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REVIEW ARTICLE

Effect of a 20% intravenous fat emulsion therapy on pregnancy outcomes in women with RPL or RIF undergoing IVF/ICSI: a systematic review and meta-analysis

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ABSTRACT

Background and Aim: The aim of this study was to evaluate the efficacy a 20% intravenous fat emulsion therapy in women suffering from recurrent pregnancy loss or recurrent implantation failure (RPL/RIF) who are undergoing *in vitro* fertilization (IVF) or intracytoplasmic sperm injection (ICSI).
Materials and Methods: We searched Cochrane Library, ISI Web of Science, MEDLINE, ClinicalTrials.gov, PubMed, and Scopus using relevant keywords during February 2020 for randomized controlled trials (RCTs) comparing the therapy versus placebo or no intervention in women suffering from RPL/RIF and undergoing IVF/ICSI.
Results: We included five RCTs with 840 patients. The intravenous fat emulsion therapy was significantly effective in increasing clinical pregnancy rates compared to the control group (risk ratios [RR] = 1.48, 95% confidence intervals [CI] [1.23, 1.79], $P < 0.001$). Furthermore, ongoing pregnancy and live birth rates were significantly higher with 20% intravenous fat emulsion therapy RR = 1.71, 95% CI [1.27, 2.32], $P = 0.005$ and RR = 1.85, 95% CI [1.44, 2.38], $P < 0.001$. Despite the statistically significant differences, the quality of evidence was only considered moderate, and this was primarily due to high risk of bias in the included RCTs.
Conclusion: Our review provides a moderate level of evidence that intravenous fat emulsion therapy is effective in improving reproductive outcomes among women with RPL/RIF performing IVF/ICSI techniques. Further, investigation is required to ascertain optimal dosage and timing of administration.
Relevance for Patients: Women suffering from RPL or RIF may wish to consider discussing with their reproductive endocrinologist the addition of a 20% fat emulsion therapy to planned IVF or ICSI cycles, which may improve outcomes.

1. Introduction

Recurrent pregnancy loss (RPL) is the recurrent miscarriage of intrauterine pregnancies [1]. Exact definitions vary, but consensus statements by major US and European Obstetrical groups define RPL as the failure of two or more pregnancies, <12 weeks gestation, which do not necessarily have to be consecutive [1,2]. Some groups have included the loss of a single pregnancy in the second trimester to meet this criteria [3], while others require three first trimester miscarriages to meet their definition [4]. Natural spontaneous miscarriage occurs in at least 25% of human pregnancies, when pregnancy is detected early and regularly, as undetected miscarriages are also common [5,6]. Recurrent implantation failure (RIF) refers to the failure of pregnancy in spite of transferring a healthy embryo after three or more

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in vitro fertilization (IVF) cycles [7]. Kumar *et al*. [8] established that the failure of implantation occurs in approximately 10% of IVF/intracytoplasmic sperm injection (ICSI) cycles.

Many factors can be responsible for RPL/RIF. These include abnormal embryonic karyotype (41%), uterine abnormalities (5%), endocrine dysfunction (6%), and antiphospholipid antibody (APA) syndrome (6%). Furthermore, it is estimated that the 25% of the time, the cause is unexplained or that 4% of the cases occur from mixed causes [9]. Different studies have proposed an immunological explanation for the RIF/RPL phenomenon, especially in those cases that lack an identified cause [6,10]. There is no consensus whether the most common cause is the failure of the apposition, adhesion, or invasion of the placenta into the uterine lining [11]. Immunological causes suspected to be responsible for RPL/RIF are extensive, and a full discussion is outside the realm of the present work. However, commonly suspected abnormalities include T-helper cells ratio imbalance, the deregulation of T-cells, the deregulation of dendritic cells, natural killer (NK) cells in the uterus, APA, and disorders of adaptive immunity and innate immunity, [12]. Various other biochemical factors have also been investigated, such as inflammatory mediators and human leukocyte antigens [13].

Accordingly, many immunomodulatory agents have been studied to reduce RPL/RIF rates. These therapies include low-molecular-weight heparin, aspirin, intravenous immunoglobulin (IVIG), corticosteroids, and 20% intravenous fat emulsion therapy [14-17]. Despite numerous studies, there is no clear consensus regarding the efficacy of these therapies in improving different pregnancy outcomes. This includes unclear efficacy in rates of achieving clinical pregnancy, maintaining ongoing pregnancies, and effect on live birth rates in patients with RPL and RIF [18].

