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Combined Hysteroscopy and Uterine intralipid injection before fertilization in women with secondary infertility or recurrent miscarriage ?

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Abstract
Although in vitro fertilization (IVF) has come a long way, the success rate of IVF is still less than 40%. Furthermore, approximately 10% of women who receive IVF with intracytoplasmic sperm injection experience repeated implantation failure (RIF).
Intralipid, which refers to a lipid emulsion comprising soybean oil, is an example of immunotherapy.
Intralipids have been proposed to effectively reduce the enhanced NK activation and production of cytokines. On the contrary, more recent data sourced by a double-blind randomized study indicated no increase in clinical pregnancy rates in patients with RM (Recurrent Miscarriage) who were subjected to intralipid therapy.
The current Intralipid treatment is done by vein infusion. It is suggested to use it by Combined Hysteroscopy and Uterine Intralipid Injection (UII) before fertilization in women with secondary infertility or recurrent miscarriage.
Key Words: *Hysteroscopy, Fertilization, Secondary Infertility, Recurrent Miscarriage, Intralipid, Uterine intralipid injection (UII)*

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I. Intralipids

Infusion of intralipids is used for parenteral nutrition and is a fatty emulsion containing soya bean oil, egg yolk, phospholipids, glycerine, and water. It is also used in emergencies to treat systemic toxicity induced by local anaesthetics. Increasingly it is being used for women with failed IVF attempts and abnormal NK cell activity (1).

A double-blind randomised control trial of 296 women with secondary infertility, recurrent miscarriage, and elevated pbNK (peripheral blood natural kill) cells showed no increase in CPR (clinical pregnancy rate) in the group of women who were treated with intralipid infusion (2). Another prospective trial in a very selected cohort of patients had to be terminated early as the results favoured the group which did not receive intralipids therapy (3).

A retrospective study of women who received intralipids infusion due to elevated pbNK cells failed to identify any benefit, and a cost-effectiveness analysis deemed that the treatment was not cost-effective (4).

Therefore, despite the relatively low cost of the intervention and the good safety profile, the evidence for its use is lacking, and prospective patients should be made aware of this.

Endometrial injury

Although injury to the endometrium prior to embryo transfer is not strictly speaking an adjuvant to IVF, we have included it in our review as it is an intervention which has gained a lot of interest over the recent years. The theory behind it was that it may positively affect implantation by inducing the release of factors such as cytokines, interleukins, and growth factors in the endometrium. The most common and easily available procedure was via the use of a pipelle known as 'endometrial scratching'. After many published studies a RCT (randomized controlled trial) was conclusive in showing that endometrial scratching does not confer any benefit to reproductive outcomes, including LBR (live birth rates) (5). An alternative to endometrial scratching which is also commonly practiced by many, is the routine use of outpatient hysteroscopy prior to starting an IVF cycle, which may diagnose subtle pathology but will also act similarly as endometrial injury. A well conducted, adequately powered, multicenter RCT failed to demonstrate any improvement in LBR by the use of the intervention for women with recurrent IVF failure (6).

Intralipid® may represent a new hope for patients with reproductive failures

Continuous failures to achieve a pregnancy despite effective embryo transfers is extremely distressing for couples. In consequence, many adjuvant therapies to IVF have been proposed to achieve an "ideal" immune environment. We here focus on Intralipid® therapy (IL) reported to have immunosuppressive properties on NK cells.

94 patients exhibited an immune profile of endometrial over-immune activation and an history of repeated implantation failures despite multiple embryos transfers (RIF). They received a slow perfusion of Intralipid®. We here report the live birth rate following the procedure at the next embryo transfer. To get new insight on its mechanism of action, a second immune profiling had been performed under Intralipid® before the embryo transfer.

The live birth rate of the RIF (Recurrent implantation failure) cohort treated with Intralipid® reached 54% (51/94) at the next embryo transfer. In patients successfully pregnant under Intralipid® who benefitted of a test of sensibility before the embryo transfer, we observed a significant decrease of the three biomarkers used to diagnose the over-immune endometrial activation (CD56 cells; IL-18/TWEAK, IL-14/FN-14).

Double blind placebo versus Intralipid® studies should be conducted. Intralipid® may be an option to explore in RIF patients who exhibit an over-immune activation of uNK cells (7).

The role of abnormal natural killer cell activity

Recurrent pregnancy loss (RPL) was first defined by the Royal College of Obstetricians and Gynecologists as three or more consecutive miscarriages before the twentieth week of pregnancy, excluding ectopic, molar and biochemical pregnancies. More recently, RPL was redefined as two or more spontaneous losses of clinical pregnancies before completing 22 weeks of gestation, affecting around 1%-2% of women (8,9).

Some cases of RPL can benefit from assisted reproduction techniques, among them in vitro fertilization (IVF), an approach where fertilization is performed outside of the body and then the embryo is transferred to the uterus; even so, the in vitro transfer can be unsuccessful. Repeated implantation failure (RIF) is a failure to achieve a clinical pregnancy in women under 40 years old after three or more consecutive transfer cycles of at least four good-quality embryos (10).

