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Systematic review

## Success pregnancy rate after use of intralipid in recurrent pregnancy loss

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### ABSTRACT

**Background:** Recurrent pregnancy loss (RPL) is a multifactorial condition, and immunological therapies have been explored in women with recurrent miscarriage (RM) or RPL when immune dysregulation is suspected. This review evaluated pregnancy outcomes after intralipid therapy in women with RPL. **Methods:** A systematic review based on PRISMA principles was conducted using PubMed, Embase, Scopus, and the Cochrane Library. We consider original studies evaluating intralipid or lipid emulsion therapy in women with RPL, RM, or related reproductive failure populations and reporting pregnancy outcomes. Data on study characteristics, treatment regimens, and outcomes were extracted and analyzed qualitatively. **Results:** Four studies published between 2015 and 2025 were included, conducted in China, the United States, France, and Japan. Study designs included one prospective randomized trial, one comparative study, and two retrospective cohort studies. One study focused on an unexplained recurrent spontaneous abortion population, while the others included mixed recurrent pregnancy loss miscarriage and recurrent implantation failure populations. Intralipid showed outcomes comparable to intravenous immunoglobulin in two studies, a significantly higher live birth frequency than controls in one RM subgroup, and no clear improvement versus historical controls in another study. **Conclusions:** intralipid have benefit in selected women with RPL, and results remain inconsistent and limited by heterogeneous populations and study designs.

**Keywords:** Recurrent pregnancy loss; Recurrent miscarriage; Intralipid; Lipid emulsion therapy; Live birth rate; Successful pregnancy rate

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## Introduction

Recurrent pregnancy loss (RPL) is an important reproductive health problem which affects a clinically significant proportion of women and couples trying to conceive, and its burden is medical, emotional and psychological because repeated losses create fear, stress, and uncertainty about future pregnancy outcomes [1–3]. Some evidences define RPL as three or more pregnancy losses while others advised for clinical evaluation after two clinical pregnancy losses, and this variation affects reported prevalence and clinical management pathways [3–6].

The field agrees that RPL is a multifactorial condition associated with parental chromosomal abnormalities, uterine anomalies, antiphospholipid syndrome, endocrine and metabolic disorders, and other maternal or fetal factors [1,2,7]. This unexplained group is important because it is the area where empirical and immunological therapies are most often considered, when couples continue to experience losses despite normal findings on routine investigations and no correctable cause is identified [2,7,8].

Increasing attention recently directed toward the role of immune dysregulation in RPL, the idea that failure of maternal immune tolerance at the maternal–fetal interface contributes to implantation problems, early embryonic loss, or inability to maintain an established pregnancy [7,9,10]. Natural killer cells received major interest because uterine natural killer cells are abundant in the endometrium and decidua and play regulatory roles in implantation, trophoblast interaction, vascular remodeling, and early pregnancy maintenance [10–12].

In some women with recurrent miscarriage or RPL physicians observed abnormal numbers, altered subsets, increased cytotoxicity, or a more pro-inflammatory NK-cell profile, which suggest that NK-cell dysregulation can be involved in at least a subgroup of affected patients [7,12,13]. This

proposed relationship is controversial because not all studies agree, peripheral and uterine NK cells are not identical in function or phenotype, and current guideline-oriented reviews still do not support routine immune testing or broad immunotherapy use for women with RPL [4,9–11].

Corticosteroids, intravenous immunoglobulin, and intralipid have been explored as options in women with RPL, mainly patients have immune-mediated reproductive failure or abnormal NK-cell activity [7,8,13]. Intralipid contain soybean oil, glycerin, and egg phospholipids that was originally used in parenteral nutrition, and later attracted interest in reproductive medicine because of its immunomodulatory effect, including suppression of abnormal NK-cell activity and reduction of excessive inflammatory response that interfere with pregnancy maintenance [7,13,14]. The present systematic review was conducted to evaluate the original studies on pregnancy outcomes after the use of intralipid in women with RPL, with attention to successful pregnancy rate (SPR) and live birth rate (LBR), to clarify whether this therapy had benefit in this population [4,14].

