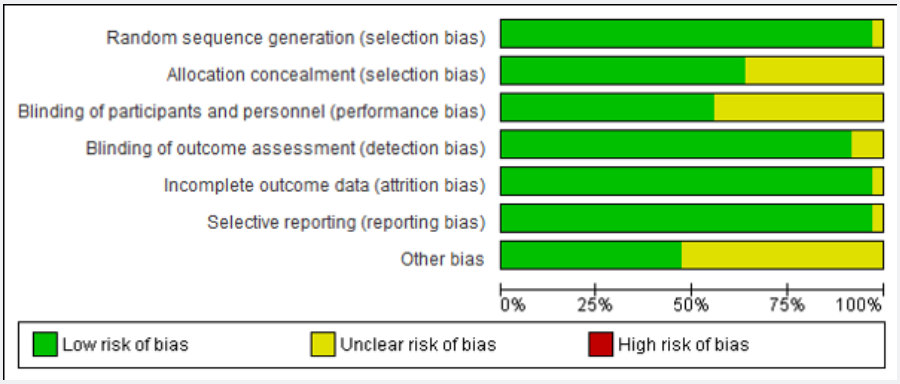


Figure 4: Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

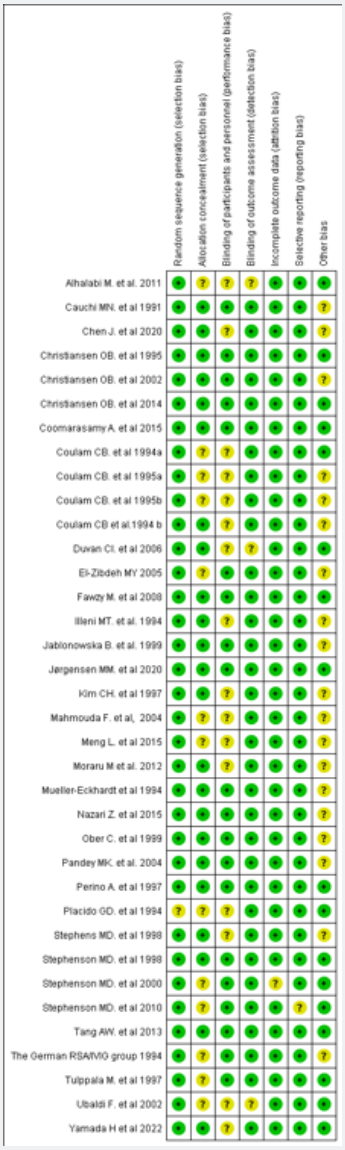


Figure 5: Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

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Table 1: Characteristics of included studies investigating for Efficacy of Immunotherapy in Recurrent Pregnancy Loss and Recurrent Implantation Failure

S. No	Author Year	Country	Study Time period	immunotherapy (n)	non-immunotherapy (n)	inclusion criteria	Population	Outcomes
1.	Cauchi MN. et al [29]	Australia	NA	21	25	≥3 consecutive first-trimester miscarriages with same partner	Idiopathic primary RPL	LBR
2.	Placido GD. et al [30]	Italy	NA	18	21	>2 early abortions or biochemical pregnancies, >3 failed IVF-ET	RIF	PR, LBR, MR
3.	Mueller-Eckhardt et al [31]	Germany	NA	27	30	≥3 miscarriages before 16 weeks gestation	Idiopathic primary RPL	LBR, MR, CPR
4.	The German RSA/IVIG group [32]	Germany	Dec 1989 – Mar 1991	33	31	URSA (≥3) <16 GW, no live birth	Unexplained primary recurrent miscarriage	LBR, MR, CPR
5.	Illeni MT. et al. [33]	Italy	Jun 1988 – Mar 1991	22	22	URSA (≥3), no live birth	Idiopathic primary RPL	LBR, MR, CPR
6.	Coulam Cb. et al [34]	Verginia	NA	16	36	≥2 consecutive spontaneous abortions (SA)	Recurrent spontaneous abortion (RSA)	MR
7.	Coulam CB [34]	Verginia	NA	17	41	≥2 consecutive recurrent spontaneous abortions (RSA)	RSA	MR
8.	Christiansen OB. et al [35]	Denmark	NA	17	17	≥3 consecutive pregnancy losses	Idiopathic secondary RPL	CPR, LBR
9.	Coulam CB. et al [36]	USA	Jul 1, 1993 – Jul 1, 1994	47	48	NA	Idiopathic primary RPL	LBR, MR, CPR
10.	Coulam CB. et al [37]	USA	Jan 1991 – Mar 1994	29	32	URSA (≥2) <20 GW	Recurrent spontaneous abortion (RSA)	LBR, MR, CPR
11.	Kim CH. et al [38]	Korea	Sep 1995 – Oct 1996	43	44	Pure tubal infertility, 165 IVF-ET cycles	Women undergoing IVF, tubal factor	CPR, LBR, MR
12.	Perino A. et al [39]	Italy	Jan 1992 – Jul 1995	22	24	≥3 first-trimester miscarriages with same partner	Idiopathic primary RPL	LBR, MR, CPR
13.	Tulppala M. et al [40]	Finland	NA	33	33	NA	RSA women with and without anticardiolipin antibodies	LBR, MR, CPR
14.	Stephens MD. et al [41]	Canada	Jun 1993 – Jun 1996	32	30	Unexplained recurrent spontaneous abortion	Idiopathic primary RPL	LBR, MR, CPR
15.	Stephenson MD. et al [41]	Canada	Jun 1993 – Jun 1996	20	21	≥2 consecutive spontaneous pregnancy losses <20 GW	Unexplained recurrent spontaneous abortion	LBR, MR, CPR
16.	Jablonowska B. et al. [42]	Sweden	Nov 1993 – Apr 1997	22	19	URSA (≥2) <20 GW	Idiopathic primary and secondary RPL	LBR, MR
17.	Ober C. et al [43]	USA	Jul 1992 – Dec 1997	86	85	≥3 spontaneous abortions of unknown cause	Idiopathic primary and secondary RPL	CPR
18.	Stephenson MD. et al [44]	Canada	Mar 1995 – Jul 1998	26	25	Unexplained IVF failure	RIF	CPR, LBR
19.	Ubaldi F. et al [45]	Italy	Sep 1999 – Oct 2000	159	156	<39 years, normal hormonal profile, <3 ICSI cycles, 2 embryos transferred	Less than three IVF cycles	CPR, LBR, MR