Although the RIF aetiology is not completely established, variables such as maternal age, elevated BMI, immunological factors, sperm quality, uterine alterations and psychological conditions should be considered to direct treatment approaches. The implantation rate in women under IVF can vary from 25% to 40% depending on the embryo transfer protocol, and about 10% of patients under IVF are affected with RIF (10, 11). Studies conducted in recent decade have been suggesting that immunological abnormalities such as self-recognition of an embryo or foetus could contribute to the implantation failure and thus explain the occurrence of RPL. The abnormal inflammatory response in RPL and RIF includes increased expression of pro-inflammatory markers, human leucocyte antigens and circulating natural killer (NK) cells (12). Given that, several randomized clinical trials have assessed immune modulators as an approach to address the RPL and/or RIF conditions (13,14).

Other recent studies discuss the effectiveness in RPL treatment of some immunomodulatory agents such as paternal leucocyte immunization (PLI), intravenous immunoglobulin (IVIg), filgrastim and intralipid (15,16,17,18). Among these, the lipid emulsion therapy (LET) has emerged as a possible new intervention therapy for women stricken by RPL and RIF. The cellular mechanisms by which intralipid acts are not completely understood, but some authors believe that the lipid emulsion restores the NK cells' abnormal activity to normal levels thereby improving embryo implantation (13, 18, 19).

Intrauterine injection of human chorionic gonadotropin (hCG) at embryo transfer (ET)

Intrauterine injection of human chorionic gonadotropin (hCG) at embryo transfer (ET) has been shown to improve the outcome of assisted reproductive techniques. The aim of this study was to confirm previous findings.

In this randomized controlled trial, 483 infertile women who were candidates for in vitro fertilization/intracytoplasmic sperm injection (IVF/ICSI) for the first time were randomly assigned to receive an intrauterine injection of 500 IU hCG or placebo (tissue culture media) before ET. The main outcome measures were implantation and clinical pregnancy rates.

Both the hCG-treated group (n = 240) and control group (n = 243) were similar at baseline in terms of demographic and obstetrical characteristics. There were significant differences between the two groups regarding the implantation rate (23.6 vs. 12.2%, $p < 0.001$), pregnancy rate (54.6 vs. 35.8%, $p < 0.001$), clinical pregnancy rate (50 vs. 32.1%, $p < 0.001$), ongoing pregnancy rate (15.3 vs. 9.2%, $p < 0.001$) and live delivery rate (14.3 vs. 8.4%, $p < 0.001$). The rate of fertilization and abortion rates were not statistically different.

Intrauterine injection of hCG before ET improves implantation and pregnancy rates and may be considered an adjuvant in IVF/ICSI (20).

Human chorionic gonadotropin (hCG)

Human chorionic gonadotropin (hCG) is a hormone for the maternal recognition of pregnancy produced by trophoblast cells that are surrounding a growing embryo (syncytiotrophoblast initially), which eventually forms the placenta after implantation.[21,22]. The presence of hCG is detected in some pregnancy tests (HCG pregnancy strip tests). Some cancerous tumors produce this hormone; therefore, elevated levels measured when the patient is not pregnant may lead to a cancer diagnosis and, if high enough, paraneoplastic syndromes, however, it is not known whether this production is a contributing cause, or an effect of carcinogenesis. The pituitary analog of hCG, known as luteinizing hormone (LH), is produced in the pituitary gland of males and females of all ages.(21,23).

Various endogenous forms of hCG exist. The measurement of these diverse forms is used in the diagnosis of pregnancy and a variety of disease states. Preparations of hCG from various sources have also been used therapeutically, by both medicine and quackery. As of December 6, 2011, the United States Food and Drug Administration has prohibited the sale of "homeopathic" and over-the-counter hCG diet products and declared them fraudulent and illegal.[24,25,26].

Efficacy of intralipid administration to improve *in vitro* fertilization outcomes

Although *in vitro* fertilization (IVF) has come a long way, the success rate of IVF is still less than 40% [27]. Furthermore, approximately 10% of women who receive IVF with intracytoplasmic sperm injection experience repeated implantation failure (RIF) [28]. RIF is generally defined as three cycles of IVF that are unsuccessful even though 1–2 good-quality embryos are transferred in each cycle [29]. Impaired endometrial receptivity has been suggested as a major cause of RIF, and immune abnormalities reduce endometrial receptivity and consequently prevent implantation. Immune abnormalities have also been reported as the cause of recurrent spontaneous abortion (RSA) [30]. Therefore, many immunotherapies have been explored to improve endometrial receptivity and increase the pregnancy rate. Immunotherapy methods suggested for immune dysfunction include leukocyte immunization, intravenous immunoglobulin (IVIG), low-molecular-weight heparin, and intralipid [31,32].