## Methods

This systematic review was conducted to evaluate pregnancy outcomes after the use of intralipid in women with RPL. The review question was focused on whether intralipid therapy was associated with successful pregnancy outcomes, mainly SPR and LBR, in women with RPL or recurrent miscarriage (RM). The review was conducted using the principles of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

A literature search was carried out in electronic databases to identify relevant original studies. The databases searched included PubMed, Embase, Scopus, and the Cochrane Library. Additional checking of reference lists was also done when needed to identify additional missed relevant article. The search strategy used combinations of keywords and subject terms related to intralipid,

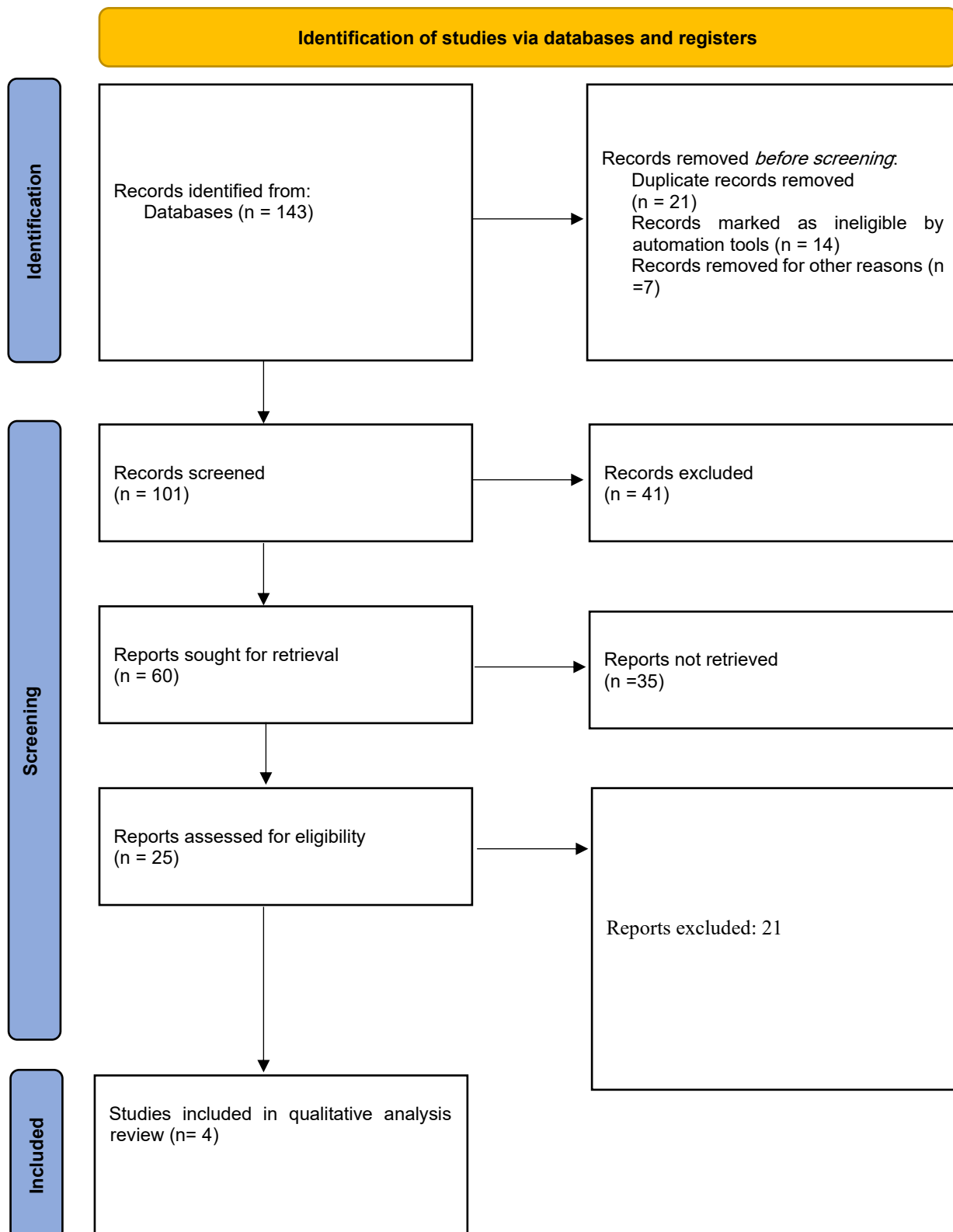
lipid emulsion, RPL, RM, recurrent spontaneous abortion, pregnancy outcome, successful pregnancy, and live birth.