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20.	Christiansen OB. et al [46]	Denmark	NA	29	29	History of >4 miscarriages	Idiopathic primary and secondary RPL	LBR, MR
21.	Mahmouda F. et al, [47]	Kuwait	NA	7	8	URSA (≥3) 6–22 GW, APS positive	Recurrent pregnancy loss (RPL)	LBR, MR, CPR
22.	Pandey MK. et al. [48]	India	NA	32	19	History of primary RM	Idiopathic primary RPL	LBR, MR, CPR
23.	El-Zibdeh MY [49]	Jordan	Jan 1994 – Dec 2000	82	48	Women (<35 years) with ≥3 consecutive miscarriages with same husband	URSA (mean 3.5 abortions)	MR, LBR
24.	Duvan CI. et al [50]	Turkey	2001 – 2002	41	40	Non-selected infertile patients undergoing first ICSI cycle	Women undergoing IVF	PR, CPR
25.	Fawzy M. et al [51]	Egypt	Jan 2004 – May 2007	53	50	≥3 fetal losses, known RM causes excluded	Idiopathic recurrent miscarriage (IRM)	MR, LBR
26.	Stephenson MD. et al 2010[52]	USA	Nov 1999 – Feb 2008	23	24	18–45 years, idiopathic secondary RM, recent conception <1 year	Idiopathic secondary recurrent miscarriage	LBR, MR
27.	Alhalabi M. et al. [53]	Syria	Feb 2009 – Aug 2010	58	54	ICSI patients with high CD69+ NK cells	Women undergoing IVF, elevated NK cells (CD69)	CPR
28.	Moraru M [54]	Spain	May 2005 – May 2011	40	24	3–11 IVF cycles	RM & RIF	MR, LBR, CPR
29.	Tang AW. et al [55]	UK	Aug 2008 – Aug 2010	20	20	Primary RM, high uterine NK cell density	High uterine NK at biopsy and idiopathic RPL	LBR, MR
30.	Christiansen OB. et al [56]	Denmark	Aug 2008 – Apr 2010	42	40	Unexplained secondary RM, ≥4 miscarriages	Idiopathic secondary RPL	LBR, MR
31.	Meng L. et al [57]	China	NA	49	40	≥3 miscarriages before 12 GW	Unexplained recurrent spontaneous abortion	LBR, MR, CPR
32.	Coomarasamy A. et al [58]	UK	Jun 23, 2010 – Oct 23, 2013	398	428	Unexplained RM (≥3 consecutive or non-consecutive first-trimester losses)	Unexplained recurrent miscarriage	MR, LBR, CPR
33.	Nazari Z. et al [59]	Iran	Mar 2010 – Mar 2013	28	32	Recurrent abortion (≥3)	Idiopathic recurrent abortion	MR, LBR
34.	Jørgensen MM. et al [60]	Denmark	NA	19	20	≥4 pregnancy losses before 26 GW, last 3 consecutive	RPL	MR, LBR
35.	Chen J. et al [61]	China	Jan 2015 – Mar 2019	134	154	>2 clinical abortions	RSA + IVF	MR, CPR, LBR
36.	Yamada H et al [62]	Japan	Jun 3, 2014 – Jan 29, 2020	50	49	URSA (≥4) <22 GW, no live birth	Unexplained recurrent pregnancy loss (RPL)	MR, LBR

