Use of intravenous immunoglobulin in antiphospholipid antibody positive patients with high risk of miscarriage: a systematic review and meta-analysis

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Objective The purpose of the present study was to evaluate the efficacy of intravenous immunoglobulin(IVIG) in antiphospholipid antibody(aPL) positive high-risk miscarriages. **Background** Positivity of aPL in pregnant women is a high-risk factor for miscarriage, and IVIG treatment has emerged as a potential intervention. **Methods** The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline was employed to search multiple electronic databases, including PubMed, Web of science, Embase, Scopus and Medline. The inclusion criteria encompassed studies assessing the efficacy of IVIG in aPL-positive patients with a high risk of miscarriage. Relevant articles were assessed for the quality and data were extracted for analysis. Two independent reviewers performed study selection, data extraction, and quality assessments. And the risk of bias was evaluated according to the Cochrane risk of bias tool. All analyses were conducted using Review Manager 5.3. **Results** A total of 9 studies were included in this systematic review, encompassing a total of 366 aPL-positive women at high risk of miscarriage . The studies included in this review were randomized controlled trials. The primary outcome measures were successful pregnancy outcomes and live birth rates. The secondary outcomes included obstetric complications, preterm deliveries, and neonatal outcomes. The comparison between the intervention and control groups revealed no significant differences in terms of obstetric complications (OR=1.67, I^2=72%, 95% CI 0.20-13.58), neonatal outcome(OR=1.42, I^2=45%, 95% CI 0.39-5.23) and birth weight (g) (MD=-186.71, I^2=68%, 95% CI -398.76-25.34). IVIG treatment demonstrated the potential to promote preterm fetal delivery (OR=2.05, I^2=46%, P□0.05, 95% CI 0.58-5.24), but also exhibited a partial improvement in live birth rates (OR=2.86, I^2=52%, P□0.05, 95% CI 1.04-7.90) and a reduction in miscarriage rates (OR=0.35, I^2=52%, P□0.05, 95% CI 0.13-0.96) in aPL-positive pregnant women. **Discussion** The findings of this systematic

review suggest that IVIG intervention shows promise in improving successful pregnancy outcomes and live birth rates in aPL-positive patients with high risk of miscarriage. However, it worth noting that IVIG intervention may also contribute to preterm delivery in pregnant women, although no significant disparities were observed in neonatal status. Due to the heterogeneity and limitations of the studies included in this review, it is imperative to conduct further extensive, meticulously designed randomized controlled trials to substantiate these findings. **Conclusion** Based on the available evidence, IVIG intervention appears to be a potentially effective approach for managing of aPL-positive pregnant women with high risk of miscarriage. Nevertheless, the benefits are somewhat limited, necessitating further studies, especially large-scale randomized controlled trials to establish a standardized protocol for its application

Use of Intravenous Immunoglobulin in Antiphospholipid Antibody Positive Patients with High Risk of Miscarriage: A Systematic Review and Meta-analysis

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Abstract

Objective

The purpose of the present study was to evaluate the efficacy of intravenous immunoglobulin(IVIG) in antiphospholipid antibody(aPL) positive high-risk miscarriages.

Background

Positivity of aPL in pregnant women is a high-risk factor for miscarriage, and IVIG treatment has emerged as a potential intervention.

Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline was employed to search multiple electronic databases for articles published until August 20, 2023, including PubMed, Web of science, Embase, Scopus and Medline. The inclusion criteria encompassed studies assessing the efficacy of IVIG in aPL-positive patients with a high risk of miscarriage. Relevant articles were assessed for the quality and data were extracted for analysis. Two independent reviewers performed study selection, data extraction, and quality assessments. And the risk of bias was evaluated according to the Cochrane risk of bias tool. All analyses were conducted using Review Manager 5.3.

Results

A total of 9 studies were included in this systematic review, encompassing a total of 366 aPL-positive women at high risk of miscarriage. The studies included in this review were randomized controlled trials. The primary outcome measures were successful pregnancy outcomes and live birth rates. The secondary outcomes included obstetric complications, preterm deliveries, and neonatal outcomes. The comparison between the intervention and control groups revealed no significant differences in terms of obstetric complications (OR=1.67, I^2=72%, 95% CI 0.20-13.58), neonatal outcome(OR=1.42, I^2=45%, 95% CI 0.39-5.23) and birth weight

(g) (MD=-186.71, I^2=68%, 95% CI -398.76-25.34). IVIG treatment demonstrated the potential to promote preterm fetal delivery (OR=2.05, I^2=46%, $P<0.05$, 95% CI 0.58-5.24), but also exhibited a partial improvement in live birth rates (OR=2.86, I^2=52%, $P<0.05$, 95% CI 1.04-7.90) and a reduction in miscarriage rates (OR=0.35, I^2=52%, $P<0.05$, 95% CI 0.13-0.96) in aPL-positive pregnant women.

Discussion

The findings of this systematic review suggest that IVIG intervention shows promise in improving successful pregnancy outcomes and live birth rates in aPL-positive patients with high risk of miscarriage. However, it worth noting that IVIG intervention may also contribute to preterm delivery in pregnant women, although no significant disparities were observed in neonatal status. Due to the heterogeneity and limitations of the studies included in this review, it is imperative to conduct further extensive, meticulously designed randomized controlled trials to substantiate these findings.

Conclusion

Based on the available evidence, IVIG intervention appears to be a potentially effective approach for managing of aPL-positive pregnant women with high risk of miscarriage. Nevertheless, the benefits are somewhat limited, necessitating further studies, especially large-scale, well-designed randomized controlled trials to establish a standardized protocol for its application.

Systematic review registration: PROSPERO CRD42023447838

Keywords: IVIG, intravenous immunoglobulin, antiphospholipid antibodies, miscarriage, systematic review, PRISMA guideline.