Studies were considered eligible if they original research articles evaluated intralipid or lipid emulsion therapy in women with RPL, RM, or related reproductive failure populations and reported pregnancy-related outcomes. Studies that reported SPR, clinical pregnancy, ongoing pregnancy, miscarriage, or live birth were eligible for inclusion. Randomized trials, comparative studies, and cohort studies were considered. Studies that focused only on recurrent implantation failure without a relevant RPL population were excluded. We also exclude review articles, conference abstracts without enough data, editorials, and non-original articles. After the database search, duplicates were removed, titles and abstracts were screened first, and then full texts

of relevant studies were reviewed for final eligibility. Articles were excluded if they did not match the review topic, did not use intralipid as the intervention of interest, or did not report pregnancy outcome data.

Data were extracted from the included studies in a structured way, and the extracted items included author name, year of publication, country, study design, study population, sample size, comparison group, intralipid regimen, and main pregnancy outcomes. The main outcomes of interest in this review were SPR and LBR. Other reported outcomes were clinical pregnancy rate, ongoing pregnancy, implantation rate, and miscarriage. The findings were analyzed qualitatively rather than combined in a formal meta-analysis. This approach was chosen to allow direct presentation of the results from each study without forcing statistical pooling in the presence of important clinical heterogeneity.

Fig 1: PRISMA flow chart



## Result

Four studies were included in this review which published between 2015 and 2025 and conducted in China, the United States, France, and Japan. The designs were different in studies and included one prospective randomized clinical trial, one comparative original study, and two retrospective cohort studies. Only the study by Meng et al. [15] focused on a pure RPL population with unexplained RSA, while the other three studies included mixed populations of RPL/RM and recurrent implantation failure.

In a randomized trial by Meng et al., [15] 76 women in the intralipid group and 78 in the IVIG group completed follow-up. The SPR was 92.1% in the intralipid group and 88.2% in the IVIG group, with no statistically significant difference between the two groups ( $P = 0.415$ ). RSA after treatment was reported in 8 patients in the intralipid group and 13 in the IVIG group, while one ectopic pregnancy occurred in each group. Among those followed until delivery, live birth was reported in 39 of 40 pregnancies in the intralipid group and 48 of 49 pregnancies in the IVIG group.

The Japanese study by Yamaya et al. showed similar results between lipid emulsion and IVIG in the RPL subgroup. In RPL cases, LBRs including ongoing pregnancies were 61.0% in the lipid emulsion group and 67.7% in the IVIG group. After excluding

biochemical pregnancies and miscarriages related to abnormal chorionic chromosomes, the LBRs were 72.5% and 75.0%, respectively, with no significant difference. The French cohort by Plaçais et al., [16] showed a favorable result for intralipid in women with RM. Among 10 women with RM who received intralipid, 7 achieved live birth (70%). This was significantly higher than the control group, where 3 of 20 women achieved live birth (15%) with  $P = 0.02$ . In the recurrent implantation failure subgroup of the same study, 9 of 16 women achieved clinical pregnancy under intralipid, and 5 of these 9 pregnancies resulted in live birth.

The findings were less supportive in the study by Martini et al. which included patients with RPL or recurrent implantation failure and elevated peripheral NK cells. The intralipid cohort had 127 patients. Clinical pregnancy occurred in 65 of 127 patients (51%), and live birth occurred in 47 of 127 patients (37%). When these outcomes were compared with the historical cohort, neither the clinical pregnancy rate nor the LBR was significantly improved ( $P = 0.12$  and  $P = 0.80$ , respectively). The included studies showed mixed findings. Two studies indicate that intralipid associated with good pregnancy or live birth outcomes, mainly in RM cases, while two studies showed that intralipid had outcomes similar to IVIG or no clear benefit over comparison groups.