Intralipid™ (20% intravenous fat emulsion) is a fat emulsion solution that consists of soybean oil, glycerin, egg phospholipid, water, and glycerol [15]. The medication is Food and Drug Administration approved for the administration of parenteral nutrition in patients with ingestion problems and is administered intravenously. It supplies the body with essential fatty acids, α-linolenic acid, and omega-3 fatty acids [19]. Interestingly, several studies have reported on benefits of intravenous fat emulsion therapy outside of the field of parenteral nutrition and the medications intended indication. These include a reduction in platelet aggregation, decline in interleukin-2 (IL-2) production, suppression of NK cell activity, and inhibition of TH1 cell activity [20]. Clearly, these properties spark an interest in the efficacy of this medication in the treatment of RPL and RIF.

While there is ample evidence that intravenous fat emulsion therapy is effective in reducing the production of proinflammatory cytokines and the production of NK cells [21-23], whether the medication actually improves outcomes in patients with RPL and RIF remains unclear. Before embarking on this review, we found conflicting bodies of evidence, with some studies reporting improved reproductive outcomes among patients with RPL/RIF undergoing IVF/ICSI when receiving the 20% intravenous fat emulsion therapy [24-26], and others failing to show any significant difference [27-30].

In light of this data, we found that there were sufficient RCTs performed on this topic to perform a meta-analysis, if the RCTs on RPL and RIF were combined (There was insufficient data separately.) Therefore, to see if a true difference exists, we aimed to design a meta-analysis to assess all of the available data regarding the effect of the 20% intravenous fat emulsion therapy on different pregnancy outcomes in women with RPL or RIF undergoing IVF/ICSI.

2. Materials and Methods

We performed this systematic review and meta-analysis accurately with the Cochrane Handbook for Systematic Reviews of Interventions [31]. We reported our findings according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [32].

We performed a computerized search in different databases (PubMed, Cochrane Library, Scopus and ISI Web of Science, MEDLINE, and ClinicalTrials.gov) during February of 2020. We used the following search strategy: (intralipid OR intralipid infusion OR soybean oil based lipid emulsion) AND (control OR comparator OR placebo OR saline OR no intervention) AND (pregnancy OR pregnant OR gestation OR recurrent pregnancy loss OR recurrent implantation failure OR RPL OR RIF) AND (clinical trial OR clinical trials OR trial OR random OR random allocation OR RCT OR randomized controlled trial OR controlled clinical trial). Two investigators performed the search strategy. There were no restrictions by language or year of publication.

Randomized controlled trials (RCTs) were included using this criteria:

(I) population: Women with RPL or RIF; (II) intervention: the 20% intravenous fat emulsion therapy; (III) comparator: placebo (normal saline) or no intervention; and (IV) study design: RCTs. We excluded studies for the following reasons: (1) reviews, (2) irrelevant studies, (3) letters to editors, and (4) studies whose data could not be extracted or entered into the analysis. Title and abstract screening and full-text screening were conducted by appropriate step by step analysis by the same two authors.

Our data were initially extracted by the two authors on a data extraction sheet. The extracted data included: list of authors, year of publication, sample size, and summary of included studies. In addition, we extracted our primary outcome (clinical pregnancy rate) and our secondary outcomes (ongoing pregnancy, miscarriage, live birth rates, and any adverse events of the 20% intravenous fat emulsion therapy). The category of adverse events was expanded to include reports of headache, dizziness, flushing, drowsiness, nausea, vomiting, and sweating.

Clinical pregnancies were defined as confirmation of fetal cardiac activity through sonography or Doppler, and this was found to be universally accepted in all included studies. Ongoing pregnancy was defined as a pregnancy that had reached more than or equal to 20 gestational weeks. Miscarriage was determined as spontaneous abortion or pregnancy loss prior to 20 weeks of gestation. Live birth was defined as the total number of deliveries

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that resulted in a neonate who was born alive, and this ratio was calculated to 100 embryo transfers.

Two authors evaluated the methodological quality and the risk of bias in included studies using the Cochrane risk of bias assessment tool [33]. This tool involves six domains as the following: selection bias, performance bias (blinding of participant and personnel), detection bias (blinding of outcome assessment), attrition bias, reporting bias, and other potential sources of bias. The authors' judgment is categorized as "low risk," "high risk," and "unclear risk" of bias. Differences were discussed between the authors and consensus reached.

