



Rationale for replacing IVIG with Intralipid (IL) for immunological pregnancy loss

Recurrent Pregnancy Loss

The reason that an embryo may not implant successfully is either because there is something intrinsically wrong with the embryo itself or there may be something wrong with the uterine environment either a physical problem or a problem at the molecular level that causes a normal embryo not to implant.

1. Problems with the embryo

The commonest problem related to the embryo itself is an abnormality of chromosomal number or aneuploidy. 95% of chromosomally abnormal embryos are abnormal as a result of a problem with the egg. The reason for this is that the egg does most of the work in accepting the DNA from sperm and then facilitating mixing of genes resulting in a new unique individual. Based on the age of the egg, the proportions of embryos that are chromosomally normal ranges from approximately 50% for eggs under age 30, to as low as 5% for eggs at approximately age 45.

In addition, each embryo that is chromosomally normal on testing, will have on average a 30% chance of going all the way to birth.

2. Problems with the uterine environment

Problems with the uterus and either the structural, hormonal or immunological

- structural problems within the uterus may inhibit implantation and these include endometrial polyps, submucous fibroids or intracavity adhesions. All of

these factors act like an intra uterine contraceptive device interfering with implantation

- the hormones estrogen and progesterone are required for the optimum preparation of the lining of the uterus, but during IVF, these hormones are very carefully controlled and supplied so it is very unusual for there to be an hormonal reason for recurrent pregnancy loss within IVF.
- Immunological problems have been identified as causes of recurrent failed implantation or pregnancy loss. The uterus needs to tolerate the implanting embryo which is always genetically different from the uterus itself and there is continuous communication and interaction between the embryo and the maternal system. These communications occur through the mediation of proteins known as cytokines which are secreted by the cells within the uterine lining. If the immune cells do not send out signals through secretion of the correct cytokines to the embryo or if these cells don't respond to signals from the embryo, there may be a problem with adhesion and implantation.

Treating immunological causes of recurrent failed implantation

Immunological problems treated by appropriate immunotherapy and treatments have been shown to be effective for the treatment of recurrent loss.

- Intravenous gamma globulin (IVIG)

IVIG has been shown through prospective randomized studies to be effective in the treatment of implantation failure. One study in women undergoing IVF, who produced good quality embryos in previous cycles and still failed, had an improvement in implantation rate per embryo from 7% in the placebo group to 18% with IVIG. Another study, also randomized showed an increase in implantation rate per embryo from 9% to 40%.

IVIg needs to be infused before the embryo transfer with the dose ranging from 20 to 30 grams. This does then needs to be repeated after the first positive pregnancy test and in some instances may be necessary every 3 to 4 weeks until the end of the first trimester.

The two problems with IVIg are cost ranging from \$2,000 - \$3,000 per infusion and the fact that it is a blood product obtained from pooled donor blood.

- Intralipid (IL)

Evidence from both animal and human studies suggests that Intralipid, administered intravenously, may enhance implantation and maintenance of pregnancy when the patient has had an abnormal NK cell level or function. Intralipid is a 20% intravenous fat emulsion which is usually used as a source of fat and calories for patients requiring parenteral nutrition. Intralipid consists of soybean oil as well as egg yolk phospholipids, glycerine and water.

In vitro investigations have revealed the ability of Intralipid to suppress the natural killer (NK) cytotoxicity. Fifty patients with abnormal natural killer levels received Intralipid infusions and 78% showed suppression of the natural killer activity to the normal range one week after infusion, 22% showed suppression but not yet into the normal range in these patients received a second infusion 2 to 3 weeks after the first and all but one of these 11 patients have normal natural killer levels the following week. Four patients required a third infusion and after the first week, all showed normal natural killer activity. Forty seven of these 50 patients continue to have normalization of their NK levels for between six and nine weeks, two patients remained normal lives five weeks and in one patient the effect lasted for four weeks.

Conclusion of the study was that Intralipid was effective in suppressing in vivo abnormal NK cell function, suggesting that Intralipid can be used successfully as a therapeutic option to

modulate abnormal NK activity in women with reproductive failure.