**Table 1. Characteristics of the included studies**

Study	Country and setting	Study design	Population	Sample size and comparison groups	Intralipid regimen	RPL specificity
Meng et al., 2015 [15]	China; miscarriage center at Sun Yat-Sen Memorial Hospital	Prospective randomized clinical trial	Unexplained RSA with $\geq 3$ miscarriages before 12 weeks and CD56+CD16+ >20%	192 randomized: intralipid 96 vs IVIG 96; 154 completed:	20% intralipid 250 mL on day 3 of menstrual cycle, then every 2 weeks before pregnancy and weekly after pregnancy until	Pure RPL/URSA population

Study	Country and setting	Study design	Population	Sample size and comparison groups	Intralipid regimen	RPL specificity
				intralipid 76 vs IVIG 78	12 weeks; comparator was IVIG 25 g	
Martini et al., 2018 [17]	USA; large reproductive endocrinology private practice, Chicago	Retrospective cohort study	Unexplained RPL or RIF with elevated peripheral NK cells; NK level considered elevated if >19%	Intralipid cohort 127; historical control 20	4 mL of 20% intralipid in 250 mL normal saline, generally 7–10 days before embryo transfer or insemination, repeated at about 6 and 10 weeks if pregnancy occurred	Mixed RPL/RIF population
Plaçais et al., 2020 [16]	France; three university hospitals in Paris	Retrospective cohort	Unexplained RM and/or recurrent implantation failure	26 intralipid-treated women total: RM 10, RIF 16; controls: RM 20, RIF 16	For non-IVF RM: infusion on day 8 of each cycle, then at 3, 5, and 9 weeks if ongoing pregnancy; IVF group received infusion on day 8 of embryo-transfer cycle, then at 3, 5, and 9 weeks of amenorrhea	Mixed RM/RIF population
Yamaya et al., 2025 [18]	Japan; Hyogo Medical University and Kameda IVF Clinic	Comparative study	Reproductive failure associated with NK abnormalities; included RPL and RIF. RPL defined as ≥2 miscarriages	Total 209 participants. Among RPL: LE 82 and IVIG 31. Among RIF: LE 67 and IVIG 29	LE was 50 g (20% in 250 mL) over 4 h. In IVF-ET patients, initial treatment was around ET; in RPL patients waiting for natural conception, treatment started soon after pregnancy confirmation; if pregnancy occurred, LE was repeated every 3 weeks	Mixed RPL/RIF population

**Table 2. Main findings and outcomes of the included studies**

Study	Main findings	Reported pregnancy outcomes
Meng et al., 2015 [15]	Intralipid and IVIG produced similar pregnancy success in unexplained RSA; the difference was not statistically significant.	SPR: 92.1% (70/76) in intralipid group vs 88.2% (67/76) in IVIG group, P = 0.415. During 2-year follow-up, 17 intralipid patients and 15 IVIG patients did not become pregnant; repeated spontaneous abortion occurred in 8 intralipid patients and 13 IVIG patients; there was 1 ectopic pregnancy in each group. Among those followed

Study	Main findings	Reported pregnancy outcomes
		until delivery, live birth was 39/40 in the intralipid group and 48/49 in the IVIG group.
Martini et al., 2018 [17]	Intralipid did not improve clinical pregnancy or LBRs compared with the historical control, and it was reported as not cost-effective.	In the intralipid cohort, outcomes were: 51 not pregnant, 10 biochemical pregnancies, 1 ectopic, 16 first-trimester losses, 2 second-trimester losses, and 47 live births. Clinical pregnancy rate was 65/127 (51%) vs 14/20 (70%) in the historical control, P = 0.12. LBR was 47/127 (37%) vs 8/20 (40%), P = 0.80. Intralipid increased cost by \$681 per live birth.
Plaçais et al., 2020 [16]	In the RM subgroup, intralipid was associated with a higher live birth frequency than the control group. In the RIF subgroup, pregnancy and live birth outcomes were numerically higher with intralipid but not clearly significant.	Among RM patients treated with intralipid, 7/10 (70%) achieved live birth, compared with 3/20 (15%) in controls. In the RIF subgroup, clinical pregnancy occurred in 9/16 (56%) under intralipid, and 5/9 (55%) of those clinical pregnancies resulted in live birth; in controls, clinical pregnancy occurred in 6/16 (38%), with 2/6 (33%) resulting in live birth.
Yamaya et al., 2025 [18]	Lipid emulsion and IVIG showed comparable effects overall. In the RPL subgroup, LBRs were similar between LE and IVIG. In the RIF subgroup, implantation rates were also similar.	For RPL, LBRs including ongoing pregnancies were 61.0% in the LE group and 67.7% in the IVIG group. When biochemical pregnancies and chromosomal-abnormality miscarriages were excluded, LBRs were 72.5% in the LE group and 75.0% in the IVIG group, with no significant difference. In RIF, implantation rates were 47.8% for LE and 48.3% for IVIG. When treatment was started before embryo transfer, clinical pregnancy rates were higher than when started on or after ET.