In addition, we assessed the methodologic quality of the evidence among the included studies using GRADEpro™ software. GRADEpro™ software provides fundamental details regarding the magnitude of the effect of the interventions examined, and the sum of available data on main outcomes in a summary of findings table produced by the software. This information is useful in examining the quality of evidence.

We pooled the dichotomous data as risk ratios (RR) with the corresponding 95% confidence intervals (CI) by the Mantel-Haenszel method. We used RevMan™ software to perform our statistical analysis. We assessed the statistical heterogeneity among included studies using I-squared (I^2) statistics, and values of ≥50% were indicative of high heterogeneity. We utilized a fixed-effect model, as heterogeneity was not significant in our selected outcomes.

We could not assess publication bias using the funnel plot method, and Egger's test is considered unreliable for less than ten included studies [34,35].

3. Results

3.1. Results of the literature search

Our search strategy resulted in 283 studies, and 23 articles were reliable for full-text screening after performing title and abstract screening. We excluded 18 full-text articles, and finally, five studies [25-29] matched our inclusion criteria and entered our final analysis. The PRISMA flow diagram for clarification is shown in Figure 1.

3.2. Characteristics of the included studies

Five RCTs [25-29] with 840 total patients were included. All included studies compared the intravenous 20% fat emulsion therapy versus placebo (normal saline) or no intervention in women with RIF/RPL undergoing IVF/ICSI. All women included in the studies were suffering from either primary or secondary infertility with RPL/RIF and intended to perform IVF/ICSI and embryo transfer technology. Controlled ovarian stimulation using different stimulation protocols was used in the included studies before the randomization process began. The summary of the included studies is shown in Table 1. All of the included RCTs used similar protocols for administration of the fat emulsion

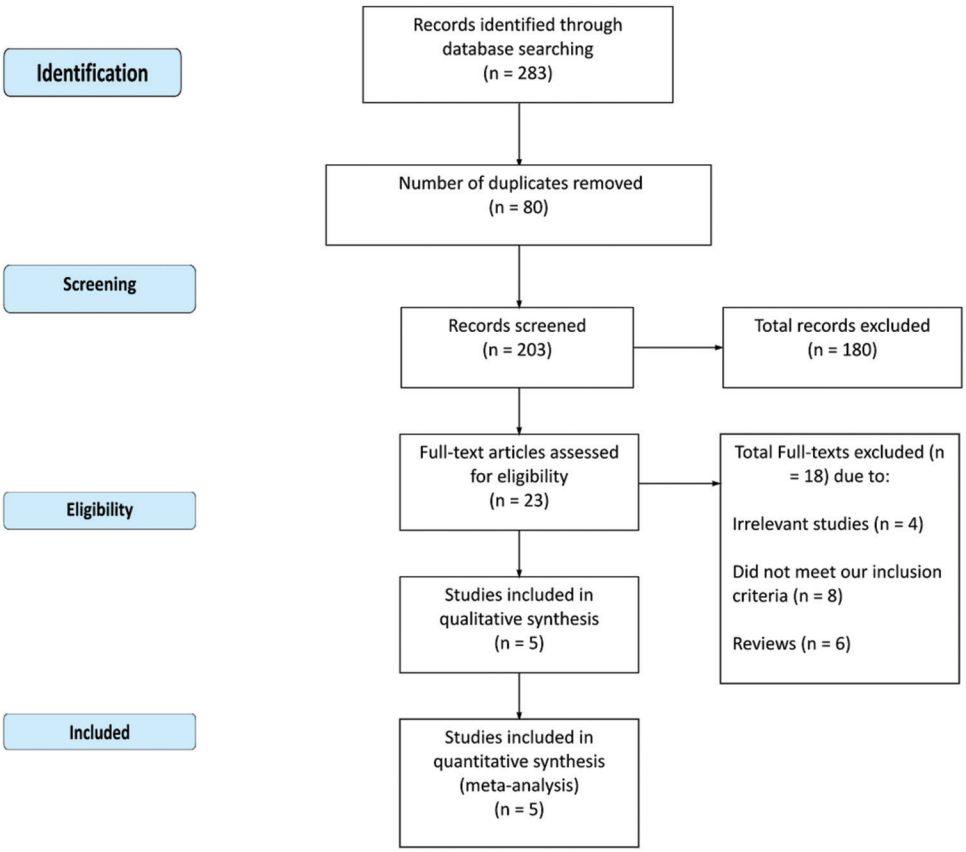

Figure 1. PRISMA flow diagram of selected studies.

