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Intralipid infusion at time of embryo transfer in women with history of recurrent implantation failure: A systematic review and meta-analysis

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Abstract

Aim: Recurrent implantation failure (RIF) affects 10% of couples undergoing assisted conception, often due to poor endometrial receptivity. We conducted a systematic review and meta-analysis to evaluate the effectiveness of Intra-venous intralipid (IVI) in improving pregnancy rates in women with history of RIF using.

Methods: We searched MEDLINE, EMBASE, and CENTRAL for any randomized trials evaluating the use of IVI at the time of embryo transfer in women undergoing assisted conception until September 2020. We extracted data in duplicate and assessed risk of bias using the Cochrane Risk of Bias tools. We meta-analyzed data using a random effect model.

Results: We included five randomized trials reporting on 843 women with an overall moderate risk of bias. All trials used 20% IVI solution at the time of embryo transfer compared to normal saline infusion or no intervention (routine care). The IVI group had a higher chance of clinical pregnancy (172 vs 119, risk ratio [RR] 1.55, 95% confidence interval [CI] 1.16–2.07, I^2 44.2%) and live birth (132 vs 73, RR 1.83, 95% CI 1.42–2.35, I^2 0%) post treatment compared to no intervention. Our findings are limited by the small sample size and the variations in treatment protocols and population characteristics.

Conclusion: There is limited evidence to support the use of IVI at the time of embryo transfer in women with the history of RIF. More research is needed before adopting it in clinical practice.

Key words: assisted reproductive technology, immunotherapy, intralipid, recurrent implantation failure, recurrent pregnancy loss.

Introduction

More and more couples rely on assisted reproductive technology (ART) to become pregnant worldwide, with an annually rising numbers of cycles performed.[1] Still, optimizing the implantation process following embryo transfer remains a clinical challenge with 10% of couples undergoing ART affected by recurrent implantation failure (RIF).[2, 3] RIF, defined as the repeated implantation failure in spite of the transfer of good quality embryos following ART treatment,[4] continues to be a clinical dilemma contributing to increased morbidity and anxiety in affected couples. Several factors are thought to increase the

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risk of RIF such as embryo quality, maternal thrombophilia, uterine abnormalities, and endocrine disorders.[4, 5] Still, we do not have a comprehensive understanding of the implantation process despite extensive research.[6]

Recently, our increased understanding of the implantation window characteristics governed by subtitle yet highly regulated pro- and anti-inflammatory responses[7, 8] highlighted the potential effect of aberrant immune responses on implantation and pregnancy outcomes.[9] The role of immunotherapy to regulate the maternal immune system has received much attention recently, with a presumed effect in improving endometrial receptivity and the chances for successful conception.[10] Mothers with history of recurrent pregnancy loss and implantation failure seem to have an impaired immunological response driven by an increased activity of uterine natural killer (uNK), macrophages, and T1 helper cells elevating cytokine production and cytotoxicity in the endometrium.[11–13] However, effective screening and diagnostic methods are lacking which limits the process of patient and treatment matching. Various immunological therapies have been evaluated as ART add-on treatments, but evidence of their value to the general population remains unclear.[14]

Intravenous intralipid (IVI), a fat-based emulsion of soybean oil, glycerine, phospholipids, egg, and polyunsaturated fatty acids, has been evaluated in several trials as a potential intervention to suppress the maternal immunological response,[15, 16] which seems to be mediated by reduced monocyte endothelial adhesion and pro-inflammatory cytokine generation.[16] Although its overall mechanistic effect on the immune system remains unclear, several studies support its role in downregulating the uNK cell macrophages pro-inflammatory mediators especially T1 helper cells.[15] This seems to be mediated by the interaction between the intralipid fatty acids of and the uNK cell peroxisome proliferator-activated receptors which decrease uNK cytotoxicity through reduced secretion of interferon-γ, demonstrated both in vivo and in vitro.[17, 18]

As such, the value and safety of selectively using IVI in women with the history of RIF to improve their reproductive outcomes need careful evaluation. We aimed to examine this hypothesis by systematically reviewing the literature for randomized trials evaluating the effectiveness of IVI to increase the chance of successful conception post ART treatments.

Materials and Methods

We performed this systematic review using a prospectively registered protocol (CRD42019148517) and reported in accordance with the PRISMA guidelines.[19]

Literature search

We searched major electronic databases (MEDLINE, EMBASE, and Cochrane CENTRAL) for any randomized trials meeting our inclusion criteria from inception until September 2020.