Introduction

Antiphospholipid antibodies (aPL) are autoantibodies targeting negatively charged phospholipids on platelet and endothelial cell membranes. These antibodies include lupus anticoagulant, anticardiolipin antibodies, and anti-β2 glycoprotein antibodies, which can be detected in individuals with various autoimmune disorders[1]. The presence of positive antiphospholipid antibodies often indicates antiphospholipid antibody-related (aPL-related) diseases, such as systemic lupus erythematosus(SLE), anticoagulant antibody syndrome(APS), and thrombocytopenic purpura[2]. Women with aPL exhibit a heightened susceptibility to pregnancy loss, and pregnancies can also be complicated by premature delivery and uteroplacental insufficiency[3, 4]. Several studies have established a relationship between pregnancy pathology (such as recurrent miscarriages, gestational hypertension and preterm delivery) and the presence of anticardiolipin antibodies. The likelihood of subsequent pregnancy miscarriage in these individuals has been estimated to exceed 60%[5-7]. Consequently, the management of aPL-positive individuals at high risk of miscarriage has been a

significant challenge for clinicians. To enhance the chances of successful live birth, various treatments have been employed. Currently, the recognized therapeutic agents to improve pregnancy outcomes include aspirin, low molecular heparin, hydroxychloroquine, prednisone, and immunoglobulin. Numerous studies have shown that aPL-related pregnancy loss can be prevented by treatment with prednisone combined with low-dose aspirin (LDA) or subcutaneous heparin alone or in combination with LDA[8]. However, the risk of serious pregnancy complications in these patients remains high. Especially, several studies have found combination prednisone and LDA were ineffective in preventing pregnancy loss[9, 10]. Meanwhile, prednisone therapy, even at a daily dose of 20 mg, may be associated with significant maternal morbidity, acne, gestational diabetes(GD), osteoporosis, increased susceptibility to infections, and worsening of pregnancy-induced hypertension syndrome(PIH). Furthermore, when aPL-positive patients present with concurrent comorbidities, such as SLE, comprehensive trials and studies become imperative.

Intravenous immunoglobulin (IVIG) is a medication derived from the plasma of thousands of healthy blood donors. It contains a diverse range of antibodies capable of modulating the immune response, and is commonly employed in the treatment of autoimmune and inflammatory diseases[11-13]. As a potential therapeutic intervention, IVIG has been suggested for patients with recurrent miscarriage[14], with studies demonstrating the utilization of IVIG in the first trimester in patients

105 with APS to prevent recurrent miscarriages[15-17]. Most of these studies explored
106 IVIG as an early pregnancy intervention for patients with APS, serving as an
107 alternative to heparin. The IVIG offers the advantage of reduction in the significantly
108 elevated risk of preeclampsia in patients with APS[10]. In contrast to heparin, IVIG
109 does not increase the risk of bone loss in patients with hypertension or potential fatal
110 bleeding. It is believed that IVIG exerts its effects in APS via various mechanisms,
111 including inhibiting autoantibodies, modulating immune cells, and suppressing pro-
112 inflammatory cytokines. These actions collectively restore the balance of immune
113 system and diminish the risk of blood clotting complications, thus improving
114 pregnancy outcomes in women with APS[18, 19]. In addition, two small open
115 studies[20, 21] have suggested that IVIG temporarily reduces clinical and serologic
116 indicators of SLE activity. However, the available evidence regarding the efficacy
117 of IVIG treatment for aPL-positive patients with high-risk miscarriage remains
118 limited and, in some cases, contradictory. Hence, this systematic review aims to
119 evaluate the feasibility of intravenous immune globulin treatment during
120 pregnancy among aPL-positive patients with high-risk miscarriage and to assess
121 the impact of such treatment on obstetric and neonatal outcomes.
122

123 **Methods**

124 This systematic review adhered to the PRISMA guideline and the present
125 protocol was registered in the PROSPERO database (registration number

CRD42023447838).

Design and search strategy

A comprehensive search was conducted across multiple databases, including PubMed, Web of Science, Embase, Scopus and Medline, to identify relevant studies published between 2000 and 2023. The search terms employed were “pregnancy loss” OR “Abortions, Spontaneous” OR “Miscarriage” AND “antiphospholipid antibodies” OR “aPL” AND “Antibodies, Intravenous” OR “Intravenous Immunoglobulin” OR “IVIG” OR “Immunoglobulins, Intravenous” AND “Randomized Controlled Trial”. Studies that evaluated the efficacy of IVIG intervention in aPL-positive patients with high risk of miscarriage were included. In addition to the electronic database search, a manual search of the reference lists of the included articles were performed. Duplicate studies identified from different electronic databases were removed and managed using EndNote software (version X20). The methodology of study selection is illustrated in Figure 1.

Eligibility criteria

□1□Studies regarding randomized controlled clinical trials in English were included.

（2）In the trial ,aPL-positive patients with history of miscarriages were eligible. There were no restrictions on age, race, course of disease, or number of abortions.

147 （3）The end point data of the literature study was complete.

148

149 **Exclusion criteria**

150 （1） Summary, reviews and meta-analysis were excluded.

151 （2） Non-clinical patient trials such as animal trials and in vitro cell culture were
152 excluded.

153 （3） Studies containing duplicates or insufficient data were excluded..

154

155 **Main outcome(s)**

156 Live birth rates (gestational age(GA) ≥ 37 weeks)

157 **Additional outcome(s)**

158 Pregnancy loss (i.e., miscarriages when GA<20 weeks and stillbirths when
159 GA≥20 weeks), preterm delivery, neonatal outcomes (infants admitted to
160 neonatal intensive care unit (NICU), ect.), birth weight, and obstetric
161 complications (GD, PIH, preeclampsia, etc.).

162

163 **Data extraction**

164 Two authors independently extracted data(Xin Yuan and Wei Zhang). Any
165 discrepancies between them were resolved by discussion or adjudicated by a third
166 author(Zong-kui Wang). The following data were extracted: (1) data covering
167 author, year of publication, country of origin, trial period, and sample size; (2)

participant characteristics including age and intervention specifics such as dosage, frequency, first time of infusion (before pregnancy or gestational week), number of infusions and duration of treatment; (3) details of the placebo including substance and pregnancy outcomes after intervention, such as live birth, clinical miscarriage, ectopic pregnancy, induced abortion and stillbirth. Standardized forms developed for this specific study were used.

Risk of bias assessment

Two investigators(Xin Yuan and Wei Zhang) independently assessed the risk of bias based on the following domains as recommended by the Cochrane Handbook[22]. The third author(Zong-kui Wang), served as the referee for resolving any disagreements that could not be settled through discussion between the initial two reviewers. The domains included: 1. random sequence generation; 2. allocation concealment; 3. blinding of participants and personnel; 4. blinding of outcome assessment; 5. incomplete outcome data and its handling; 6. selective reporting of the outcomes; 7. any other biases. The results of bias assessment were presented in Figure 2 indicating low (L), high (H), or unclear (U) risk of bias for each of the 7 items in each trial.

Strategy for data synthesis

The study design and demographic characteristics of each included study have

been summarized in Table 1, which provides an overview of details such as authors, year of publication, country of origin, trial duration, and trial size. All outcome data were analyzed using RevMan 5.3 software.