Abbreviations: LBR: Live Birth Rate, LIT: Lymphocyte Immunotherapy, IVIG: Intravenous Immunoglobulin, CPR: Clinical Pregnancy Rate, MR: Miscarriage Rate, URSA: Unexplained Recurrent Spontaneous Abortion, IVF: In Vitro Fertilization, IRM: Idiopathic Recurrent Miscarriage, NK Natural Killer, RM: Recurrent Miscarriage, RIF: Recurrent Implantation Failure, RPL: Recurrent Pregnancy Loss, RSA: Recurrent Spontaneous Abortion, RPL: Recurrent Pregnancy Loss, NA-Not available

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Table 2: Subgroup analysis based on Immunotherapy Types used in Recurrent Pregnancy Loss and Recurrent Implantation Failure

Outcome	Immunotherapy Types	No. of studies	OR (95% CI)*	Degree of Heterogeneity	
				I2 (%)	P*value
LBR	LIT	4	1.76 (0.78 to 4.00)	70.1	0.01
	IVIG	20	1.20 (0.98 to 1.47)	0	0.84
	Prednisolone	4	1.24 (0.92 to 1.67)	0	0.59
	Aspirin	1	1.00 (0.47 to 2.12)	0	-
	Dydrogesterone	2	1.06 (0.87 to 1.30)	0	0.58
	Overall	**31**	**1.26 (1.09 to 1.47)**	**18.2**	**0.18**
MR	LIT	3	0.88 (0.47 to 1.65)	38.9	0.19
	IVIG	19	0.88 (0.69 to 1.12)	0	0.97
	Prednisolone	4	0.59 (0.35 to 0.93)	28	0.25
	Aspirin	1	1.29 (0.43 to 3.86)	0	-
	Dydrogesterone	2	0.90 (0.69 to 1.17)	60.6	0.011
	Overall	**28**	**0.85 (0.73 to 1.00)**	**0**	**0.83**
CPR	LIT	4	1.40 (1.07 to 1.84)	59.9	0.005
	IVIG	15	1.09 (0.88 to 1.34)	0	0.89
	Prednisolone	3	1.14 (0.84 to 1.54)	0	0.51
	Aspirin	2	0.94 (0.54 to 1.63)	0	0.56
	Dydrogesterone	1	1.04 (0.83 to 1.29)	0	-
	Overall	**25**	**1.12 (1.00 to 1.27)**	**0**	**0.65**

Abbreviations: LBR: Live Birth Rate, LIT: Lymphocyte Immunotherapy, IVIG: Intravenous Immunoglobulin, CPR: Clinical Pregnancy Rate, MR: Miscarriage Rate, OR: Odds Ratio, CI: Confidence Interval

Quality Assessment

The quality assessment of the included studies was conducted using the Cochrane Risk of Bias tool, which evaluated various domains such as random sequence generation, allocation concealment, blinding of participants and personnel, incomplete outcome data, selective reporting, and other potential sources of bias. Overall, the studies demonstrated a low to moderate risk of bias, indicating a reasonable level of methodological rigor (Figure 4). However, some studies exhibited concerns related to blinding procedures, allocation concealment, and incomplete reporting of outcomes, which could potentially influence the reliability of the findings. These limitations highlight the importance of interpreting the results with caution and considering the potential impact of bias on the overall conclusions drawn from this meta-analysis.

Discussion

This systematic review and meta-analysis provide a comprehensive evaluation of the efficacy of immunotherapy in improving pregnancy outcomes among women with RPL and RIF. Our findings suggest that immunotherapy, including IVIG, LIT, corticosteroids, TNF inhibitors, and G-CSF, is associated with a significant improvement in LBR and CPR, particularly in women with RIF. However, its impact on MR remains inconclusive. Our findings indicate that immunotherapy significantly improves LBR, with a more pronounced effect in RIF, though with considerable heterogeneity. This aligns with previous studies suggesting a stronger immunological component in implantation failure compared to pregnancy loss. While MR showed a non-significant reduction, RPL exhibited a borderline protective effect, whereas RIF showed no significant impact, reinforcing the notion that immunotherapy may support pregnancy viability rather than directly prevent miscarriage. The modest overall improvement in CPR, with a minimal effect in RPL but a stronger benefit in RIF, suggests that immunotherapy enhances implantation success, possibly through modulating endometrial receptivity and immune tolerance. These findings are consistent with prior research indicating mixed efficacy, emphasizing the need for standardized treatment protocols and further exploration of immunological pathways to optimize outcomes (Figure 5).