We used the following MeSH search terms and combined them using the Boolean operators AND/OR to screen for relevant trials ("intralipid," "pregnancy outcomes," "pregnancy," "biochemical pregnancy," "clinical pregnancy," "ongoing pregnancy," "live birth," "birth," "pregnancy loss," "implantation failure," "miscarriage," "reproductive technology," "ART," "assisted reproductive technology," "IVF," "in vitro fertilisation," "ICSI," "intracytoplasmic sperm injection," and "embryo transfer"). No search filters or language restrictions were applied. We manually searched the bibliographies of any relevant articles to identify any missing studies. We contacted two groups of authors[20, 21] seeking further information before confirming eligibility for inclusion in our review.

Study inclusion and data extraction

Two independent reviewers (M.P. Rimmer and N. Black) completed the study selection and inclusion process in two stages. Initially, we screened titles and abstracts to identify potentially relevant trials and then reviewed the full texts against our inclusion criteria. We included all randomized trials evaluating the use of IVI during IVF/ICSI in women with history of RIF. Any discrepancies were resolved in consensus with a third reviewer (B.H. Al Wattar). We excluded non-randomized studies, animal studies, and review articles. We extracted data in duplicate (M.P. Rimmer and N. Black) using a piloted electronic data extraction tool reporting on the number of participants, inclusion and exclusion criteria, treatment protocols, clinical pregnancy or implantation rate (defined as biochemical testing or ultrasound), and live birth or ongoing pregnancy beyond 12 weeks' gestation.

Risk of bias

Two reviewers (M.P. Rimmer and N. Black) assessed the methodological quality of the included RCTs using the Cochrane risk of bias tool.[22] We evaluated

each study in five domains: randomization and sequence generation, allocation concealment, blinding and outcome assessment, completeness of outcome data, and selective outcome reporting.

Statistical analysis

We conducted a pairwise effectiveness meta-analysis using a random-effects model and adjusted using restricted maximum likelihood.[23] We reported on dichotomous outcomes using risk ratio (RR) and 95% confidence interval (CI). We assessed the heterogeneity in included trials using the I^2 statistics. We conducted all statistical analyses using Stata, version 14 (StataCorp, College Station, TX, USA).

Results

Characteristics of included studies

Our electronic search identified 318 potentially relevant citations; of these, we evaluated 10 articles in full against our inclusion criteria. We excluded three non-randomized studies, one study that did not report on women undergoing assisted conception and another study reporting on the same cohort of women (Figure 1). We included a total of five trials in our meta-analysis (n = 843 women).[20, 21, 24–26] Two trials were from Egypt and one was from each of the United Kingdom, India, and Saudi Arabia. All trials used 20% IVI solution at the time of embryo transfer but there were variations in the volume given and the duration of the protocol. Two trials administered the first dose of intralipid prior to or at the time of oocyte retrieval. Four trials administered a second dose of intralipid following a positive pregnancy test and one continued intralipid administration fortnightly until the end of the first trimester. All trials used a normal saline infusion or no intervention (routine care) as a comparator (Table 1). All trials included women with previous implantation failure although the inclusion threshold varied across included trials. Four trials excluded women with other known causes for RIF while one did not report clear exclusion criteria.[20]

Risk of bias

There was an overall moderate risk of bias of the included studies with four studies (80%) showing low risk of bias for randomization and three (60%) for allocation concealment. Three (60%) studies had low risk for missing outcome data while two (40%) studies