Measures of effect

Dichotomous data were expressed as odds ratio (OR) and 95% confidence intervals (CIs), while continuous data were expressed as the mean difference (MD) and 95% CIs. To assess the heterogeneity among the included studies, Cochran's Q test and the Higgins I^2 statistic were employed. If $p \geq 0.10$ or $I^2 \leqslant 50\%$, it indicates that the heterogeneity among the studies is acceptable, fixed effect model was employed for analysis. Conversely, if $p<0.10$ or $I^2>50\%$, suggesting significant heterogeneity, a random effect model was applied for analysis. Publication bias was analyzed for the total effective rate.

Analysis of subgroups or subsets

Due to data limitation, neither subgroup nor sensitivity analysis were performed. The meta-analysis presented the statistical results for different clinical presentations.

Result

Search characteristics and risk of bias assessment

The search yielded a total of 73500 articles. After filtering the titles and abstracts,

1195 papers were obtained and assessed for eligibility, and then duplicates were removed. Based on the eligibility criteria, a final selection of 9 studies were enrolled (Figure 1)[23-31]. These articles were published between 2000 and 2023, with 3 originating from the USA[23, 24, 29], 3 from Italy[25, 28, 30], and the remaining three from Japan[31], Germany[27] and Greece[26]. Among the selected studies, 3 addressed pregnancy complications such as GD, PIH, etc.[23, 27, 30], 4 mentioned the status of newborns regarding the need for intensive care after birth[23, 25, 29, 31], and 5 involved the birth weight(g) of infants[23, 25, 26, 28, 31]. Table 1 presents specific details of the included studies. All analyses were conducted using either random effects model or fixed effects model using Review Manager 5.3. No sensitivity analysis was conducted owing to limited data. Table 1 provides a summary of the results of risk of bias assessment.

Live births and miscarriage rates

The primary objective of the present meta-analysis is to investigate the effectiveness of IVIG intervention in improving the live birth rate in pregnancies of aPL-positive patients at high risk for miscarriage. Upon consolidating all the included literature in Review Manager 5.3, an initial analysis revealed no discernible difference between the intervention and control groups (result not shown). It's worth noting that 3 RCTs excluded patients with SLE[23, 25, 26]. Upon excluding these 3 RCTs, a distinct pattern emerged. Specifically, in cases involving aPL-positive high-risk miscarriage patients with SLE or other autoimmune diseases, IVIG treatment

231 demonstrated a notable increase in live birth rate across the 6 RCTs (n=317):
232 OR=2.86, p=0.07, I^2=52%, $P<0.05$, 95% CI 1.04-7.90 (Figure 3A). Furthermore, a
233 statistical analysis of miscarriage rate in the 6 RCTs (n=317) indicated that IVIG
234 intervention significantly reduced the miscarriage rate of aPL-positive patients at
235 high risk for miscarriage: OR=0.35, p=0.06, I^2=52%, $P<0.05$, 95% CI 0.13-0.96
236 (Figure 3B).

237 **Preterm delivery**

238 A comprehensive statistical analysis of the preterm delivery rates of all the
239 9 included RCTs (n=307) unveiled that the IVIG intervention group exhibited
240 a higher preterm delivery rate (OR=2.05, p=0.07, I^2=46%, $P<0.05$, 95% CI 0.58-
241 5.24, Figure 3C). This suggested a potential association between IVIG
242 intervention and an increased likelihood of preterm birth in patients.

243 **Obstetric complications and neonatal outcome**

244 Complications in the pregnant woman after IVIG administration and the state of
245 the infants were also of concern. Three of the included RCTs (n=135) addressed
246 maternal pregnancy complications including GD, PIH, etc., and 4 RCTs (n=112)
247 mentioned infants birth outcomes such as infants admitted to NICU. It was founded
248 that no significant associations between IVIG intervention group and placebo group
249 in obstetric complications (OR=1.67, p=0.03, I^2=72%, 95% CI 0.20-13.58, Figure
250 3D) and neonatal outcomes (OR=1.42, p=0.16, I^2=45%, 95% CI 0.39-5.23, Figure
251 3E). Meanwhile, the analysis of 5 RCTs (n=155) revealed no difference in birth

weight between the IVIG intervention group and the placebo group (MD=-186.71, p=0.01, I^2=68%, 95% CI -398.76-25.34, Figure 4).

Discussion

Repeated spontaneous abortions pose a growing challenge in contemporary society, especially as more and more women delay childbearing into their 30s and 40s. Within this age group, various immune abnormalities affecting successful pregnancy increases. Emerging evidences suggest that both maternal immune tolerance to the fetus and adequate immune activation against pathogenic microorganisms are crucial for a successful pregnancy[32]. Several studies have established a correlation between pregnancy pathology (such as recurrent miscarriage, gestational hypertension, and gestational pregnancy) and the presence of anticardiolipin antibodies. The risk of recurrent miscarriage in these individuals has been estimated to exceed 60%[5-7]. Positive a-PLs typically indicates aPL-associated diseases, such as SLE and APS, which have been proved to be associated with an elevated risk of intrauterine growth restriction, miscarriage, stillbirth and preterm delivery[33-35]. In recent years, advances in treatment during pregnancy have improved outcomes. However, it should be given that fetal and maternal morbidity and mortality remain high. The management of patients who do not respond to conventional therapy in the latter stage of pregnancy poses significant challenges, particular due to the development of preeclampsia [36, 37].

IVIG, successfully employed in a variety of autoimmune disorders, such as Kawasaki disease and idiopathic thrombocytopenic purpura, has been explored as a treatment for aPL-positive patients [35, 38]. Carreras *et al.* first reported IVIG treatment in patients with lupus anticoagulant positivity and recurrent spontaneous abortion (RSA)[39]. Subsequently, several case reports have emerged regarding the treatment of RSA and antiphospholipid antibodies with IVIG in combination prednisone, or IVIG in conjunction with heparin and aspirin[29, 40]. For high-risk female patients with a history of prior treatment failure, the estimated overall success rate of IVIG intervention was 71% (11 of 17 patients), indicating the potential beneficial of IVIG therapy for a specific subset of patients[23]. The results of Clark *et al* provided the supports for IVIG treatment in RSA patients with a-PL[10]. The proposed mechanism of action involves the dissolution of immune complexes or the downregulation of autoantibody production by anti-idiotypes. In pregnancies characterized by severely compromise and growth restriction, IVIG therapy offers a low-risk strategy for reducing autoantibody-mediated disease and improving placental function. Spinnato *et al*[41] demonstrated that immunoglobulin treatment during pregnancy resulted in a decrease in anticardiolipin antibody levels in a cohort of women with APS. Studies on unexplained RSA also suggest a potential role of IVIG in the treatment of recurrent miscarriage. Additionally, with respect to IVIG treatment in RSA patients associated with a-PL, the rates of successful live births ranged from 70% to 100%, with a lower incidence of gestational complications

compared to traditional protocols[10, 23, 42].

