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Intralipid® may represent a new hope for patients with reproductive failures and simultaneously an over-immune endometrial activation

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ABSTRACT

Problem: 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.

Method of study: 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.

Results: The live birth rate of the RIF 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).

Conclusions: 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.

1. Introduction

With up to one in six couples affected by infertility, in vitro fertilization (IVF) become often the best option to overcome various barriers to conception. In Europe, 500 000 IVF attempts are performed each year with a 10% yearly increase. IVF protocols include ovarian stimulation, oocyte collection and fertilization, with the final stage in the process as embryo transfer. Despite a well- mastered process, 70–80% of transferred embryo still failed to implant. Multiple factors may contribute to this failure, but the majority of the early pregnancy loss and implantation failure cases are attributed to a poor oocyte quality conjugated with a poor uterine receptivity (Lessey, 1998; Coughlan et al., 2014).

Repeated and unexplained embryo implantation failures (RIF) after IVF/ICSI is extremely distressing for couples and represent a significant challenge in routine. Couples need to understand the reasons of failures and claim for an active management based on a true understanding, especially in case of multiple transfers of so- said "good quality embryos". In consequence, many adjuvant therapies to IVF with a wide variety of different mechanisms of action have been proposed to achieve an "ideal" immune environment (Shirlow et al., 2017). In this study, we will exclusively focus on Intralipid® therapy.

The endometrium is remodeled throughout the menstrual cycle and exhibits only a short period of receptivity in the mid luteal phase, known as the "implantation window", which is crucial for both implantation and gestation (Gellersen et al., 2007). Within the endometrial environment during this stage, known as 'the period of uterine receptivity', a very peculiar influx of immune cells occurs and a

Abbreviations: RIF, repeated embryo implantation failure; uNKcells, uterine natural killer cells

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nearly complete switch of local immunity from the adaptive (Th1) to the innate (Th2) type profile is observed (Lee et al., 2011). This switch is crucial for a successful implantation. During this period, 65–70% of the immune cells in the endometrium are uterine natural killer (uNK) cells that belong to the innate immunity compartment. Macrophages and dendritic cells as member of innate immunity are also detected, together with adaptive immune T cells, such as T regulatory cells (Tregs)(Loke et al., 1995; Hanna et al., 2006; Liu et al., 2017).

Human implantation may be simply described as a three-step process that starts with apposition of a competent blastocyst followed by the adhesion to the endometrial epithelium (attachment). The third step is the extensive invasion of the trophoblast cells covering the blastocyst in the receptive endometrium. Embryo attachment requires an active local endometrial reactivity on the maternal side. The adhesion step should be immediately followed by an anti-inflammatory reaction to enable the induction of the mechanisms of local immune tolerance required for effective invasion. Early on, the ideal immune environment during the implantation window was thought to contain mainly Th-2 (compared with Th-1) cytokines. Such environment of cytokines would selectively allow the development of local mechanisms that promote immunotrophism and angiogenesis at the same time that they down-regulate inflammation and cytotoxic pathways (Wegmann et al., 1993). Over time, the concept of pregnancy as a Th2 phenomenon has evolved. Both the absence and a large excess of Th1 cytokines are thought to be deleterious for implantation and placentation, as is the absence of Th2 cytokines (Chaouat, 2003, 2007). This transient immune switch with an adequate activation of uNK but also T regulatory cells and dendritic cells, appears fundamental in enabling the establishment of a local maternal tolerance and the survival of the fetus (Chaouat et al., 2010).

Corticoids are often the first line of immunotherapy prescribed in the painful context of RIF for their potent and broad-spectrum anti-inflammatory and immune-suppressive properties (Franchimont, 2004; Rhen and Cidlowski, 2005). In theory, the objective of such prescription is to prevent an engagement of the uterus into a non-receptive state or early post implantation termination via a rejection like process. However, we previously reported that some patients are resistant to corticoids with a paradoxical degradation of the endometrial immune parameters in 29% of the patients whom we tested even if we documented a local over-immune activation (Lédée et al., 2018). As an alternative option, intravenous infusion of Intralipid® have been proposed and reported to be effective in some context of local over-immune activation.