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Table 1. Summary of the included studies

Study	Study arms	Country	Sample size	Age (year), mean±SD	Body mass index, mean±SD	GnRH analogue	GnRH protocol	Gn type	HCG dose	Number of oocytes retrieved, mean±SD	Number of embryos transferred, mean±SD	Infertility causes				Main findings
												Tubal	PCOS	Unexplained	Male	
Singh *et al.* (2019)[25]	Fat emulsion group (Two doses of 4 mL of 20% fat emulsion in normal saline of 250 mL; 1 dose at oocyte recovery, 1 dose on day of embryo transfer)	India	52	31.64±3.96	4.06±3.12	Leuprolide acetate/ Cetrorelix	Agonist/ Antagonist	rFSH	250 µg rHCG	5.96±3.45	2.09±1.1	13	6	19	13	Showed a significant increase in live birth rate and implantation rates in women who received the fat emulsion infusion after IVF/ICSI
	Control group (normal saline)		50	32.12±3.50	24.61±3.32					4.62±1.99	2.48±1.07	21	3	18	11	
Al-Zebeidi *et al.* (2019)[27]	Fat emulsion group (Two doses 20% 20% fat emulsion 100 mL diluted in 500 mL normal saline; 1 dose on day of embryo transfer, 1 dose on day of pregnancy test)	Saudi Arabia	71	35.32±4.23	28.30±4.66	Cetrorelix	Long antagonist	rFSH/ HMG	10,000 IU	NA	1.8±0.54	5	3	10	39	There was an improvement in the pregnancy rate among women with unexplained RIF who received the fat emulsion therapy; however, this improvement did not reach statistical significance.
	Control group (no intervention)		71	35.21±4.77	28.30±4.66					NA	1.9±0.51	2	5	10	45	
Dakhly *et al.* (2016) [29]	Fat emulsion group (Multiple doses of 2mL 20% fat emulsion diluted at 20% in 250 mL saline; infusions within 1 week of positive pregnancy test and every 2 weeks until end of first trimester)	Egypt	144	35.5±3.7	22.6±2.6	Triptorelin acetate	Long agonist	HMG	10,000 IU	8.5±2.8	2.5±0.5	NA	NA	NA	NA	Fat emulsion therapy did not increase chemical pregnancy rates. However, live birth and ongoing pregnancy rates were increased in the fat emulsion group.
	Control group (normal saline)		152	36±3.7	22.9±2.2					8.8±2.4	2.6±0.5	NA	NA	NA	NA	

(*Contd...*)

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Table 1. (*Continued*)

El-Khayat and El Sadek (2015)[26]	Fat emulsion group (Two doses of 2 mL 20% fat emulsion in 250 mL normal saline; infusion between days 4–9 of ICSI and 1 dose within first week of positive pregnancy test)	Egypt	101	35.1±3.5	24.7±4.7	Triptorelin acetate	Long agonist	HMG	10,000 IU	5.1±1.4	1.94±0.31	NA	NA	NA	N	Fat emulsion infusion significantly improved clinical pregnancy rate, implantation rate, and the live birth rates in IVF/ICSI in women with RIF.
	Control group (normal saline)		102	35±3.6	24.1±4.3					4.9±1.7	1.93±0.33	NA	NA	NA	NA	
Gamaleldin *et al*. (2018)[28]	Fat emulsion group (Two doses of 2 mL 20% fat emulsion in 250 mL normal saline)	United Kingdom (UK)	48	35±3.4	NA	Triptorelin acetate	Long agonist	HMG	10,000 IU	NA	NA	NA	NA	NA	NA	Fat emulsion therapy did not significantly improve live birth rates in women with unexplained RIF undergoing IVF treatment.
	Control group (normal saline)		49	35.4±3.2	NA					NA	NA	NA	NA	NA	NA	

NA: Not available, IVF/ICSI: *In vitro* fertilization/intracytoplasmic sperm injection, RIF: Recurrent implantation failure, HMG: Human menopausal gonadotropin, HCG: Human chorionic gonadotropin, GnRH: Gonadotropin-releasing hormone, Gn: Gonadotropin, rFSH: Recombinant Follicle-stimulating hormone, rHCG: Recombinant human chorionic gonadotropin, IU: International unit, SD: Standard deviation

therapy, which included two or three doses of 2–4 mL of the 20% fat emulsion each diluted in saline, given in the time period surrounding embryo transfer [25-29]. While these protocols were similar in timing and dosage, they were not identical.

