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1 **Intralipid therapy for unexplained recurrent miscarriage and implantation failure:**
2 **case-series and literature review**

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20 **Running title:**

21 Intralipid in unexplained recurrent miscarriage and implantation failure

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26

27 **Key words:** recurrent miscarriages, implantation failure, intralipids, live birth

28

29 **ABSTRACT**

30

31 **Introduction:**

32 In retrospective cohort study of women with unexplained recurrent implantation failure (RIF)
33 and miscarriage (RM), we analyzed the efficacy and safety of intralipid therapy to obtain a
34 live birth.

35 **Patients and methods:**

36 Women with unexplained RM and/or RIF were included from 2015 to 2018 from three
37 French university hospitals.

38 **Results:**

39 Among 187 women treated for unexplained recurrent miscarriages and implantation failures,
40 26 women with median age of 36 years (29-43) received intralipid therapy. Among these 26
41 women, 10 women with a median age of 33 years (31-40) had a history of spontaneous
42 recurrent miscarriages, with a median of 5 (4-8) previous miscarriages. Live births occurred in
43 7 (70%) pregnancies under intralipids and were significantly more frequent than in women
44 with recurrent miscarriages who did not receive intralipid therapy (n=20, p=0.02). Age,
45 number of previous miscarriages, and additional therapies did not significantly differ between
46 the two groups. Among the 26 included women, 16 had a history of recurrent implantation
47 failures, with median age of 37 years (29-43) and median 9.5 (3-19) embryo transfers.
48 Clinical pregnancy occurred in 9 (56%) women receiving intralipids after embryo transfers
49 under intralipids among which 5 (55%) resulted in a live birth. Comparing successful
50 pregnancies under intralipids with those with fetal loss, no significant differences have been
51 noted.

52

53

54 **Conclusion:**

55 Intralipids could be an effective and safe therapy in women with unexplained recurrent
56 miscarriages and infertility.

57 **INTRODUCTION**

58

59 Recurrent miscarriage (RM) is a frequent condition concerning about 1-3% of couples¹.

60 Recurrent implantation failure (RIF) is considered after at least 3 unsuccessful transfers of
61 good quality embryos, and remain unexplained in 45% of infertile couples². Various
62 conditions can cause RM and RIF. A standard workup includes search for uterine
63 malformations, genetic abnormalities, and endocrine, infectious or autoimmune diseases.

64 Immune abnormalities have been reported in women with RM and RIF, such as increased
65 blood natural killer (NK) cell levels, regulatory T cell deficiencies and increased
66 proinflammatory cytokines³. Uterine NK cells (uNK) represent up to 70% of the cells in
67 endometrium during the implantation phase and secrete several cytokines (IL-12, IL-15, Fn-
68 14, IL-18, LIF, TWEAK) modulating the uterine environment. An excessive number of uNK
69 cells and the imbalance between IL-12/Fn-14 and IL-18/TWEAK have been recently shown
70 as markers of immune profile dysregulation in women with RIF⁴.

71 The direct effect of intralipids on fertility is unclear but seems to rely on the inhibition of NK
72 cell cytotoxicity, possibly mediated through short fatty acids stimulating PPAR γ receptors.
73 Intralipids were proposed as an immunomodulatory therapy in 1994⁵. A decrease of NK cell
74 cytotoxicity has been shown several weeks after a single infusion of intralipids^{6,7}. Intralipid
75 therapy has been mostly reported in women with increased peripheral NK cells, whereas
76 recent metanalysis did not demonstrate an association of NK cell rates in preconception with
77 the fetal loss⁸. We analyzed the efficacy and safety of intralipid therapy in a retrospective

78 cohort study of women with unexplained RIF and RM, and compared live birth rates in
79 treated women to untreated women with similar obstetrical history.