Intralipid® is a fat emulsion containing soy bean oil, glycerin and egg phospholipids commonly used as a component of parenteral nutrition in patients unable to tolerate an oral diet. Whilst the exact mechanism in which immune modulation is achieved by Intralipid® remains unclear, its active ingredient, soya oil, is reportedly capable of inhibiting pro-inflammatory mediators, specifically Th1 cells (Granato et al., 2000). Some authors suggested that supplementation of fatty acids with Intralipid® has a positive effect on surgical patient outcome by lowering inflammation and modulating their immune response (Liang et al., 2008). Roussev and al reported in the context of reproductive failures that Intralipid® has immunosuppressive properties on circulating NK cells (Roussev et al., 2007, 2008). Roussev and al postulated that fatty acids within the emulsion serve as ligands to activate peroxisome proliferator-activated receptors expressed by the NK cells. Activation of such nuclear receptors would decrease NK cytotoxic activity to enhance implantation. Meng reported a decrease of the circulating NK recruitment and related cytotoxicity under Intralipid® (Meng et al., 2016). Shreeve and Sadek, however, stated that large-scale confirmatory studies are necessary to prove the efficacy of diluted Intralipid® infusion before any recommendation for its use in routine (Shreeve et al. 2012). Indeed, the underlying premise that high levels of NK cells in peripheral blood are of clinical significance in repeated implantation failures continues to be debated. Circulating NK cells were indeed shown to be different in origin, function and phenotype from uterine decidual NK cells (Manaster and Mandelboim, 2008; Melsen et al., 2016; Feyaerts et al., 2018).

Large cohort studies as well as a better understanding on the specific action of Intralipid® are required to clearly define which set of patients would benefit of such a procedure. In that perspective, in the present study, we retrospectively selected the 94 cases of patient with a RIF history who benefitted of a slow perfusion of Intralipid® during the embryo transfer cycle. The objective of this study is to report their history, the tolerance to the therapy and the outcome of the next embryo transfer under Intralipid® therapy. Moreover, to get new insight on its mechanism of action, a test of sensitivity to Intralipid® have been performed before the embryo to study the variations of our biomarkers under therapy.

2. Materials and methods

2.1. Protocol approval and patient consent

The Institutional Review Board of St Louis Hospital approved this study. Patient undergoing an endometrial biopsy provided their written inform consent allowing uterine immune analysis and a prospective follow-up. All patients included in the assisted reproductive therapy program gave their informed consent before any fertility treatment (IVF/ ICSI/ Frozen Embryo transfer).

2.2. Study design

94 patients with a history of unexplained RIF underwent an endometrial profile before their next embryo transfer with the administration of a slow perfusion of Intralipid® to control the observed endometrial over-immune activation between 2012 and 2017.

80 patients were patients with a history of implantation failures despite multiple embryos transfers. Inclusion criteria were the absence of embryo implantation despite the transfer of at least 6 Day-3 embryos or at least 4 Day-5 embryos. The mean age of patients included was 35.8 years old (28–43). They all previously failed to implant to IVF/ICSI despite 3.7 (2–8) oocyte pick-up and repeated transfer of a mean of 7.5 (4–15) fresh or freeze-thawed embryos.

14 patients were patients with a history of implantation failures despite oocyte donation (OD). The mean age of patients included was 37 years old (29–42). They all, according to the inclusion criteria, previously failed to implant after IVF-OD despite repeated transfer of a mean of 7 fresh or freeze-thawed embryos (2–18).

The basal exploration was set up in the mid-luteal phase of a cycle (monitored natural cycle or mock cycle). An endometrial biopsy was realized by aspiration with a Cormier pipelle. As previously described in detail (Ledee et al., 2016), after histological dating of the endometrial biopsy sample to confirm the mid-luteal phase, RNA was extracted with the RNeasy Plus kit (Qiagen, Courtabeuf, France), according to the manufacturer's instructions. The RNA was reverse-transcribed into cDNA with the first-strand cDNA synthesis kit for RT-PCR (Roche Diagnostic, Meylan, France). IL-15/Fn-14 and IL-18/TWEAK mRNA ratios were determined by quantitative RT-PCR with the Light Cycler 480 SYBR Green I Master mix (Roche Diagnostic), and uNK cells were counted after CD56 + immunohistochemistry.

The association of three biomarkers defines the uterine immune profiling. The norm has been previously defined in a fertile cohort (Ledee, Petitbarat et al. 2016):

- The IL-18/TWEAK mRNA ratio, which reflects the local immune-regulated Th1/Th2 balance and the local angiogenesis.
- The IL-15/Fn-14 mRNA ratio, which reflects uNK cell maturation.
- The number of CD56 positive cells.

All 94 patients were diagnosed as having -according to our criteria-

an over-immune activation. Over-immune activated profile was characterized by high IL-18/TWEAK mRNA ratio, and/or high IL-15/Fn-14 mRNA ratio.

The choice to use a slow perfusion of Intralipid® instead of corticoids as usually prescribed in this context of documented high local immune activation was guided either by

- An absence of normalization of the local immune biomarkers under corticoids therapy (n = 21)
- An improvement of their immune profile under Intralipid® (n = 34)
- Or according to our criteria an immune profile suggesting a resistance to corticoids (n = 53) (cf infra).

We indeed previously published that prednisone was unable to significantly decrease basal elevated IL-18, IL-15 mRNA normalized expressions but seems locally effective through the induction of a better immunoregulation (Ledee et al., 2018).