3.3. Risk of bias assessment

The risk of bias assessment for the included RCTs is shown in Figure 2. We performed the quality assessment of the included RCTs based on the Cochrane risk of bias assessment tool.

3.4. Outcomes

3.4.1. Clinical pregnancy rate

The intravenous fat emulsion therapy was effective in improving the clinical pregnancy rate when compared to the control group (RR = 1.48, 95% CI [1.23, 1.79], $P < 0.001$), as shown in Figure 3.

The pooled studies were homogeneous ($P = 0.13$, $I^2 = 45\%$). The quality of evidence was moderate, as shown in Figure 4.

3.4.2. Ongoing pregnancy rate

The intravenous fat emulsion therapy was beneficial in improving the ongoing pregnancy rate when compared to the control group (RR = 1.71, 95% CI [1.27, 2.32], $P = 0.005$), as shown in Figure 5. We found homogeneity among the pooled studies ($P = 0.50$, $I^2 = 0\%$). The quality of evidence was moderate, as shown in Figure 4.

3.4.3. Miscarriage rate

We found no significant difference between the intravenous fat emulsion group and the control group regarding miscarriage rate (RR = 0.78, 95% CI [0.50, 1.20], $P = 0.26$), as shown in Figure 6. We found homogeneity among the pooled studies ($P = 0.38$, $I^2 = 0\%$). The quality of evidence was moderate, as shown in Figure 4.

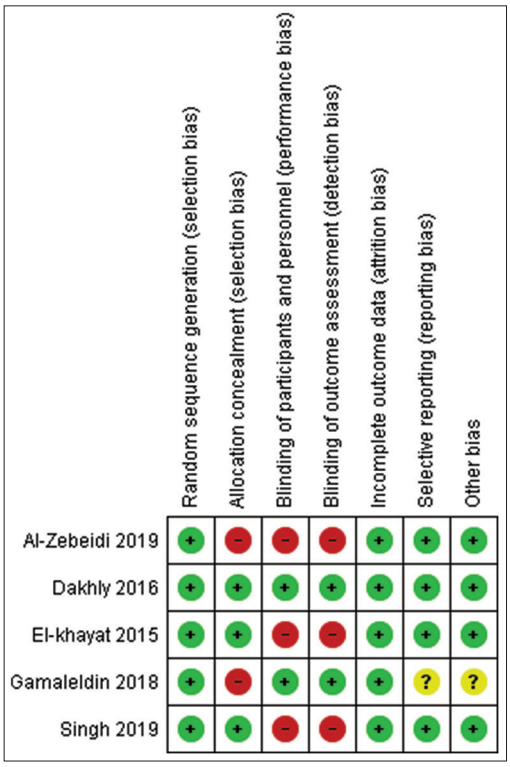

Figure 2. Risk of bias summary.

3.4.4. Live birth rate

The intravenous fat emulsion therapy significantly improved live birth rate over the control group (RR = 1.85, 95% CI [1.44, 2.38], $P < 0.001$), as shown in Figure 7. We found homogeneity among the pooled studies ($P = 0.55$, $I^2 = 0\%$). The quality of evidence was moderate, as shown in Figure 4.

3.4.5. Subgroups

As stated previously, there was insufficient data from the RCTs to perform a subgroup analysis for RPL and RIF separately.

3.4.6. Adverse events

There were no adverse events from the intravenous fat emulsion therapy administration reported by the included studies.

4. Discussion

Our study demonstrated a significant benefit on pregnancy outcomes in IVF/ICSI cycles of patients with a history of RIF or RPL with intravenous fat emulsion therapy. There was higher incidence of clinical pregnancy, ongoing pregnancy, and live birth rates in the fat emulsion therapy arm, which was statistically significant. However, the miscarriage rate did not show a significant difference between the fat emulsion therapy and control groups.

According to Moffett and Colucci, the prevailing theory for this difference stems from treatment of a hypothesized dysfunction of the immune system in the endometrium [36]. It is further theorized that this dysfunction, including a higher level of NK cell activity, may be one of the main causes of RPL and RIF. In addition, an elevated level of NK cell activity may actually be predictive of future pregnancy loss in subsequent pregnancies in patients who have RPL/RIF [37]. The theorized mechanisms by which the intravenous fat emulsion therapy produces its immune modulation effects include mitochondrial-dependent platelet aggregation reduction [20], decline in secretion of hepatic apolipoprotein M and insulin sensitivity amplification [38], alteration in the composition of the platelets (especially phospholipid membrane and consequently reduced platelets aggregation) [39], reduced secretion of IL-2, tumor necrosis factor-α, and IL-1β [21], and long-standing inhibition of the NK cells activity [23]. Singh *et al*. [25] demonstrated that intravenous fat emulsion therapy may also produce changes in the endometrium that favor the production of TH2 cytokines and may modify the NK cells to a phenotype more compatible with pregnancy [25].