80

81 **PATIENTS AND METHODS**

82 Women with unexplained recurrent miscarriage and/or recurrent implantation failure were
83 included from 2015 to 2018 in three university hospitals (Saint-Antoine, Tenon and Trousseau
84 Hospitals, Assistance Publique-Hopitaux de Paris Sorbonne Université, Paris, France).
85 Inclusion criteria were (1) at least 3 recurrent miscarriages before 12 weeks of gestation
86 and/or at least 3 implantation failures of at least 2 good embryos transfers; (2) absence of any
87 cause for recurrent miscarriages and implantation failures among uterine, genetic, infectious,
88 hormonal, thrombophilia and autoimmune diseases; (3) at least one infusion of intralipids for
89 the treated group.

90 Clinical data were collected as follows: age, number of pregnancies and live births, number of
91 miscarriages, number of in vitro fertilization (IVF)/intracytoplasmic sperm injection (ICSI) and
92 embryo transfers, body mass index, tobacco and alcohol use, prior medical and surgical
93 history and medications during each previous pregnancy. For each pregnancy treatments were
94 analyzed: low dose aspirin, LMWH, steroids (prednisone 10 mg/day), progesterone and
95 vitamin D supplementation.

96 Laboratory data included AMH levels, antinuclear and antiphospholipid autoantibodies,
97 peripheral NK cell levels, and levels of circulating cytokines TNF α , IL-1, IL-6 and IL-10 at
98 the time of the first intralipid infusion. The non-criteria anti-phospholipid antibodies (anti-
99 phosphatidyléthanolamines IgG and IgM, anti-PS/PT IgG/M and anti-annexin V IgG) were
100 also analyzed. Endometrial immune profiling was performed, as previously described (12),
101 and total uNK cells numbers, IL-15/TWEAK and IL-12/Fn-14 mRNA levels were recorded if

102 available. Overactivated immune profiles were characterized by high IL-18/TWEAK mRNA
103 ratio, and/or high IL-15/Fn-14 mRNA ratio (12).

104 Women in the non –IVF group (RM) received intralipid infusion at Day-8 of each cycle, and
105 then at 3, 5 and 9 weeks of gestation in the case of ongoing pregnancy. Women undergoing
106 IVF received an infusion at Day-8 of the cycle of embryo transfer then at 3, 5 and 9 weeks of
107 amenorrhea in the case of ongoing pregnancy. Intralipid therapy was chosen based on
108 endometrial immune overactivation, pervious ineffective steroid therapy, or in overweight
109 women who couldn't receive steroid therapy.

110 Patients from the control group have been matched on age, number of previous miscarriages
111 (2 matched controls by case) or previous embryo transfers with implantation failure from our
112 ongoing cohort (1 matched control by case).

113 The primary outcome was the live birth rate, and clinical pregnancy rates and safety were also
114 analyzed.

115

116 **Literature Review and Meta-analysis**

117 *Search Strategy*

118 Two investigators (LP and AM) searched MEDLINE via PubMed, Web of Science, congress
119 programs and the Cochrane Library for English-language articles published up to January
120 2019 by assessing the following keywords in the title and abstract: early RMs, unexplained
121 miscarriages, miscarriages, IVF, in vitro fertilization, fertilization in vitro, intracytoplasmic
122 sperm injection, sperm injection intracytoplasmic, assisted reproductive techniques, embryo
123 transfer, embryo implantation, and intralipids. All articles with sufficient data were included
124 in the literature review.

125 **Statistical analysis**

126 Data are described with frequencies (%) for categorical variables and medians (ranges) for
127 continuous variables. Fisher's exact test was used to compare qualitative variables and Mann-
128 Whitney/Wilcoxon test for continuous variables according to the distribution. Linear
129 regression was performed to identify factors associated with fetal losses. A p value < 0.05 was
130 considered as statistically significant. Statistical analyses were performed with GraphPad
131 Prism v7.0 (GraphPad Software, San Diego, CA, USA).

132 **Literature review and meta-analysis**

133 The meta-analysis was performed according to the recommendations of the Cochrane
134 Collaboration (Bero and Rennie 1995). Relative risks from individual studies were meta-
135 analyzed with fixed-effects and random-effects models as appropriate. Heterogeneity of the
136 exposure effects was evaluated graphically with forest plots and statistically with the *I*² test to
137 quantify heterogeneity across studies. We explored the causes of heterogeneity by population
138 features, exposure and study quality. Meta-analysis involved use of Review Manager
139 (RevMan) v5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen,
140 2014).