In the initial analysis, we included all the screened studies, revealing no significant effects of IVIG on the live birth rate of a-PL positive patients (result not shown). Subsequently, upon comprehensive examination of the enrolled RCTs, it's found that three of the RCTs explicitly excluded a-PL positive patients with SLE and some other autoimmune disorders. After excluding these three RCTs, the subsequent re-analysis demonstrated varying levels of success in improving live birth rates and reducing miscarriage rates through IVIG intervention in aPL-positive patients with recurrent miscarriage. Furthermore, this effect was more prominent and statistically significant in aPL-positive patients in combination with SLE or other similar autoimmune diseases. The mechanism of action of IVIG in SLE and APS as with other autoimmune diseases appears to be multifactorial, and Dwyer *et al*. demonstrated this efficacy may be attributed to the presence of anti-unique antibodies in IVIG preparations. These antiidiotypic antibodies manipulate the immune system by neutralizing a-PL (unique type) through the formation of a unique anti-unique dimer, thereby enhancing the clearance of a-PL. Antiidiotypic antibodies can induce a decrease in a-PL production through interaction with B-cell antigen receptors. Additionally, the beneficial effects of IVIG are attributed to the altered structure, function, and dynamics of the unique-type network that can be restored and returned to normal[43]. Similar mechanisms, involving distinctive type interactions on the surface of T cells (via interactions with distinctive type

315 determinants on T cell antigen receptors), may alter T cell function. Likewise,
316 unique type interactions with B cells (via the B cell antigen receptor) and as well as
317 the bingding of Fc fragment of IgG in IVIG preparations to the Fc receptor (FcgRIIb)
318 may down-regulate B cell proliferation and autoantibody production[44]. In
319 idiopathic thrombocytopenic purpura, the blockade of Fc receptors by phagocytes
320 prevents the reticuloendothelial system from eliminating platelets and other cells that
321 are coated with autoantibodies. And this phenomenon may also manifest in SLE and
322 APS[45, 46]. Another potential explanation for the observed effectiveness of IVIG
323 treatment could be its capacity to enhance endometrial receptivity. Dysfunctional
324 immune alterations are involved in procreative failure. The appropriate
325 differentiation and development of the components of the fetal-maternal interface
326 are crucial for successful conception and maintenance of pregnancy. IVIG has been
327 shown potent inhibitory effects on P-selectin–dependent rolling and β2-integrin–
328 dependent adhesion, resulting in decreased leukocyte recruitment and vascular
329 dysfunction in postischemic micro-vessels[47]. Additionally, IVIG regulates
330 pregnancy-related vascular remodeling and trophoblast invasion by modulating
331 decidual NK cells[48], potentially promoting embryo implantation. These findings
332 suggest IVIG therapy contributes to a higher rate of successful pregnancies in
333 women with autoimmune disorders.

334 With regard to other important indicators, such as preterm delivery, neonatal
335 outcome and birth weight, our finding indicated that the IVIG-treated group

exhibited a higher incidence of preterm labor, of which the underlying mechanisms remain unidentified. Four of the RCTs included in the meta-analysis dealt with neonatal outcomes, and five RCTs assessed birth weight, revealing no significant differences in neonatal outcomes and birth weight between the IVIG-treated group and the placebo-control group. This suggests that there is no negative impact on the general status of surviving infants and the general vital signs of the infants did not to be affected by prematurity. Furthermore, Branch *et al.* explicitly indicated that IVIG intervention reduced neonatal admissions to NICU[23]. Part of the explanation of this phenomenon is that IVIG treatment supplements additional immunoglobulins to the fetus during the early stages when the fetus is unable to produce immunoglobulins independently. Furthermore, despite a high rate of preterm delivery, there are evidence of high live birth rates and low miscarriage rates.

In addition to live birth rates and infant status, evaluating the safety of IVIg treatment in patients with a-PL positive autoimmune disorders, who are at a high risk of miscarriage, is crucial in determining the suitability of incorporating IVIG into routine adjuvant therapy. Among the 3 RCTs that addressed obstetric complications, Vaquero and colleagues found an increased likelihood of GD and PIH in women treated with prednisone plus LDA compared to IVIG (14% vs 5%, (3/22 patients) vs (2/41 patients), $P < 0.05$) [30]. . It is worth noting that IVIG therapy is generally well tolerated, with rare occurrences of side effects. Only one of the included RCTs reported side effects occurred in patients following IVIG

357 therapy, however the side effects were predominantly mild allergic reactions, such
358 as chest pain, headache, nausea and flushing [26]. Furthermore, other relevant
359 studies that were not included in this review also indicated that serious side effects
360 did not occur when IVIG used. In fact, most patients experienced no or minimal
361 side-effects, such as flu-like symptoms which could be easily managed with
362 paracetamol [49, 50]. More severe side effects such as aseptic meningitis were found
363 to be very rare, and aseptic meningitis is similar to renal failure in that they occur
364 reflecting the formation of immune complexes which usually resolve spontaneously
365 or be managed therapeutically with steroids. The limitations of IVIG therapy include
366 its substantial financial burden and the potential risk of viral transmission. The
367 substantial cost of IVIG therapy may be deemed justified due to its ability to mitigate
368 adverse maternal and fetal complications, which frequently necessitate expensive
369 hospitalization. Nonetheless, IVIG therapy remains one of the safest blood
370 components available for current birth procedures, with no documented cases of
371 viral transmission thus far. In fact, none of the enrolled RCTs reported viral
372 infections in either the mother or the fetus. However, it is important to note that the
373 efficacy of IVIG varies among individuals, and the decision to use IVIG in patients
374 should be made in consultation with healthcare professionals.