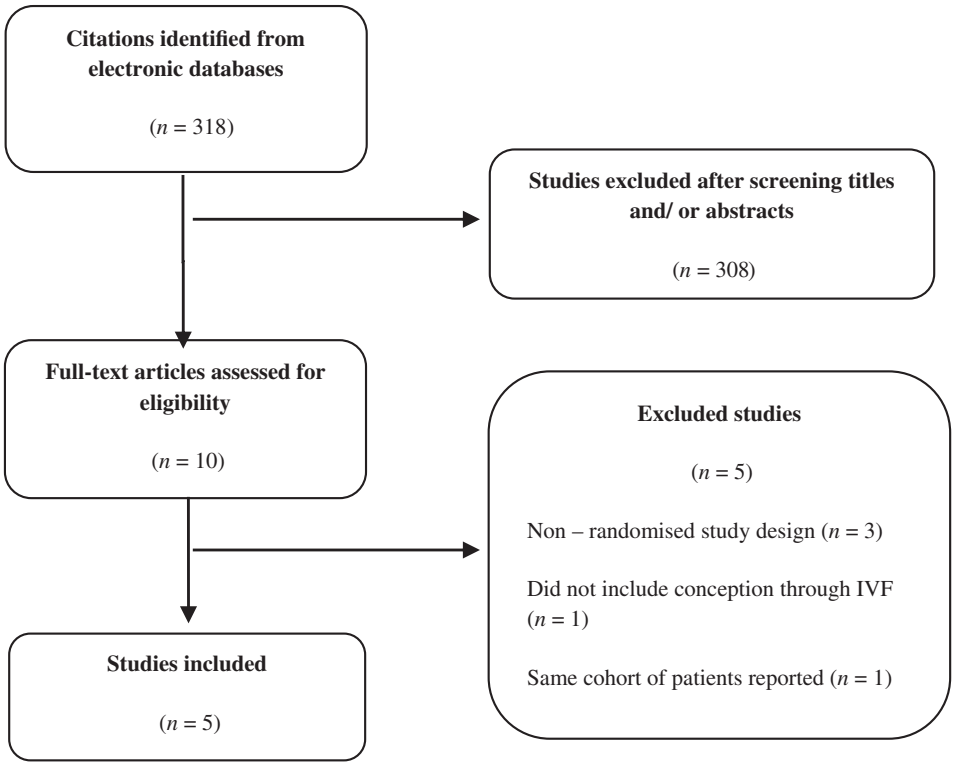

FIGURE 1 Selection and inclusion process of studies on the effectiveness of intralipid during assisted conception in women with history of recurrent implantation failure

TABLE 1 Characteristics of randomized trials on the effectiveness of intralipid during assisted conception in women with history of recurrent implantation failure

Study	Country	Numbers randomized	Intervention	Control	Inclusion criteria	Exclusion criteria
Al-Zebeidia 2019	Saudi Arabia	142	20% (100 mg) intralipid in 500 mL NaCl infused over 2.5 h on the day of embryo transfer Repeated dose was given on the day of the pregnancy test	Routine care	Recurrent implantation failure defined as failure to achieve a pregnancy despite >3 ICSI cycles	Age >42, BMI >30 kg/m^2, medical contraindications for intralipid infusion, uterine fibroid, endometrial polyp, endometriosis, hydrosalpinx, intrauterine adhesion, uterine abnormality, thrombophilia, diminished ovarian reserve, severe male factor, any chronic medical illness
Singh 2019	India	105	20% (4 mL) intralipid in 250 mL NaCl infused over 1 h twice, after oocyte retrieval and 1 h prior to embryo transfer	Normal saline infusion	Primary infertility, age 20–40, undergoing non donor oocyte IVF/ICSI with >1 previous implantation failure	Recurrent miscarriages, BMI <20 or >32 kg/m^2, abnormal oocytes or embryos, uterine abnormalities, medical or endocrine comorbidities, thrombophilia, eggs or soy allergy, male factor infertility
Gamaleldin 2018	UK	97	Intralipid 20% starting 6–7 days before embryo transfer followed by a repeated dose in case of a positive pregnancy test	Placebo starting 6–7 days before embryo transfer followed by a repeated dose in case of a positive pregnancy test	Unexplained recurrent implantation failure	None specified
Dakhly 2016	Egypt	296	20% (2 mL) intralipid in 250 mL NaCl infused over 30–60 min on the day of embryo transfer, repeated within 1 week of positive pregnancy test and then every 2 weeks until the end of the first trimester	Normal saline infusion	Unexplained secondary fertility OR three or more consecutive clinical miscarriages AND elevated level (>12%) of NK cells	Age >40, fetal chromosomal abnormalities, antiphosholipid syndrome, thrombophilia, uterine abnormalities, endocrine or medical comorbidities,

(*Continues*)

TABLE 1 Continued

Study	Country	Numbers randomized	Intervention	Control	Inclusion criteria	Exclusion criteria
						parental karyotype abnormalities, egg allergy, hyperlipidaemia
El-khayat 2015	Egypt	203	20% intralipid infusion day 4–9 of ovarian stimulation and second dose within 1 week of positive pregnancy test	Routine care	Repeated implantation failure defined as failed pregnancy after 2–6 ICSI cycles with transfer of more than 10 high grade embryos	Women with uterine fibroid, endometrial polyp, endometriosis and hydrosalpinx, disturbances of normal fat metabolism, allergy to eggs, soybean oil, liver disease, kidney disease, lung disease and blood clotting disorder

Abbreviations: BMI, body mass index; ICSI: intracytoplasmic sperm injection; IVF, in-vitro fertilization.