Investigations have been performed in the roles of the uterine (endometrial) and peripheral measurements of NK cells as well in the treatment of RPL/RIG [16]. Studies performed by Seshadri and Sunkara [37] originally found a high percentage of NK cells in the periphery in women with RIF and RPL versus the control group [37]. However, such a significant difference was not

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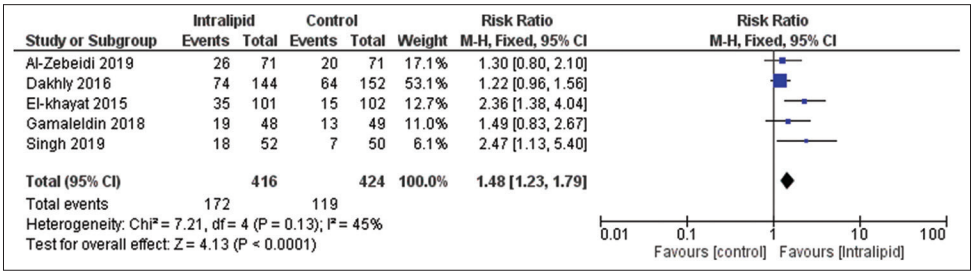
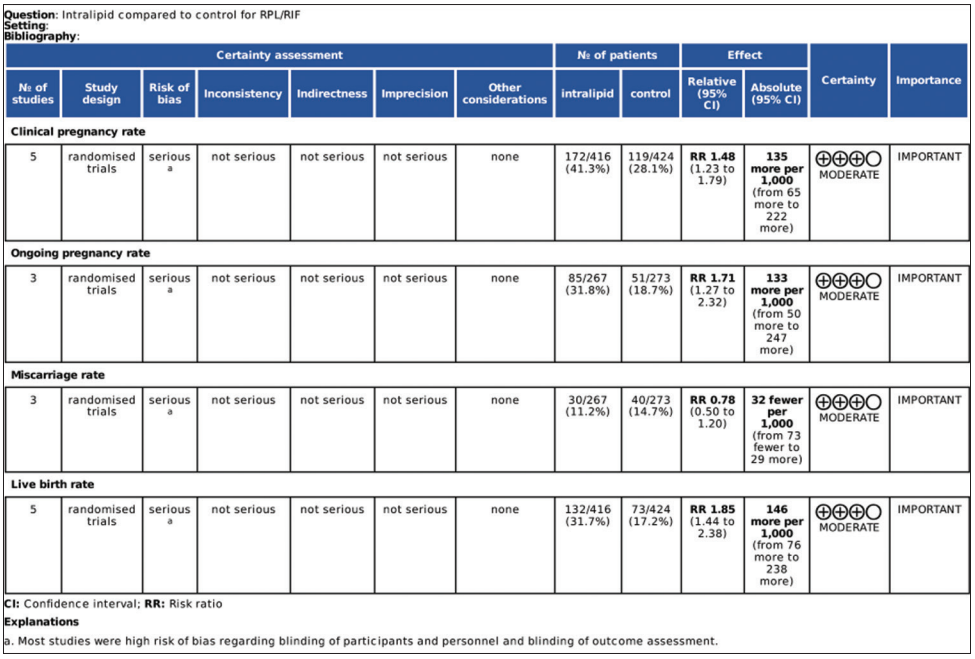


Figure 3. Forest plot of clinical pregnancy rate.