375 Notwithstanding the overall positive results, it crucial to consider the
376 heterogeneity and limitations among the included studies. Disparities in study
377 design, limited sample sizes and varying dosage may have influenced the obtained

outcomes. Additionally, the lack of standardized diagnostic criteria for recurrent miscarriage have further contributed to the heterogeneity. Future studies should aim to address these issues to provide more robust evidence on the efficacy of IVIG therapy. The varying follow-up duration of the included studies in this review also poses challenges in drawing definitive conclusions regarding the long-term efficacy and safety of IVIG treatment in this patient cohort. Therefore, further investigations, particularly large-scale randomized controlled trials with longer follow-up time, is needed to establish the most effective protocol and evaluate the safety and efficacy of IVIG intervention in this specific patient population. However, it is indisputable that IVIG serves as an supplementary or alternative effective therapy for aPL-positive high risk of miscarriage patients combined with SLE or other autoimmune diseases, or for women with side effects or contraindications to heparin and aspirin.

Conclusion

Our meta-analysis suggests that IVIG therapy improves pregnancy outcomes in a-PL-positive patients with a history of recurrent miscarriage. However, further study is necessary to optimize treatment protocols and reduce heterogeneity among studies. Furthermore, long-term follow-up studies are needed to assess the impact of IVIG therapy on maternal and neonatal outcomes.

Statement of Ethics

399 This systematic review does not address relevant human or animal ethical.

400

401 **Conflict of Interest**

402 The authors declare no conflicts of interest related to this systematic review.

403

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409

410 **Author Contributions**

411 YX, ZW, WT, JP, WZK, and LCQ were involved in the conceptualization and
412 design of the review. YX and LCQ developed the review protocol. ZW, WT, and JP
413 conducted searches, identified publications to be included in the review, and
414 integrated the results. YX wrote the original draft of the review. WZK critically
415 reviewed the manuscript. All authors read and approved the final manuscript.

416

417 **Availability of data and materials**

418 All data generated or analyzed during this review are included in this article.

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Figure 1

Literature screening flowchart.

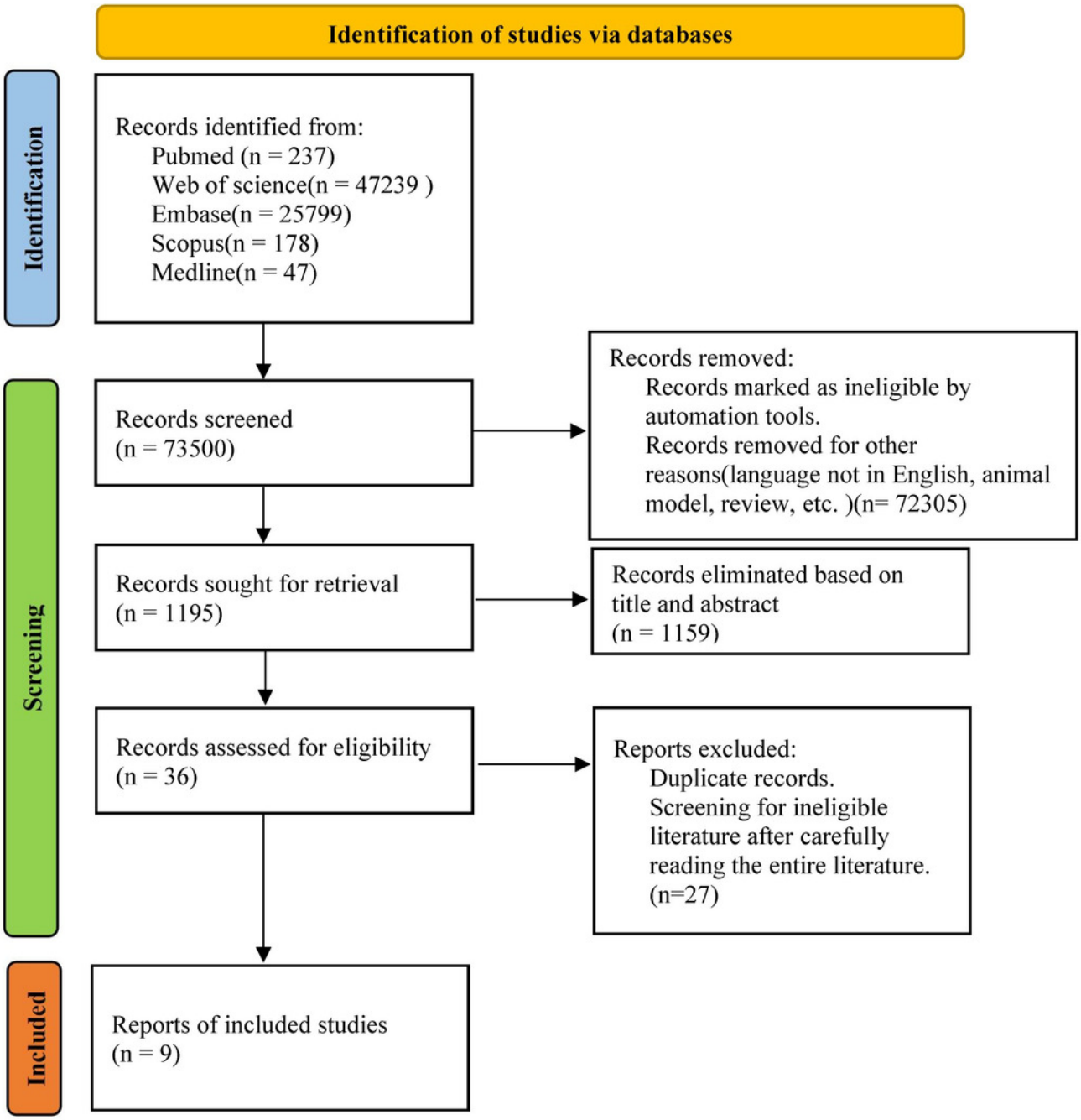
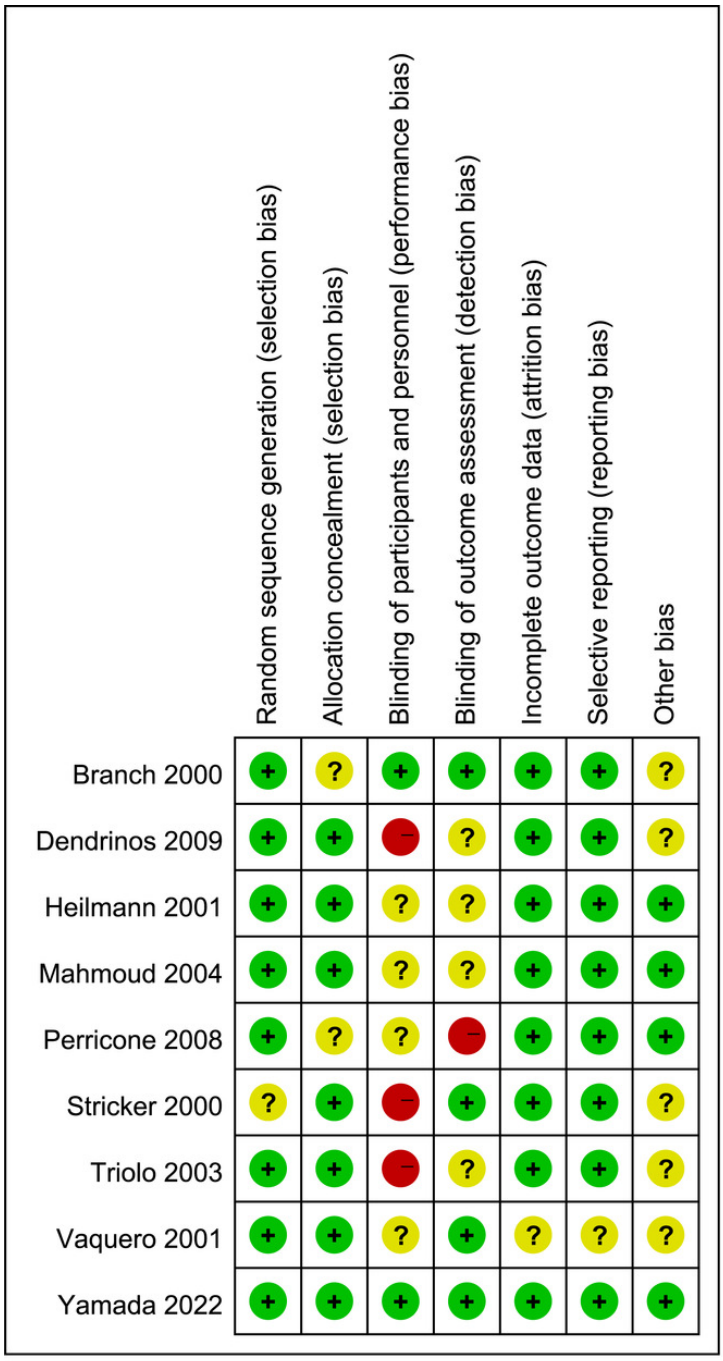