## Discussion

This review showed that the effect of intralipid in women with RPL is still not clearly proven. Meng et al., give strong RPL-specific evidence where intralipid achieved a successful pregnancy rate comparable to IVIG. The French cohort indicate a benefit in women with RM, and the sample was very small, while Martini et al. did not show improvement in live birth rate in a mixed RPL/RIF population with elevated peripheral NK cells. Yamaya et al. found that lipid emulsion and IVIG had comparable results in the RPL subgroup. Our findings indicate that intralipid help some selected women [15–18].

Canella et al. found that intralipid has been explored mainly in women with abnormal NK-cell activity and reported positive and negative studies, including the neutral findings of Martini et al. and the comparable intralipid-versus-IVIG findings of Meng et al. Kumar et al. also reported improved

implantation, pregnancy, and live birth outcomes in pooled analyses, and they still stated that intralipid should not be considered routine treatment and it can be suitable only in selected cases with immunological risk factors. A similar finding appears in the newer review by Garmendia et al., which described encouraging results in some studies and show that effectiveness depends on a well-defined subgroup rather than broad use in all women with RPL or RIF [7,13,14].

One important explanation for this is the biological uncertainty in NK cells. The literature explains that abnormal immune activation, altered NK-cell number, phenotype, or cytotoxicity, contribute to reproductive failure in some patients, and Fukui et al., Sfakianoudis et al., [10] and Vomstein et al. [9] found that the relationship between NK-cell abnormalities and pregnancy loss is controversial, and peripheral blood NK cells are not equivalent to uterine NK cells. This matters because several intralipid studies selected women using immune

markers, but the markers, thresholds, and testing methods were not uniform [9–11].

Most included studies did not evaluate pure RPL populations. Three of the four included studies mixed RPL or RM with recurrent implantation failure, and these conditions overlap. Treatment regimens, timing of infusion, comparison groups, and reported outcomes differed between studies. Carp also noted that immunotherapy in unselected RM populations fail to show benefit because spontaneous prognosis is good in many women, while treatment effects is easier to detect in poor-prognosis or immune-selected cases.

## Conclusion

Two included studies reported positive pregnancy or live birth outcomes, while the rest showed results similar to intravenous immunoglobulin or no clear benefit over comparison groups. Interpretation is restricted by small sample sizes, mixed RPL and recurrent implantation failure populations. Intralipid until now cannot be considered an established therapy for all women with RPL. Larger, well-designed studies focused on clearly defined RPL populations are still needed to clarify its true clinical value.

## References

1. Ford HB, Schust DJ. Recurrent Pregnancy Loss: Etiology, Diagnosis, and Therapy. vol. 2. 2009.
2. El Hachem H, Crepaux V, May-Panloup P, Descamps P, Legendre G, Bouet PE. Recurrent pregnancy loss: Current perspectives. *Int J Womens Health* 2017;9:331–45. <https://doi.org/10.2147/IJWH.S100817>.