They received in hospital under medical supervision around Day-8 of the cycle of embryo transfer a single 4¨% slow diluted perfusion of Intralipid® (Fresenius-Kabi) (Intralipid® 20% : 100 ml to be diluted in a 400 ml of saline water slow IV perfusion over 90 min).

If a pregnancy occurred, the procedure was re-applied at 5 and 9 weeks of amenorrhea.

Medical contraindication was known previous allergy to soya or eggs or severe hepatic insufficiency.

27 patients had benefitted of a second immune profiling under Intralipid® to document its ability to control the documented over-immune activation before the next embryo transfer and will be successfully pregnant under Intralipid®. We will used this sub-group for a paired comparison of each immune biomarkers before and under Intralipid®, each patient being her own control.

2.3. Statistical analysis

Variations of immune biomarkers were observed (CD56 cells Count, IL-18/TWEAK and IL-15/Fn-14 mRNA ratio) before and under IL among the cohort with the paired t-test. A p value below 0.05 was considered as significant

3. Results and discussion

3.1. Tolerance to Intralipid®

The tolerance to the perfusion was excellent. We did not observe any symptoms related to an allergic reaction or as it is described with non-diluted intralipids infusion headache, dizziness, flushing, drowsiness, nausea or sweating. None of the patient reported side effects during or after the slow intralipid infusion.

3.2. Immune profiles of the cohort

All 94 patients were diagnosed as having -according to our criteria- an over-immune activation profile before the treatment. Such an over-immune activated profile was characterized by high IL-18/TWEAK mRNA ratio, and/or high IL-15/Fn-14 mRNA ratio.

- 60% (57/94) had an elevated IL-18/TWEAK ratio attesting of local excess of Th-1 cytokines
- 57% (54/34) had an elevated IL-15/FN-14 ratio attesting of an over-activation of uNK cells in killer cells through IL-15
- 37% (35/94) had an excessive CD56 recruitment
- 52 (55%) had one parameter altered, 30 (32%) two parameters altered and 12 (13%) three parameters altered.

3.3. Outcome at the next embryo transfer

6 RIF patients were spontaneously pregnant within the three months following the exploration after the immune testing under therapy among 5 successfully delivered. They all benefit a slow infusion of Intralipid® at 5 weeks of amenorrhea and 9 weeks

Over the 88 RIF patients, 61 had a fresh embryo transfer (ET), 14 patients a freeze-thawed ET (FT-ET) after intra-conjugal IVF/ICSI and 12 an ET after oocytes donation. The pregnancy rate at 8 weeks of amenorrhea were respectively according to the type of transfer 64% (39/61) after fresh ET, 57% (8/14) after FT-ET and 66% (8/12) after ET from OD. The delivery rate were 51% (31/61) after fresh ET, 50% (7/14) after FT-ET and 66% (8/12) after ET from OD.

So regarding the entire cohort and despite their history of RIF, the rate of delivery was 54%, higher than expected in this context.

3.4. Comparison of immune biomarkers before and under treatment in the selected group who gave birth under Intralipid®

In patients successfully pregnant under Intralipid® who benefitted of a test of sensitivity before the embryo transfer, we were able to document a significant decrease of all the three biomarkers which we use to diagnose an over-immune endometrial activation (CD56 cells count; IL-18/TWEAK, IL-14/FN-14) as described in Table 1.

The decrease of IL-18/TWEAK is mainly induced by a decrease of the pro-inflammatory IL-18 cytokine. The significant decrease of IL-15/Fn-14 is mainly drove by a decrease of the IL-15 expression.

Intralipid® administration seems therefore to decrease the hyperactivation of uNK cells through a regulation of their recruitment and a downregulation of pro-inflammatory cytokines. Intralipid® administration seems to have no impact on local immunoregulators as TWEAK and Fn-14.

4. Discussion

Intralipid® infusion is mainly used in UK, USA and India while being almost unknown in Europe. Allahbadia described it as the current Favorite of Gynecologists for Immunotherapy in India (Allahbadia, 2015) and diverse mediatic scoops along the past years ((BBC, 2011; Macrae, 2011) attracted the public attention. In contrast, rare clinical studies have been published (Shreeve and Sadek, 2012) and no large cohort controlled studies or RCT have been conducted leaving its old clinical interest unsolved (Clark, 1994).

We here report the detailed outcome of 94 patients with a past

Table 1
evolution of immune biomarkers under Intralipid® in patients successfully pregnant under therapy.