Figure 2

Assessment for risk of bias in included studies.


Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias)
Blinding of outcome assessment (detection bias)
Incomplete outcome data (attrition bias)
Selective reporting (reporting bias)
Other bias
Branch 2000
Dendrinos 2009
Heilmann 2001
Mahmoud 2004
Perricone 2008
Stricker 2000
Triolo 2003
Vaquero 2001
Yamada 2022

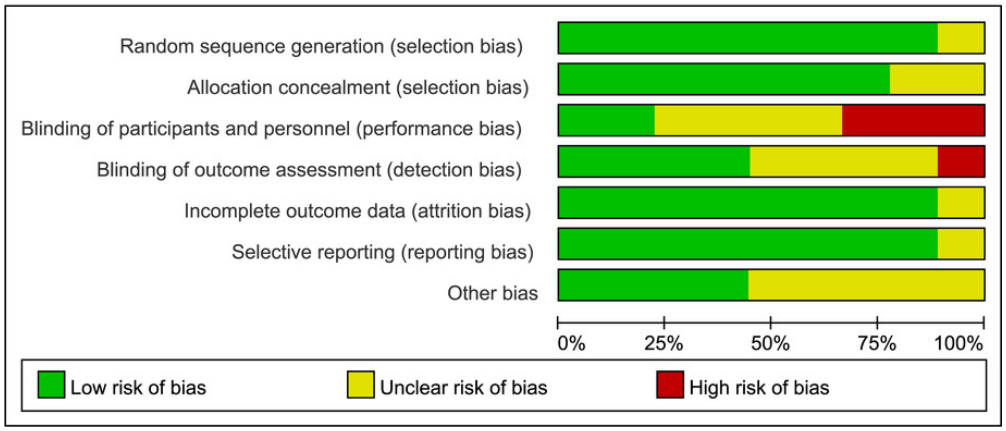
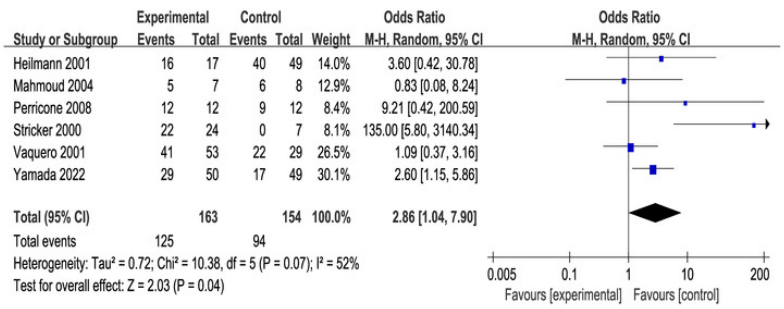

Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias)
Blinding of outcome assessment (detection bias)
Incomplete outcome data (attrition bias)
Selective reporting (reporting bias)
Other bias
0%
25%
50%
75%
100%
Low risk of bias
Unclear risk of bias
High risk of bias

Figure 3

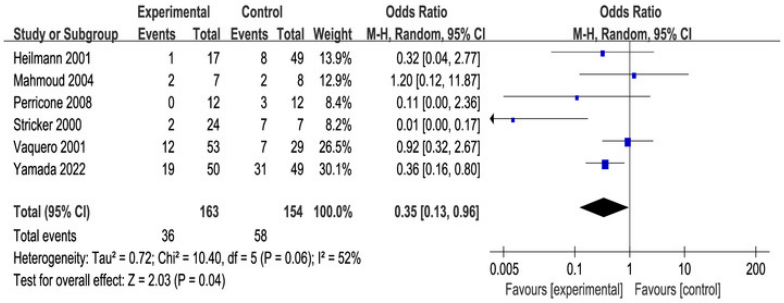
Forest plots of included studies

A. Live birth rates(6 comparisons, n = 317), B. Miscarriage rates(6 comparisons, n = 317), C. Preterm delivery rates(9 comparisons, n = 307), D. Obstetric complications(3 comparisons, n = 135), E. Neonatal outcome (4 comparisons, n = 112).