141

142 **RESULTS**

143

144 Among 187 women treated for unexplained recurrent miscarriages and implantation failures
145 from 2014 to 2018, 26 women with median age of 36 years (29-43) received intralipid therapy
146 (**Table 1**). Among these 26 women, 10 women with a median age of 33 years (31-40) had a
147 history of spontaneous recurrent miscarriages, with a median of 5 (4-8) previous miscarriages
148 (**Table 1 and Supplementary Table 1**). Intralipids were used at least once during
149 preconception in 9 (90%) women previously refractory to other therapies. Seven of these ten
150 women received additional treatments including combinations of aspirin, prednisone,

151 progesterone, or heparin. Live births occurred in 7 (70%) pregnancies under intralipids and
152 were significantly more frequent than in women with recurrent miscarriages which did not
153 received intralipids (control group; n=20) ($p=0.02$); whereas age, number of previous
154 miscarriages, and associated therapies were not significantly different (**Table 1**).

155 Among 26 included women, 16 women had recurrent implantation failures, with median age
156 of 37 years (29-43) and 9.5 (3-19) embryo transfers (**Table 1 and Supplementary Table 2**).

157 Intralipids were used at least once before the embryo transfer, as first-line therapy in 10 (63%)
158 women, and in 6 (37%) pregnancies refractory to previous therapies. Additional treatments
159 have been combined in 13 (81%) cases, mostly aspirin, LMWH and prednisone. Age,
160 previous miscarriages and embryo transfers, blood cytokine levels, and additional therapies
161 were not significantly different between women treated or not by intralipids (**Table 1**).

162 Clinical pregnancy occurred in 9 (56%) women receiving intralipid therapy after embryo
163 transfers and resulted in 5/9 (55%) live births compared to 6 (38%) and 2/6 (33%) in control
164 group (n=16), respectively. Interestingly, in 2 women who suffered fetal losses after embryo
165 transfers, clinical pregnancy occurred under intralipid therapy for the first time in these
166 women who experienced previous embryo transfer failure.

167 Overall, 16 patients had immune endometrial profiling analysis, and 14 of these women had
168 endometrial over-activated immune responses. Among 12 women with over-activated
169 immune responses and clinical pregnancy, 5 experienced live birth (42%). Among 10 women
170 with live births without immune endometrial profiling before intralipid therapy, 5 women had
171 a live birth (50%).

172 Age, previous obstetrical history, peripheral NK cell percentages and associated therapies
173 were similar in case of pregnancies under intralipids resulting in live births compared to those
174 with fetal loss, except a trend to higher preconception uNK levels in women with live births
175 56 (43-100) versus 38 (19-51, $p=0.07$, **Table 2**). Using univariate analysis, age < 35 years,

176 NK cells > 10%, and associated therapies were not significantly associated with live births in
177 women with recurrent miscarriages, whereas AMH levels <1 ng/ml and intralipid therapy
178 were significantly associated. In multivariate analysis, only intralipid therapy was
179 significantly associated with live births with odds ratio of 17 [95% CI 1.01-286] (p=0.049).
180 No side effects (flushing, nausea, vomiting, fever, sweating) have been noted during or after
181 the intralipid infusion.

182

183 **Meta-analysis**

184 The literature review of studies evaluating intralipids in RM and infertile populations is
185 presented in **Table 3**. The literature search yielded 5 citations and only 3 studies had relevant
186 data and were included in the meta-analysis. The meta-analysis of 3 studies (including our
187 results) showed an odds ratio of 1.7 [95% confidence interval (CI) 1.1-2.61; p=0.02] live birth
188 in women receiving intralipids as compared to those not receiving intralipid therapy
189 (**Supplementary Figure 1**). The heterogeneity between the studies was high with *I*² of 56%
190 (*p* =0.1).