Question: Intralipid compared to control for RPL/RIF
Setting:
Bibliography:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	intralipid	control	Relative (95% CI)	Absolute (95% CI)		
Clinical pregnancy rate												
5	randomised trials	serious [a]	not serious	not serious	not serious	none	172/416 (41.3%)	119/424 (28.1%)	**RR 1.48** (1.23 to 1.79)	**135 more per 1,000** (from 65 more to 222 more)	⨁⨁⨁◯ MODERATE	IMPORTANT
Ongoing pregnancy rate												
3	randomised trials	serious [a]	not serious	not serious	not serious	none	85/267 (31.8%)	51/273 (18.7%)	**RR 1.71** (1.27 to 2.32)	**133 more per 1,000** (from 50 more to 247 more)	⨁⨁⨁◯ MODERATE	IMPORTANT
Miscarriage rate												
3	randomised trials	serious [a]	not serious	not serious	not serious	none	30/267 (11.2%)	40/273 (14.7%)	**RR 0.78** (0.50 to 1.20)	**32 fewer per 1,000** (from 73 fewer to 29 more)	⨁⨁⨁◯ MODERATE	IMPORTANT
Live birth rate												
5	randomised trials	serious [a]	not serious	not serious	not serious	none	132/416 (31.7%)	73/424 (17.2%)	**RR 1.85** (1.44 to 2.38)	**146 more per 1,000** (from 76 more to 238 more)	⨁⨁⨁◯ MODERATE	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Most studies were high risk of bias regarding blinding of participants and personnel and blinding of outcome assessment.

Figure 4. GRADEpro™ assessment of methodologic quality of evidence.

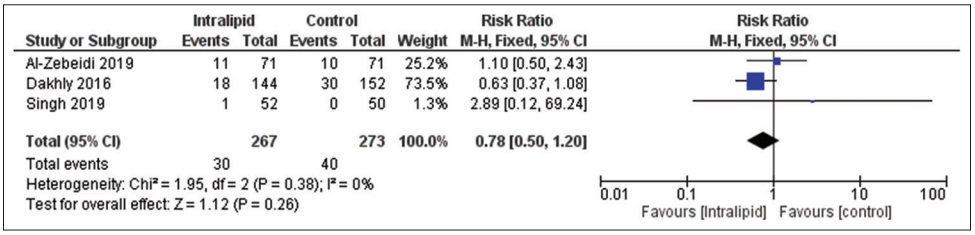


Figure 5. Forest plot of the ongoing pregnancy rate.

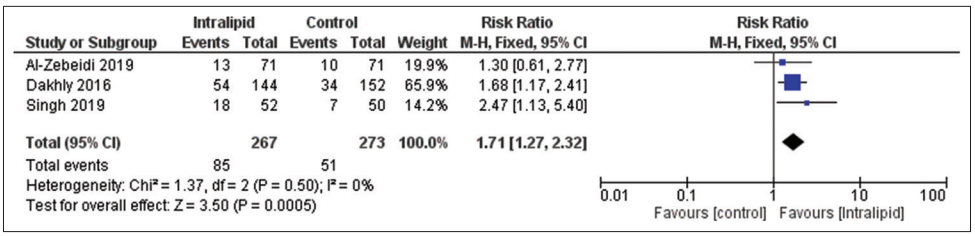


Figure 6. Forest plot of the miscarriage rate.

observed when NK cells were measured in uterine samples in the same study groups [39]. Evidence has been presented to show that uterine NK cells are detrimental to a newly invading placental trophoblast [40,41]. In addition, newer studies have found direct

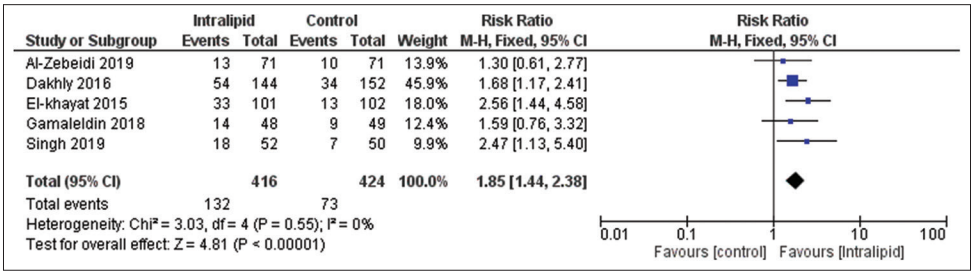


Figure 7. Forest plot of the live birth rate.

correlations between certain NK cell receptors and RPL [42].

At present, in the United States, intravenous 20% fat emulsion therapy is administered by many fertility clinics for patients with RPL/RIF, especially in the setting of empiric treatment of suspected fertility-related immunological dysfunction [43,44]. This may be secondary to the high cost of other investigations. IVIG therapy, for example, is extremely expensive, with a single course of therapy costing up to $14,000 [43]. In addition, the efficacy of IVIG for improving pregnancy outcomes (clinical pregnancy, ongoing pregnancy, and live birth rates) in RPL/RIF remains unproven. Risks with IVIG administration include the possibility of anaphylaxis and a low—but possible—risk for transmission of infections [44]. Thus, many clinicians feel that intravenous fat emulsion therapy may be safer, in addition, to being less expensive. There is, however, no universal consensus. Martini *et al*., [10] for example, failed to find that fat emulsion therapy was cost-effective despite an average cost of only $681.00 for the therapy in their case series. The lack of cost effectiveness was a result of finding very little efficacy versus their control [10].