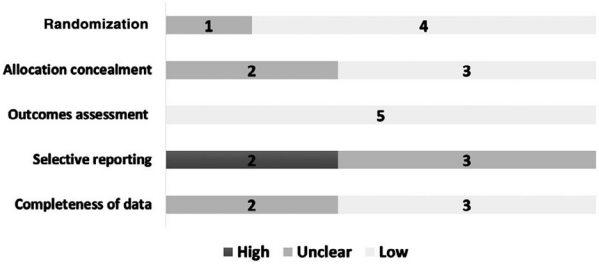

FIGURE 2 Risk of bias in included randomized trials on the effectiveness of intralipid during assisted conception in women with history of recurrent implantation failure

had high risk of bias for selective outcome reporting (Figure 2). None of the included studies conducted appropriate blinding thus raising the risk of performance bias.

Outcomes

All five trials reported on clinical pregnancy rates and live births contributing to our meta-analysis. Women in the IVI group had a higher chance of achieving clinical pregnancy (172 vs 119, RR 1.55, 95% CI 1.16–2.07, I^2 44.2%) and live birth (132 vs 73, RR 1.83, 95% CI 1.42–2.35, I^2 0%) post ART treatment compared to no intervention (Figure 3). Only two trials reported on miscarriage with no clear benefit in the IVI group (18 vs 30 in Dhakly et al.; 11 vs 10 in Al-Zebeidi et al.). Similarly, only two trials reported on biochemical pregnancy (84 vs 76 in Dhakly et al.; 21 vs 8 in Singh et al.); thus, a meta-analysis was not possible for those two outcomes. One trial reported two cases of congenital middle ear anomalies in the intralipid group (n = 2/14, 14%), but no statistical testing was reported.[20]

Discussion

Summary of findings

Our meta-analysis suggests that compared to routine care, providing IVI at the time of embryo transfer could increase the rate of clinical pregnancy and live birth in women with the history of RIF. The effect estimates were consistent for both outcomes which could suggest a persistent benefit through both the implantation phase and later till the first trimester of the pregnancy. Such effect could be explained by an improvement in the endometrial receptivity driven by

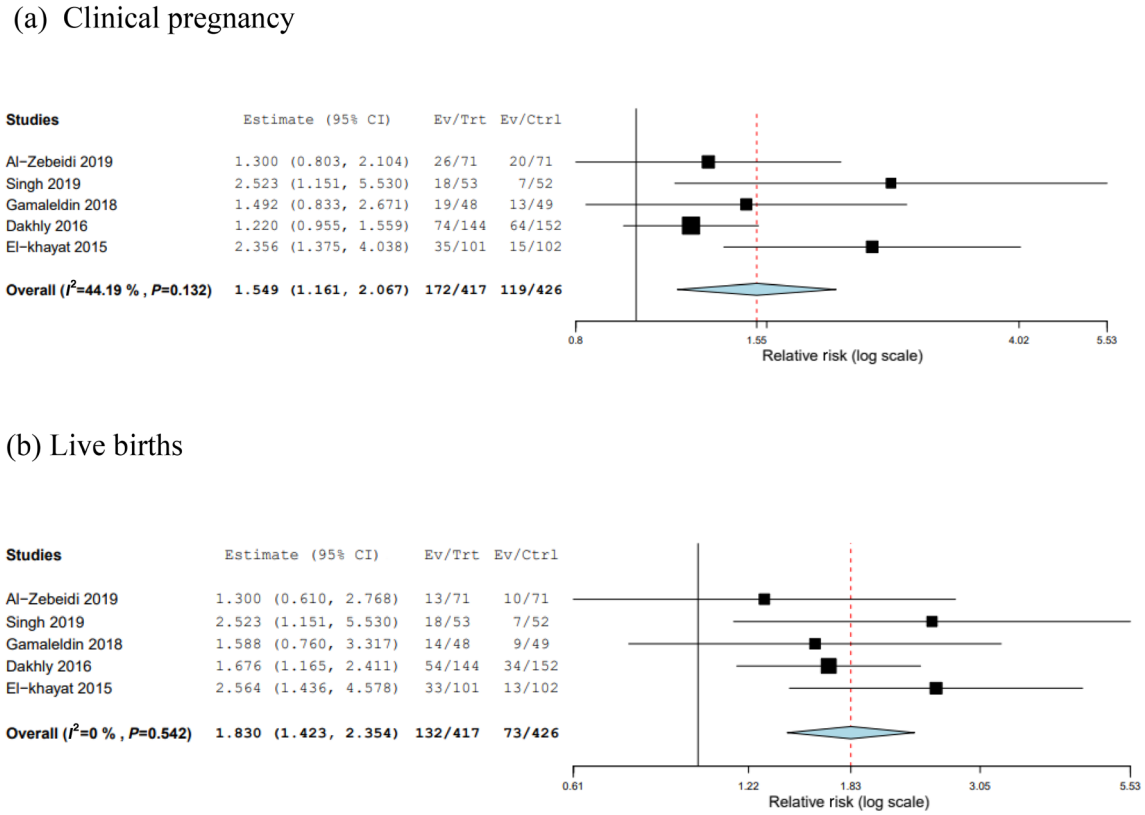

FIGURE 3 Forest plots of pooled data from studies on the effectiveness of intralipid during assisted conception in women with history of recurrent implantation failure. (a) Clinical pregnancy and (b) live births