191

192 **DISCUSSION**

193 In this cohort study of women with recurrent miscarriages and implantation failures,
194 we analyzed the efficacy of intralipid therapy. Intralipids use resulted in 63% of live births in
195 patients with previous infertility, 70% in women with recurrent miscarriages and 55% with
196 recurrent implantation failures, which was significantly higher than in women not receiving
197 intralipid therapy. Intralipid therapy was the only significant factor associated with live births
198 in women with previous RM in multivariate analysis. Our data were confirmed using meta-
199 analysis of studies from the literature, although analyzed studies have important
200 heterogeneities and low number of included patients.

201 Our findings reinforce results of previous studies analyzing the potential benefit of intralipids
202 in infertility (**Table 3**). In a randomized trial comparing intralipids and immunoglobulins in
203 women with recurrent miscarriages with more than 20% of peripheral NK cell levels, the rate
204 of successful pregnancies were 91% in intralipid group and 88% in immunoglobulin group⁹.
205 A randomized trial using an intralipid infusion on the day of oocyte retrieval versus placebo in
206 296 women with unexplained infertility and peripheral NK cells >12% showed 54% of live
207 births in intralipid group versus 34% under placebo (p=0.005), whereas the frequencies of
208 clinical pregnancy and miscarriages were not different between 2 groups¹⁰. A cohort study of
209 127 women with unexplained miscarriages and infertile women having peripheral NK cells
210 >19% showed no differences of live births in comparison to the historical cohort¹¹. Based on
211 endometrial immune profiling in 94 women with recurrent implantation failure, the live birth
212 rate was 55% under intralipid therapy¹². Our study analyzed intralipids in women with
213 unexplained infertility, showing that intralipid therapy could be beneficial even in women
214 without increased peripheral NK cell levels. We did not find any significant factor associated
215 with live birth except intralipid therapies, even considering blood cytokine levels, peripheral
216 NK cells and endometrial immune profiling. Various intralipid regimens have been previously
217 used, from single infusion to weekly infusions, and the best regimen remains to be
218 determined.

219 While the mechanism underlying improvement of live birth rate with intralipid therapy
220 remains unclear, data previously showed that intralipids modulate several immune functions,
221 in particular NK cell cytotoxicity. NK cell activity was significantly decreased under
222 intralipid therapy⁶, and this effect lasted from 4 to 9 weeks⁷. A previous study also reported an
223 in vitro effect on T lymphocytes (decreased activation) and on cytokine secretion (decreased
224 TNF- α , IL-2 and IL-1 β levels) ^{12,13}.

225 In conclusion, intralipids are an effective and safe therapy in women with unexplained
226 recurrent miscarriages and infertility, even in those without increased peripheral NK levels
227 and dysregulated endometrial immune profiling.

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229 commercial, or not-for-profit sectors.

230 **Conflicts of interest:** The authors declare that they have no conflict of interest.

231 **Ethical approval:** All procedures performed in studies involving human participants were in
232 accordance with the ethical standards of the institutional and/or national research committee
233 and with the 1964 Helsinki declaration and its later amendments or comparable ethical
234 standards (Saint Antoine ethical committee).

235 **Informed consent:** Informed consent was obtained from all individual participants included
236 in the study.

237

238 **Authors contributions:**

239 All coauthors participated to the study design, data extraction and analysis, paper review and
240 redaction. AM and LP have the responsibility of data provided in the manuscript.

241

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282

283

284 **Table 1 – Characteristics of women with recurrent miscarriage and implantation failure who received**
 285 **intralipid therapy.**

Characteristics	Implantation failure (N=16)	Implantation failure without intralipids (N=16)	Recurrent miscarriages under intralipids (N=10)	Recurrent miscarriages without intralipids (N=20)
Age (n range)	37 (29-43)	36 (29-42)	33 (31-40)	35 (27-41)
Thyroiditis (n,%)	2 (13)	2 (13)	0	0
Endometriosis (n,%)	4 (25)	1 (6)	0	1 (5)
Tubular involvement (n,%)	2 (13)	3 (19)	1 (10)	0
Overweight (n,%)	6 (38)	0	3 (30)	6 (30)