3. Turesheva A, Aimagambetova G, Ukybassova T, Marat A, Kanabekova P, Kaldygulova L, et al. Recurrent Pregnancy Loss Etiology, Risk Factors, Diagnosis, and Management. *Fresh Look into a Full Box. J Clin Med* 2023;12. <https://doi.org/10.3390/jcm12124074>.
4. Evaluation and treatment of recurrent pregnancy loss: A committee opinion. *Fertil Steril* 2012;98:1103–11. <https://doi.org/10.1016/j.fertnstert.2012.06.048>.
5. Atik RB, Christiansen OB, Elson J, Kolte AM, Lewis S, Middeldorp S, et al. ESHRE guideline: recurrent pregnancy loss: an update in 2022. *Hum Reprod Open* 2023;2023. <https://doi.org/10.1093/hropen/hoad002>.
6. Shahine L, Lathi R. Recurrent pregnancy loss: Evaluation and treatment. *Obstet Gynecol Clin North Am* 2015;42:117–34. <https://doi.org/10.1016/j.ogc.2014.10.002>.
7. Garmendia JV, De Sanctis CV, Hajdúch M, De Sanctis JB. Exploring the Immunological Aspects and Treatments of Recurrent Pregnancy Loss and Recurrent Implantation Failure. *Int J Mol Sci* 2025;26. <https://doi.org/10.3390/ijms26031295>.
8. Carp H. Immunotherapy for recurrent pregnancy loss. *Best Pract Res Clin Obstet Gynaecol* 2019;60:77–86. <https://doi.org/10.1016/j.bpobgyn.2019.07.005>.
9. Vomstein K, Feil K, Strobel L, Aulitzky A, Hofer-Tollinger S, Kuon RJ, et al. Immunological risk factors in recurrent pregnancy loss: Guidelines versus current state of the art. *J Clin Med* 2021;10:1–21. <https://doi.org/10.3390/jcm10040869>.
10. Sfakianoudis K, Rapani A, Grigoriadis S, Pantou A, Maziotis E, Kokkini G, et al. The role of uterine natural killer cells on recurrent miscarriage and recurrent implantation failure: From pathophysiology

- to treatment. *Biomedicines* 2021;9. <https://doi.org/10.3390/biomedicines9101425>.
11. Fukui A, Kamoi M, Funamizu A, Fuchinoue K, Chiba H, Yokota M, et al. NK cell abnormality and its treatment in women with reproductive failures such as recurrent pregnancy loss, implantation failures, preeclampsia, and pelvic endometriosis. *Reprod Med Biol* 2015;14:151–7. <https://doi.org/10.1007/s12522-015-0207-7>.
  12. Guerrero B, Hassouneh F, Delgado E, Casado JG, Tarazona R. Natural killer cells in recurrent miscarriage: An overview. *J Reprod Immunol* 2020;142. <https://doi.org/10.1016/j.jri.2020.103209>.
  13. Canella PRBC, Barini R, Carvalho P de O, Razolli DS. Lipid emulsion therapy in women with recurrent pregnancy loss and repeated implantation failure: The role of abnormal natural killer cell activity. *J Cell Mol Med* 2021;25:2290–6. <https://doi.org/10.1111/jcmm.16257>.
  14. Kumar P, Marron K, Harrity C. Intralipid therapy and adverse reproductive outcome: is there any evidence? *Reproduction and Fertility* 2021;2:173–86. <https://doi.org/10.1530/RAF-20-0052>.
  15. Meng L, Lin J, Chen L, Wang Z, Liu M, Liu Y, et al. Effectiveness and potential mechanisms of intralipid in treating unexplained recurrent spontaneous abortion. *Arch Gynecol Obstet* 2016;294:29–39. <https://doi.org/10.1007/s00404-015-3922-8>.
  16. Plaçais L, Kolanska K, Kraiem Y Ben, Cohen J, Suner L, Bornes M, et al. Intralipid therapy for unexplained recurrent miscarriage and implantation failure: Case-series and literature review. *European Journal of Obstetrics and Gynecology and Reproductive Biology* 2020;252:100–4. <https://doi.org/10.1016/j.ejogrb.2020.06.017>.
  17. Martini AE, Jasulaitis S, Fogg LF, Uhler ML, Hirshfeld Cytron JE. Evaluating the utility of intralipid infusion to improve live birth rates in patients with recurrent pregnancy loss or recurrent implantation failure. *J Hum Reprod Sci* 2018;11:261–8. [https://doi.org/10.4103/jhrs.JHRS\\_28\\_18](https://doi.org/10.4103/jhrs.JHRS_28_18).
  18. Yamaya A, Fukui A, Kawai K, Yano M, Honda H, Nakagawa K, et al. A Comparative Study of Intravenous Immunoglobulin and Lipid Emulsion in Patients With Reproductive Failures Associated With NK Cell Abnormalities. *Reprod Med Biol* 2025;24. <https://doi.org/10.1002/rmb2.12662>.