Some of the most compelling evidence for fat emulsion therapy came from Singh *et al*., [25] which demonstrated a significant improvement in clinical pregnancy, ongoing pregnancy, and live birth rates in women with a history of RIF undergoing intravenous fat emulsion therapy. The adjusted odds ratio for clinical pregnancy in the fat emulsion therapy group, compared to placebo, was 3.1, 95% CI [1.02–9.70], $P = 0.046$. Another RCT, El-Khayat and El Sadek [26] agreed with these findings by concluding a significant improvement in clinical pregnancy, implantation, and live birth rates among women receiving the intravenous fat emulsion therapy [26]. In addition, Coulam and Acacio [24] proposed an estimated 61% increase in live birth rates after treatment with the intravenous fat emulsion therapy in cases of RPL/RIF with increased NK activity. Moreover, this effect was not different when compared against a cohort of IVIG.

Several of the analyzed RCTs had different conclusions. Al-Zebeidi *et al*. [27] failed to demonstrate a significant difference between the intravenous fat emulsion and control groups in terms of clinical pregnancy, miscarriage, and live birth rates. Similarly, Dakhly *et al*. [29] did not illustrate any significant difference in chemical pregnancy among women with RPL after intravenous fat emulsion therapy (58.3% vs. 50.0%, $P = 0.129$ for intravenous fat emulsion vs. control group, respectively). Furthermore, in a recent retrospective study, Lédée *et al*. [16] found that there was a benefit to fat emulsion therapy in RIF patients who exhibited an over-immune activation of uNK cells. They found an improvement to a 54% live birth rate with fat emulsion therapy in RIF patients [16]. Gamaleldin *et al*. [28] found that fat emulsion therapy did not create any significant improvement in live birth and clinical pregnancy rates in cases with RIF, and Cohen *et al*. [30] reported a similar lack of efficacy in patients aged 40–42 years with history of miscarriage [30].

To the best of our knowledge, this meta-analysis is the first to investigate the effect of intravenous fat emulsion therapy on different pregnancy outcomes in women suffering from recurrent miscarriage or implantation failure. Strengths of our study include that the characteristics of most of the included RCTs were extremely similar, with relatively few variables to control for. Other strengths include our strict adherence to the PRISMA guidelines and accepted principles of a systematic review.

Our main limitation was the heterogeneity of inclusion criteria in some of the included studies, although as stated above, we noted great similarity in the adhered protocols. Secondary to this increased heterogeneity, our strict grading of the studies led to a higher than expected risk of bias. This ultimately resulted in a moderate level of evidence. As noted in our quality of evidence assessment (Figure 4), this is almost entirely due to concerns of a lack of proper blinding of participants and personnel in four of the included studies. This led to an increased risk of bias and, thus, lowered the quality of our overall evidence. It is likely that if more well-designed RCTs are undertaken, this level of evidence would increase, especially if the researchers were able to specifically document that correct patient and personnel blinding procedures were followed.

Another limitation of this study was the necessity to combine the RPL and RIF groups to reach statistical significance among the included RCTs. A greater wealth of RCTs on this topic would allow for subgroup analysis or individual analysis to ascertain exactly which condition, if either, benefits more from fat emulsion therapies.

Furthermore, complicating our understanding of the usage of fat emulsion therapy, there is still no universal consensus as to the mechanism of action of intravenous fat emulsion therapy in patients with RPL and RIF, which may be limiting the interest in developing future RCTs. We would also recommend that future studies could focus on the cost-effectiveness of the fat emulsion therapy, as this is an important factor for many clinicians.

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5. Conclusion

Our findings show moderate-level evidence that intravenous 20% fat emulsion therapy is effective in improving clinical pregnancy, ongoing pregnancy, and live birth rates in IVF/ICSI procedures in women with RPL/RIF. Further RCTs are needed and improved methodologic evidence quality in those trials would greatly improve the quality of this recommendation.

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Conflicts of Interest

The authors have no conflicts of interest to declare.

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