Obstetrical history

Same conceptor (n,%)	15 (94)	15 (94)	7 (70)	11 (55)
Parity, median (IQR)	0 [0-2]	0 [0-3]	1 [0-2]	1 [0-2]
Gravidity, median (IQR)	1 [0-5]	1 [0-6]	7 [5-10]	6 [4-12]
Number of miscarriages, median (ranges)	0 [0-3]	0 [0-4]	5 [4-8]	6 [4-11]
Cumulative embryo transfers (n,%)	9.5 [2-19]	10.5 [5-14]	-	-

Laboratory data

Antinuclear antibodies	3 (19)	2 (13)	1 (10)	1 (5)
AntiTPO / TG antibodies	3 (19)	3 (19)	0	1 (5)
Anti-PS/PT/AnnexinV/PE antibodies	0	0	0	0
AMH, median (ranges)	2 [0.1-9.8]	1.3 [0.3-6.7]	2.1 [0.5-7.8]	2.3 [1-7.8]
NK56+ cells, median (ranges)	9.5 [4-32]	12 [5-32]	10 [3-14]	8 [3.5-16]
TNF α , median (ranges)	24 [8-140]	18 [5-53]	25 [13-61]	23 [4.8-48]
IL-1, median (ranges)	19 [13-43]	17 [3-113]	15 [5-45]	9.5 [5.1-26]
IL-6, median (ranges)	5 [1.1-97]	9 [2-13]	3.6 [1.1-82]	9.9 [1.1-15]
IL-10, median (ranges)	0.1 [0.1-1.1]	1.1 [0.1-9] $\$$	0.1 [0.1-12]	0.1 [0.1-3.3]
uNK, median (ranges)	45 [25-70]	45 [25-54]	45 [19-100]	45 [23-100]
IL-18/TWEAK mRNA ratio	0.14 [0.1-6]	0.2 [0.1-0.3]	0.5 [0.16-3]	-
IL-15/Fn-14 mRNA ratio	9 [1-79]	9 [1.5-23]	15 [7-80]	-
Immune over-activated profile	8/11 (73)	2/5 (40)	5/5 (100)	-

Pregnancy and treatments

Clinical pregnancy	9/16 (56)	6/16 (38)	10 (100)	10 (100)
Live births	5/9 (55)	2/6 (33)	7 (70)	3 (15)*
Term live birth	39 [36-40]	39 [36-40]	39 [38-40]	-
Additional therapies	13 (81)	14 (88)	7 (70)	7 (35)
Aspirin / low molecular weighted heparin	13 (81) / 13 (81)	8 (50) / 8 (50)	4 (40)* / 5 (50)	5 (25) / 4 (20)
Prednisone	11 (69)	8 (50)	6 (60)	2 (10)*
Progesterone / Vitamin D	3 (19) / 14 (88)	7 (44) / 5 (31) $\$$	1 (10) / 7 (70)	2 (10) / 4 (20)*

286 BMI – body mass index, AMH – anti-Müllerian hormone, TSH – thyroid stimulating hormone, 1,25-OH vitamin

287 D – 1,25-dihydroxy-vitamine D, ANA – antinuclear antibodies, CH50 – total haemolytic complement, anti-TPO

288 – anti-thyroid peroxidase, anti-TG – anti-thyroid globulin

289 *p<0.05 recurrent miscarriages under intralipids versus recurrent miscarriages without intralipids
290 \$p<0.05 implantation failures with intralipids versus implantation failures without intralipids
291

292 **Table 2 – Characteristics of women with live births and fetal loss or without pregnancy despite embryo**
 293 **transfer who received preconception intralipid therapy.**
 294