Our meta-analysis provides valuable insights into the efficacy of immunotherapy in women with RPL and RIF. Current guidelines from the American Society for Reproductive Medicine (ASRM) and the European Society of Human Reproduction and Embryology (ESHRE) do not recommend routine testing for immune abnormalities due to low-quality evidence[14,15]. However, our findings suggest that pre-screening for immunological biomarkers, such as natural killer (NK) cells, might help identify patients who could benefit from intravenous immunoglobulin (IVIG) therapy, despite the limited evidence available. NK cells are the most

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abundant leukocytes in the early pregnancy decidua, playing a crucial role in facilitating implantation and placental development. They interact with fetal trophoblasts, allowing controlled invasion essential for proper pregnancy establishment [16]. Moreover, NK cells secrete cytokines that support angiogenesis, which aids in transforming spiral arterioles into high-capacitance, low-resistance vessels, ensuring adequate blood supply to the growing fetus[17]. Disruptions in their function may contribute to implantation failure or pregnancy loss[18]. Additionally, regulatory T cells help maintain maternal-fetal immune tolerance, and their deficiency has been linked to adverse outcomes[19–21]. Given these roles, further investigation is needed to determine how IVIG influences immune modulation in pregnancy.

In clinical practice, peripheral blood lymphocyte testing is often used as a surrogate for assessing immune function in the uterus [22,23]. However, uterine lymphocytes have distinct immunological properties, and recent studies have identified molecularly unique subgroups in the decidua[24,25]. This suggests that blood-based immune markers may not accurately reflect intrauterine immune dynamics. The challenge remains in characterizing uterine lymphocytes, as it requires invasive sampling, cycle-specific timing, and histological standardization[26,27]. Hence, peripheral immune assessments should be interpreted with caution, as they may not fully represent local immune responses in pregnancy. As a human plasma-derived product, IVIG theoretically carries risks of blood-borne infections, though studies have reported its safety in pregnancy. A study involving women with reproductive failures found no increased risks of preterm birth, gestational diabetes, preeclampsia, placental abnormalities, or fetal teratogenicity [28]. Common side effects, including headache, fever, nausea, and muscle pain, are typically mild and can be managed by adjusting the infusion rate. Many studies have not sub-analyzed women with immunological disturbances, potentially masking beneficial effects. Considering the biological plausibility of immunotherapies, future research should focus on well-defined patient populations to establish clear guidelines for clinical use. Large, well-powered RCTs are needed to optimize treatment protocols, ensuring better reproductive outcomes for affected women.

Despite the promising findings, several limitations must be acknowledged. First, the included studies exhibited variability in treatment protocols, dosages, and duration of immunotherapy, contributing to heterogeneity in results, particularly in the RIF subgroup. Second, while most studies had a low to moderate risk of bias, issues related to blinding, allocation concealment, and incomplete reporting may have influenced the findings [29-62]. Third, the sample sizes of individual trials varied significantly, and some studies had limited power to detect clinically meaningful differences in outcomes. Lastly, the long-term safety and potential adverse effects of immunotherapy were not consistently reported, necessitating further investigation into its risk-benefit profile. Future research should focus on well-designed, large-scale RCTs with standardized immunotherapy protocols to confirm these findings and establish clinical guidelines. Additionally, mechanistic studies exploring the immunological pathways involved in RPL and RIF could help identify specific patient populations that would benefit the most from immunotherapy. Furthermore, the integration of personalized medicine approaches, such as immune profiling and biomarker-guided therapy, may optimize treatment efficacy and minimize unnecessary interventions.

Conclusion

Our findings suggests that immunotherapy may improve live birth and clinical pregnancy rates, particularly in women with RIF, while its impact on miscarriage reduction remains inconclusive. The high heterogeneity in the RIF subgroup suggests variability in study outcomes. Further well-designed, large-scale RCTs are needed to establish standardized immunotherapy approaches in clinical practice.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Authors contributions

VS, AM and SS contributed to data searching, data extraction, quality assessment and analysis, writing the original draft, and methodology. IS, WM and PS helped in data extraction, and quality assessment. IS and VC helped in drafting and writing the manuscript. VC assisted in the conceptualization. KS and NM drafted the full protocol, conceptualized, executed the study and finalized the draft version of the manuscript.

*Bold Values denotes for statistical significance

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