Intralipid has also been shown to be effective in enhancing live birth rates among women with elevated NK cell cytotoxicity and a history of recurrent implantation failure and pregnancy loss. Of 64 women under age 40 who were experiencing recurrent implantation failure with elevated NK cell activity, the pregnancy rate for IVF cycle was 42%. Ten of 11 women experiencing recurrent pregnancy loss had a successful pregnancy.

The advantages of Intralipid include the fact that it has been used for intravenous feeding for more than 30 years with very few side effects, and infusion costs between \$450 - \$700 and it is not a blood product.

Based on this in vitro as well as in vivo confirmation of the effective normalization of natural killer activity by Intralipid and also based on the significant cost saving, we will be recommending offering Intralipid as an alternative to IVIG, at a dose of 100 mL of 20% product diluted in 250 or 500 mL of normal saline infused over 1 to 2 hours.

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Duration of Intralipid's Suppressive Effect on NK Cell's Functional Activity

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Full Abstract

BACKGROUND:

In vitro investigations have revealed the ability of intralipids to suppress natural killer (NK) cytotoxicity. Evidence from both animal and human studies suggests that intralipid administered intravenously may enhance implantation and maintenance of pregnancy when the patient has an abnormal NK cell level or function.

PROBLEM:

The aim of this study was to establish the duration and efficacy of Intralipids suppressive effect on NK cell functional activity.

METHOD OF STUDY:

Fifty patients with abnormal NK activity results (NKa) received intralipid 20% i.v. (9 mg/mL total blood volume -corresponds to 2 mL of intralipid 20% diluted in 250 mL saline; or 18 mg/mL - corresponds to 4 mL of intralipid 20% diluted in 250 mL saline) infusions and their Nka were tested periodically. The determination of NK cell function was performed by flow cytometry using K562 cells as targets.

RESULTS:

Fifty women with abnormal Nka-testing received intralipid infusions. 39 (78%) showed Nka suppression within the normal range the first week after infusion, 11 (22%), showed suppression, but still above the normal threshold. They received second infusion 2-3 weeks later. In 10, the Nka activity was normalized the following week. Four patients had three intralipid infusions in 2-week periods in between and after the third infusion, and all showed Nka normal activity. In 47 patients the suppressive effect of the Intralipid after the normalization of Nka lasted between 6 and 9 weeks, in two patients this benefit lasted 5 weeks, and in one patient the effect was 4 weeks.

CONCLUSION:

Intralipid is effective in suppressing in vivo abnormal NK-cell functional activity. The results suggest that Intralipid can be used successfully as a therapeutic option to modulate abnormal NK activity in women with reproductive failure.

Pregnancy Outcome After Intralipid Infusion Among Women Experiencing Recurrent Pregnancy Loss

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Article Outline

Objective: We have previously reported that Intralipid suppresses natural killer (NK) cell cytotoxicity both in vitro and in vivo. The current study was undertaken to determine whether Intralipid treatment is associated with increased live birth rates.

Methods: 79 patients with elevated NK-cell activity and a history of recurrent pre- or post-implantation pregnancy loss were treated with IV Intralipid, 2-4 mL of 20% solution. Of the 79 women, 68 had a diagnosis of recurrent implantation failure and 11 experienced recurrent pregnancy loss. Recurrent implantation failure was defined in this study as a cumulative total of 8 cleaved embryos transferred or 4 blastocysts transferred with human chorionic gonadotropin (hCG) serum concentrations <5 mIU/mL 14 days after embryo transfer. Recurrent pregnancy loss consisted of at least 2 or more consecutive spontaneous abortions.

Results: Among the 68 women with a history of recurrent implantation failure, 27 (40%) became pregnant after in vitro fertilization and embryo transfer with intralipid treatment. Four of the 68 patients were over the age of 40 years and none of these became pregnant. Of 64 women under the age of 40 years who were experiencing recurrent implantation failure with elevated NK-cell activity, the pregnancy rate per cycle was 42%. Ten of the 11 women experiencing recurrent pregnancy loss (91%) had a successful pregnancy.

Conclusions: Intralipid is effective in enhancing live birth rates among women with elevated NK-cell cytotoxicity and a history of recurrent implantation failure and recurrent pregnancy loss.

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