a favorable immunological response to the invading trophoblast during the implantation phase. None of the included studies reported serious adverse events in women receiving IVI. Similar trials in the literature reported minor side effects such as a flushing feeling, nausea, and headache.[27] Two cases of congenital abnormalities were reported in one trial of relatively small sample size. While it is difficult to ascertain causality due to statistical limitation, we highlight the importance of reporting fetal anomalies in any future studies planning to evaluate IVI use pre-pregnancy.

Strength and limitations

We used a prospectively registered protocol and a standardized methodology to conduct this review. We assessed the risk of bias in all included studies and extracted data in duplicate. We contacted two groups of authors[20, 21] to ensure study eligibility for inclusion. Still, our findings are not without limitations. While all trials used 20% IVI solutions, there were variations in the used doses, frequency of IVI administration, and in the ART protocols which could increase the performance bias. For example, three trials used a diluted form of IVI in normal saline[20, 24, 25] while the other two used a concentrated form of IVI prior to its use.[23, 27] Due to the small number of included studies, we were unable to explore this further using a meta-regression. The comparison varied among included trials (normal saline vs no intervention) with limited information on blinding efforts (as IVI is of white color). As the reported outcomes are objective (pregnancy and live births), we perceive little placebo effect on the quality of reporting, although performance bias is possible. Finally, we were unable to investigate the effect of potential effect modifiers such as the process of ovulation stimulation, the number and quality of transferred embryos and the use of additional add-on treatments. Such effect could be best evaluated with individual patient data meta-analysis; however, given the relatively small number of women included in this meta-analysis, such an approach is unlikely to yield significant

findings pending the conduct of larger trials in the future. Our findings are, therefore, important to harmonize the standardize future trial conduct to yield more efficient evidence synthesis.

Implications for future practice

The value of several ART add-ons has been heavily debated with concerns regarding the ethicality of offering such additional treatments without clear evidence of benefit.[28] Our meta-analysis of five randomized trials offers a pragmatic overview on the potential role of IVI to help a specific group of women affected by RIF. However, given the limitations and the quality of included trials, we conclude that adopting the use of IVI in ART practice is at present immature and offering it a-la-carte to all couples undergoing ART should not be adopted until larger RCTs are published with a clear persistent beneficial effect.

This imprecision in effect size is largely driven by the variation in treatment protocols and use of IVI across included studies. There is a need to focus future research work on evaluating the perceived immunological effect on IVI on the endometrium at the implantation phase within larger cohorts of women with history of recurrent pregnancy loss. More specifically, there is a need to delineate this perceived impact in both subgroups of RIF and recurrent pregnancy loss in the first trimester. As the mechanistic effect of IVI on the maternal innate immunological system remains unclear, there is also a need for more discovery research to aid the stratification and selection of women who might benefit the most of IVI.[29] Novel tests are now available to aid the identification of women with nonreceptive endometrium such as microarray technology which could offer more precise evaluation of the effectiveness of IVI in future studies,[30] but they remain of limited use in clinical practice. Several methodological improvements are required to enhance the quality of future studies on IVI such as standardizing the definition and management pathways for women with RIF[3] and following more transparent reporting using an established core outcome set for fertility treatments.[31]

We were unable to evaluate any long-term protective effect of IVI later on in pregnancy. As it is argued to promote healthy implantation and placentation, IVI might reduce the risk of placenta mediated pregnancy complications (e.g. pre-eclampsia) which are more common in women undergoing ART.[32] Planned long-term follow-up of randomized cohort is essential to precisely evaluate such protective effects and aid more robust evidence synthesis on ART add-ons. Despite our meta-analysis results suggesting IVI intralipid increased both clinical pregnancy rate and live birth, the small number of studies makes it challenging to draw firm conclusions as to the benefit of intralipid.

In conclusion, evidence to support the use of IVI at the time of embryo transfer in women with a history of RIF is limited; more research is needed before adopting it in clinical practice.

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Author contributions

MPR and NB conducted the search and extracted the data. BHA drafted the protocol, conducted the analysis and drafted the final manuscript. SK and SQ supervised the study conduct and critically improved the final manuscript.

Conflict of Interest

All authors declared no potential conflicts of interest.

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