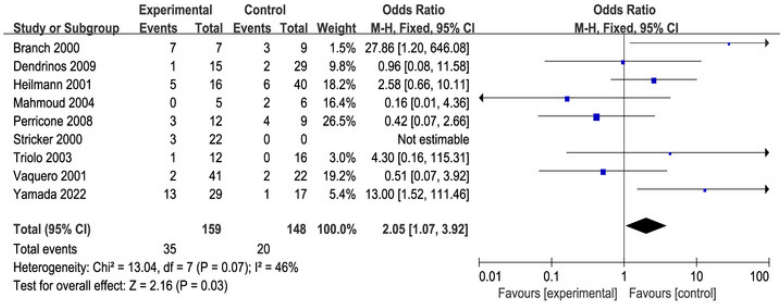
A


Experimental Control Odds Ratio Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI M-H, Random, 95% CI
Heilmann 2001 16 17 40 49 14.0% 3.60 [0.42, 30.78]
Mahmoud 2004 5 7 6 8 12.9% 0.83 [0.08, 8.24]
Perricone 2008 12 12 9 12 8.4% 9.21 [0.42, 200.59]
Stricker 2000 22 24 0 7 8.1% 135.00 [5.80, 3140.34]
Vaquero 2001 41 53 22 29 26.5% 1.09 [0.37, 3.16]
Yamada 2022 29 50 17 49 30.1% 2.60 [1.15, 5.86]
Total (95% CI) 163 154 100.0% 2.86 [1.04, 7.90]
Total events 125 94
Heterogeneity: Tau² = 0.72; Chi² = 10.38, df = 5 (P = 0.07); I² = 52%
Test for overall effect: Z = 2.03 (P = 0.04)
0.005 0.1 1 10 200
Favours [experimental] Favours [control]

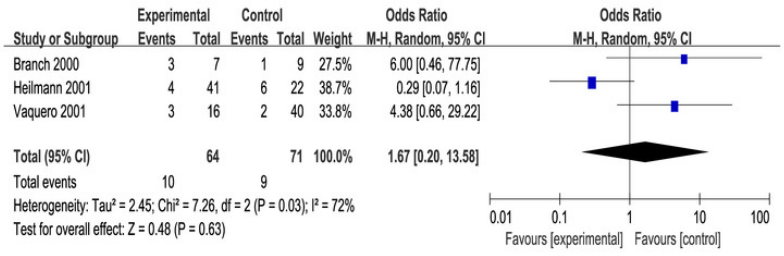
B


Experimental Control Odds Ratio Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI M-H, Random, 95% CI
Heilmann 2001 1 17 8 49 13.9% 0.32 [0.04, 2.77]
Mahmoud 2004 2 7 2 8 12.9% 1.20 [0.12, 11.87]
Perricone 2008 0 12 3 12 8.4% 0.11 [0.00, 2.36]
Stricker 2000 2 24 7 7 8.2% 0.01 [0.00, 0.17]
Vaquero 2001 12 53 7 29 26.5% 0.92 [0.32, 2.67]
Yamada 2022 19 50 31 49 30.1% 0.36 [0.16, 0.80]
Total (95% CI) 163 154 100.0% 0.35 [0.13, 0.96]
Total events 36 58
Heterogeneity: Tau² = 0.72; Chi² = 10.40, df = 5 (P = 0.06); I² = 52%
Test for overall effect: Z = 2.03 (P = 0.04)
0.005 0.1 1 10 200
Favours [experimental] Favours [control]

C


Experimental Control Odds Ratio Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI M-H, Fixed, 95% CI
Branch 2000 7 7 3 9 1.5% 27.86 [1.20, 646.08]
Dendrinos 2009 1 15 2 29 9.8% 0.96 [0.08, 11.58]
Heilmann 2001 5 16 6 40 18.2% 2.58 [0.66, 10.11]
Mahmoud 2004 0 5 2 6 16.4% 0.16 [0.01, 4.36]
Perricone 2008 3 12 4 9 26.5% 0.42 [0.07, 2.66]
Stricker 2000 3 22 0 0 Not estimable
Triolo 2003 1 12 0 16 3.0% 4.30 [0.16, 115.31]
Vaquero 2001 2 41 2 22 19.2% 0.51 [0.07, 3.92]
Yamada 2022 13 29 1 17 5.4% 13.00 [1.52, 111.46]
Total (95% CI) 159 148 100.0% 2.05 [1.07, 3.92]
Total events 35 20
Heterogeneity: Chi² = 13.04, df = 7 (P = 0.07); I² = 46%
Test for overall effect: Z = 2.16 (P = 0.03)
0.01 0.1 1 10 100
Favours [experimental] Favours [control]

D


Experimental Control Odds Ratio Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI M-H, Random, 95% CI
Branch 2000 3 7 1 9 27.5% 6.00 [0.46, 77.75]
Heilmann 2001 4 41 6 22 38.7% 0.29 [0.07, 1.16]
Vaquero 2001 3 16 2 40 33.8% 4.38 [0.66, 29.22]
Total (95% CI) 64 71 100.0% 1.67 [0.20, 13.58]
Total events 10 9
Heterogeneity: Tau² = 2.45; Chi² = 7.26, df = 2 (P = 0.03); I² = 72%
Test for overall effect: Z = 0.48 (P = 0.63)
0.01 0.1 1 10 100
Favours [experimental] Favours [control]

E

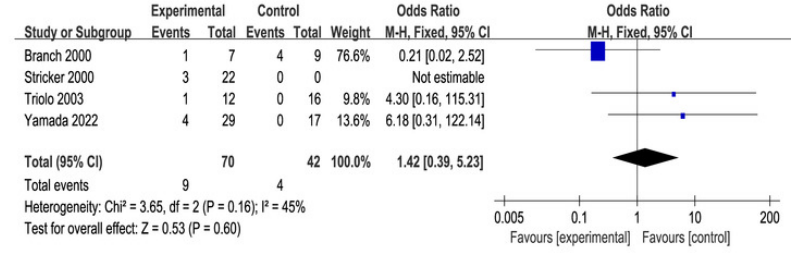

Experimental Control Odds Ratio Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI M-H, Fixed, 95% CI
Branch 2000 1 7 4 9 76.6% 0.21 [0.02, 2.52]
Stricker 2000 3 22 0 0 Not estimable
Triolo 2003 1 12 0 16 9.8% 4.30 [0.16, 115.31]
Yamada 2022 4 29 0 17 13.6% 6.18 [0.31, 122.14]
Total (95% CI) 70 42 100.0% 1.42 [0.39, 5.23]
Total events 9 4
Heterogeneity: Chi² = 3.65, df = 2 (P = 0.16); I² = 45%
Test for overall effect: Z = 0.53 (P = 0.60)
0.005 0.1 1 10 200
Favours [experimental] Favours [control]