Immune profile Median (95% CI from the median)	Initial immune profile (n = 27)	Immune profile after Intralipid® (n = 27)	wilcoxon paired test
CD56 cells count (number of + cells/ field)	62,8 [20–105]	45.5 [15–105]	0,04
IL-18/TWEAK ratio	0,18 [0,15–0,26]	008 [0,05–0,10]	0,0004
Normalized IL-18 expression	0,36 [0,29–0,55]	0.24 [0,14–0,35]	0,03
Normalized TWEAK expression	2,23 [1,4–2,8]	2,7 [2–3,4]	0,09
IL-15/Fn-14 ratio	3,6 [1,1–20]	0,79 [0,31–1,2]	0,0001
Normalized IL-1 5 expression	1,22 [0,83–2,25]	0,63 [0,26–1,3]	0,03
Normalized Fn-14 expression	0,43 [0,19–0,68]	0,66 [0,50–0,94]	008

history of reproductive implantation failures. Regarding their history, the live birth rate of 54% was unexpected. In France, in this specific RIF context, the expected LBR was more around 20–25%. This cohort however was ultra-selected either by testing the endometrial profile under therapy before the embryo transfer or either by the documented very specific profile of over-immune activation (through IL-15). We indeed previously observed that RIF patients with over-immune endometrial activation attested by an high IL-15 expression with simultaneous excessive mobilization of uNK cells were often resistant to corticoids (Lédée et al., 2018).

The absence of side effects observed, its excellent tolerance while being an inexpensive therapy are some argument of value if efficacy of Intralipid® infusion may be proved.

The two RIF previous cohort studies using immune biomarkers (cytotoxicity of circulating NK cells for Coulam et al (Coulam and Acacio, 2012), Th-1/ Th-2 equilibrium for Ndukwe (Ndukwe (2018)) reported the same very high live birth rate as observed here. Dakhly et al conducted a randomized control study comparing intralipids infusion with saline infusion in patients with unexplained infertility, history of recurrent abortion and elevated circulating NK cells. He did not observed a significant higher chemical pregnancy (58% versus 50%) but did not reported the ongoing and live birth rate in the two observed groups (Dakhly et al., 2016). In contrast, clinical study for which Intralipid® infusion was only based on the clinical history of past reproductive failures, but with no immune exploration to guide its indication, were clearly negative (Check and Check, 2016).

The use of individual specific biomarkers to characterize patients is at the basis of the emerging field of personalized medicine (Goetz and Schork, 2018). In that context, intralipids are perhaps as a new option of therapy (among others) of the future precision reproductive medicine. When exploring large cohort of RIF patients, we documented that only 55% of the RIF patients exhibited an over-immune activation (25% were in low immune activation and 18% with no immune deregulation) (Ledee, Petitbarat et al. 2016; Ledee et al., 2017). Among this over-activated immune group, less than 25% would have a profile potentially responders to intralipids®. Its prescription may therefore be monitored by immune biomarkers to evaluate its efficacy.

Intralipid® does not regulate all the cases of over-immune activation. We were indeed able to observe a degradation of the profile under intralipids for 27% of the patients tested (data not shown). More-over, as no control group or placebo have been administrated, the demonstration is incomplete. Nevertheless, in the clinical context of reproductive implantation failures, we claim as previous authors- for more investigations based on the comprehension of its mechanism of action (Mekinian et al., 2016), specifically Th1 cells (Granato et al., 2000) and to decrease the cytotoxicity of circulating NK Cells (Roussev, Ng et al. 2007). Bolus of Intralipid® may also be a strong acute contributor for the regulation of innate immune cells (Horvath et al., 2015). However, data regarding the role of Intralipid® in pregnancy are however perceived as rare and unconvincing.

In the present study, we were able to evidence a clear positive effect of Intralipid® on biomarkers in patients who will be pregnant after its administration. In this group we observed a significant decrease of the expression of pro-inflammatory cytokines as IL-15 and IL-18 as well as a decrease of mobilization of CD56 positive cells while no effect on the local immunomodulation was observed. We used the IL-18/TWEAK ratio as a biomarkers of the Th-1/ Th-2 immunoregulated equilibrium. In patients who get pregnant under Intralipid® and who had initially an excess of Th-1 cytokines (high IL-18/TWEAK ratio), we observed the normalization of the ratio under therapy. The ratio IL-15/Fn-14 is used in our hands as a criterion of maturity of uNK cells but also if elevated as a criterion of IL-15 driven hyper-activation of uNK cells in lymphocytes activated killers cells. Intralipid® in RIF patients who get pregnant with an initial high IL-15/Fn-14 expression induced a normalization of the ratio under therapy.

To conclude, we here suggest that Intralipid® seems to be a new option to explore in RIF patients who exhibit an over-immune activation of uNK cells. A normalization of the immune profile under therapy is the best method to test its sensitivity before any transfer. Double blind studies evaluating Intralipid® versus Placebo are a mandatory and should be conducted. However, personalization of assisted reproductive treatments based on a clear understanding of the underlying problem may represent the next future of the reproductive medicine.

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Competing interests

None.

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