Intralipid, which refers to a lipid emulsion comprising soybean oil, is an example of immunotherapy. Because intralipid is a source of fat, it has traditionally been used as a nutritional supplement for patients unable to eat orally. In addition to its nutritional role as an energy source, intralipid has biological functions, including immune function [33]. Although the immunological mechanism of intralipid is not fully understood, several studies have reported that its active component, soybean oil, inhibited the cytotoxic activity of natural killer (NK) cells [33,34]. Increased NK cell cytotoxicity has been associated with RSA and RIF [35,36]. In this context, many studies have explored the use of intralipid for women with/without RIF or RSA undergoing IVF [37-42].

The Role of Uterine Natural Killer Cells on Recurrent Miscarriage and Recurrent Implantation Failure

Natural killer (NK) cells are large granular lymphocytes and have been described as an essential factor of the innate immune system [43]. The cytotoxic ability of NK cells depends on balancing activating and inhibitory signals received from surface receptors [44]. A special category of NK cells localized in uterus are described as uterine natural killer (uNK) cells. During the early pregnancy period, uterine NK (uNK) cells are the largest leukocyte population in the endometrium accounting for over 70% of total endometrial leukocytes [45]. uNK cells significantly differ from the peripheral bloodstream NK cells, since their gene expression program is associated with increased production of cytokines and a relatively low cytotoxic activity. In contrast to peripheral NK cells, uNK cells present a unique pattern of surface markers and are characterized as $CD45^{+}CD56^{bright}CD16^{+}CD9^{+}$ cells [46]. Data provided following a comprehensive transcriptomic analysis employing single-cell RNA-sequencing (scRNA-seq) in tissue samples collected from first-trimester decidua revealed that there are at least three different uNK subpopulations, expressing different patterns of surface markers [47]. This, in turn, leads to the conclusion that these distinct uNK cell subsets exhibit diverse functions and roles [46]. Irrespective of their complicated nature, it is well-established that uNK cells present with increased numbers both in the luteal phase endometrium as well as in early pregnancy decidua [48]. Great focus has been paid to the role of uNK cells in the complex phenomenon of embryo implantation. Contrary to their previously suspected “hostile” characteristics, uNK cells appear to be essential regulators towards achieving successful implantation and pregnancy [49,50]. During pregnancy, uNK cells are involved in numerous crucial physiological events, such as remodeling of the placental vasculature, regulating invading trophoblast cells, and providing immune tolerance.

Intralipid Therapy

On the same note of immune modulating therapies, several studies have suggested the potential effect of intralipids in modulating the cytotoxicity of NK cells along with the secretion of pro-inflammatory cytokines [51,52,53]. Intralipid therapy is a 20% intravenous fat emulsion, which has been introduced in the medical practice for parenteral nutrition [54]. As a result, the implementation of intralipid therapy in order to mitigate the detrimental effects of elevated uNK cell count has been proposed in the literature. The molecular mechanism that enables intralipids to suppress NK function is elusive; however, an extrapolation on the already established knowledge on fatty acids may be of significance. Intralipid molecules act as ligands for the G-protein-coupled receptor that results in activating the cAMP signaling pathway that is associated with the NFkB pathway. The NFkB pathway ultimately modulates the transcription of the DNA and controls essential immune responses [53]. Several studies have suggested that intralipid therapy may be employed in cases of reproductive failure. Not only is the abnormal activity of NK cells modulated, but live birth rates appear enhanced following this therapeutic protocol [51,55]. Intralipids have been proposed to effectively reduce the enhanced NK activation and production of cytokines [51,55]. On the contrary, more recent data sourced by a double-blind randomized study indicated no increase in clinical pregnancy rates in patients with RM who were subjected to intralipid therapy [56]. No improvement in live birth rates in patients with RIF following intralipid therapy has been reported by Martini et al., in accordance with numerous studies that showcase no clinically significant impact of this therapeutic approach [57,58,59]. The lack of sufficient evidence to allow for safe conclusions to be drawn on the efficiency of intralipid therapy in women undergoing repeated implantation failures is clear. Large-scale studies are required to solve this conundrum prior to recommending it for routine use [57]. Thus far, recommendations that advise against routinely offering intralipid therapy for the treatment of RIF or RM have been voiced. The financial cost of intralipid administration outweighs their beneficial effect while failing to substantially enhance the live birth outcome [59]. Intralipids' immunosuppressive properties should be further evaluated, since the research concerning their implementation in reproductive disorders has been limited. Safety concerns have been raised, and as suggested in several medical conditions, they include thrombophlebitis, dyspnea, nausea, hyperlipemia, and allergic reactions. Nonetheless, no side effects have been reported in cases of young women with reproductive failure [53]. Intralipids are considered a safe immunomodulatory agent with no reported adverse effects [56]. Reduced risk of teratogenesis and congenital abnormalities has been identified [60]. Large randomized controlled trials to determine the benefit of intralipids in the treatment of recurrent implantation failure or miscarriage are yet to be conducted [60].

II. Conclusion

Intralipid, which refers to a lipid emulsion comprising soybean oil, is an example of immunotherapy.

The current Intralipid treatment is done by vein infusion. It is suggested to use it by Combined Hysteroscopy and Uterine Intralipid Injection (UII) before fertilization in women with secondary infertility or recurrent miscarriage.

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