Figure 4

Forest plots of birth weight (5 RCTs, n = 155)

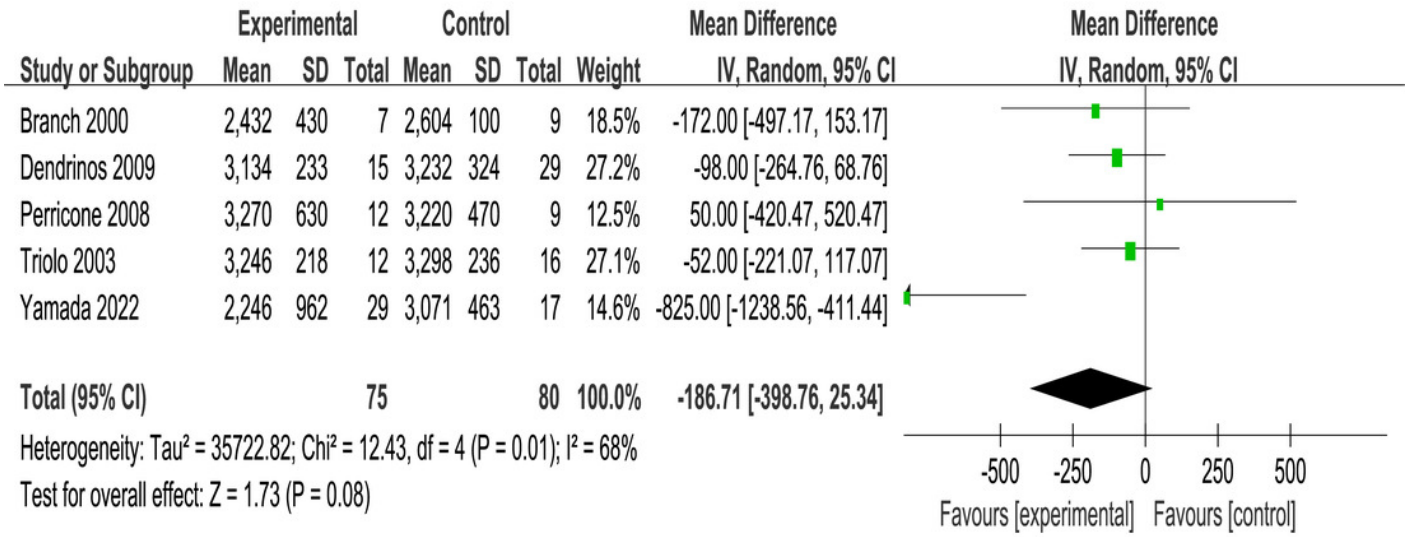


Table 1(on next page)

Characteristics of included studies.

Source Country	Study design	Trial size	Participant age (years)	Intervention (doses and placebo)	First time of infusion	Number of infusions	Trial period	Pregnancy outcome	aPL	Risk of bias
USA	RCT	16	28.8+3.8	10% IVIG 1 g/kg vs 5% albumin solution	As soon as the presence of a live embryo or fetus was confirmed by ultrasonography	2 consecutive days each month	Until 36 weeks' gestation	7 Live-born infants	(16)	L,U,L,L,L,L,U
USA	RCT	31	228	IVIG 0.2 g/kg every 4 weeks vs No treatment	After conception occurred	24	26-30 weeks of gestation	22 had a term pregnancy and 2 miscarried	(15)	U,L,H,L,L,L,U
USA	RCT	15	unknown	IVIG 0.5 g/kg intravenously daily vs Multivitamins	Once the patients had a positive pregnancy test	7	Until about 34 weeks of gestation	Two abortions, none preterm delivery	(15)	L,L,U,U,L,L,L
Japan	RCT	99	unknown	5% IVIG 0.4g/kg vs Physiological saline	Between 4 weeks 0 8 days and 6 weeks 6	5 days after injection administered by intravenous drip	days of gestation after gestational	29 women gave live birth, 19 had miscar	(99)	L,L,L,L,L,L,L

						infusion for five consecutive days.	sac was identified	riages, one had stillbirth, and one had unknown outcome		
Italy	RCT	24	34.67+4.27 vs 34.92+3.53	IVIG 0.5 g/kg every 3 weeks over a 6-h infusion vs Prednisolone 0.25 - 0.5 mg/kg and aspirin (100 mg daily)	As soon as pregnancy was confirmed	The 33rd week of pregnancy	Full-term birth(9) Preterm delivery(3)	(4)	L,U,U,H,L,L,L	None
Italy	RCT	82	31.9+4.7 vs 30.5+5.1	IVIG 0.5 g/kg for 2 consecutive days, once a month vs Prednisone(15-20mg till 28th week,	The Sth week of pregnancy	The 32nd week of pregnancy	41 had successful pregnancies and 12 miscarried	(82)	L,L,U,L,U,U,U	None

				10 - 15 mg till 32nd week) combined with a daily dose of 100 mg of aspirin.						
Italy	RCT	40	18-39	IVIG 400 mg/kg/day given for 2 consecutive days followed by a single dose each month vs Low-dose aspirin (75 mg daily) and heparin (self-administered injection; 5,700 IU/day)	As soon as patients had a positive result on a pregnancy test	34 weeks' gestation or at the time of miscarriage	12 live births, 7 spontaneous abortions, 1 intrauterine death, 1 preterm deliveries, 1 Infants admitted to NICU, 2 Fetal loss after 13 weeks	(40)	L,L,H, U,L,L,U	None
Greece	RCT	78	18-39	IVIG 400 mg/kg	As soon as patients	32 weeks of gestation(	2 intrauterine	(78)	L,L,H, U,L,L,U	None

				every 28 days vs 75 mg of low-dose aspirin and 4500 IU of heparin	had a positive result on a pregnancy test	IVIG, aspirin) 38 weeks of gestation(heparin)	death, 1 preterm deliveries, 21 First trimester abortion			
German y	RCT	102	26-43	IVIG 0.3 g/kg for 5 days, followed by 0.3 g/kg for 3 days every 3 to 4 weeks vs No treatment (All patients were given additional low-molecular weight heparin (3,000 anti-Xa U_ certoparin/d) and lowdose aspirin (100	The fifth to sixth week of gestation	The 28th to 32nd week of gestation.	16 live births, 1 fetal growth retardation, 5 preterm deliveries, 1 miscarried	(7)	L,L,H, U,L,L,U	None

				mg/d).)						

1