Characteristics	Live births (N=12)	Fetal loss (if ongoing pregnancy) (N=7)	Fetal loss / no pregnancy despite embryo transfer (N=14)
Age	32 [31-42]	35 [31-43]	35 [30-43]
Medical history			
Thyroiditis (n,%)	0	0	2 (14)
Endometriosis (n,%)	1 (8)	0	3 (21)
Tubular involvement (n,%)	1 (8)	2 (29)	2 (14)
Overweight (n,%)	5 (42)	2 (29)	4 (29)
Procreation history			
Same conceptor (n,%)	10 (83)	6 (86)	12 (86)
Parity, median (ranges)	1 [0-2]	0 [0-1]*	0 [0-1]**
Gravidity, median (ranges)	5.5 [1-10]	2 [1-7]	1 [0-7]**
Number of miscarriages, median (ranges)	4 [0-8]	2 [0-6]	0 [0-6]§
Number of embryo transferred (n,%)	9 [2-19]	16 [10-19]	10 [5-19]
Laboratory data			
AMH, median (ranges)	2 [0.1-7.8]	2 [0.2-9.8]	2 [0.2-9.8]
NK56+ cells, median (ranges)	7 [3-12]	13 [4-32]£	12.5 [4-32]**
TNFa, median (ranges)	26 [8-140]	24 [10-48]	24 [9-92]
IL-1, median (ranges)	20 [5-45]	12 [9.5-16]	17 [10-43]
IL-6, median (ranges)	3.6 [1.1-82]	2 [1.1-21]	4.6 [1.1-97]
Il-10, median (ranges)	0.1 [0.1-12]	0.1 [0.1-3.3]	0.1 [0.1-3.3]
Uterine NK cells, median (ranges)	56 [43-100]	38 [19-51]£	42 [19-70]
Immune over-activated profile	5/6 (83)	5/6 (83)	8/10 (80)
Pregnancy under intralipids			
Spontaneous pregnancy	7 (58)	3 (43)	3 (21)
Live births	12 (100)	0	0
Additional therapies	10 (83)	6 (86)	12 (86)
Aspirin / low molecular weighted heparin	8 (67) / 6 (50)	5 (71) / 6 (86)	9 (64) / 12 (86)
Prednisone	8 (67)	4 (57)	9 (64)
Progesterone / Vitamin D	4 (33)	3 (43)	4 (29)

295 *p<0.05 live births versus fetal loss
 296 £ p=0.07 live births versus fetal loss
 297 **p<0.05 live births versus fetal loss or no pregnancy
 298 § p=0.06 live births versus fetal loss or no pregnancy
 299
 300
 301
 302

303 **Table 3. Characteristics of women who received intralipid therapy: literature review.**

Author / year	Type of study N	Inclusion criteria	Age (years)	Number of Miscarriages / embryos transfers	Intralipid protocol	Live birth (%)
Meng 2016	Randomized versus intravenous immunoglobulins N=76 each group	≥3 unexplained miscarriages before 12 wg ; peripheral NK cells >20%	31.6±4.2	3.5±2.7 /NA	On third day of menstrual cycle and every week after pregnancy until 12 weeks	70/76 (91) intralipid vs 67/76 (88) IGIV (p=0.4)
Dakhly 2016	Randomized versus placebo N=144 each group	≥3 unexplained miscarriages or infertility; peripheral NK cells >12%	35.5±3.7	4.1±0.9 / 2.5±0.5	On the day of oocyte retrieval	54 (37.5) vs 34 (22.4) in placebo (p=0.005)
Martini 2018	Retrospective cohort study N=127	≥3 unexplained miscarriages or infertility; peripheral NK cells >19%	35.9±4.5	1.4±1.4 /NA	7-10 days before embryo transfer or insemination and repeated at 6 and 10 weeks of gestation if pregnant	47/127 (37) vs 8/20 (40) in historical cohort (p=0.12)
Ledée 2018	Retrospective cohort study N=94	Implantation failure despite embryo transfer (n=80) or oocyte donation (n=14); based on endometrial over-immune activation	35.8 (28-43)	NA/ 7 (2-18)	Day-8 of the cycle of embryo transfer and 5 and 9 weeks of amenorrhea if pregnancy	46/88 (54)
Our study	Retrospective cohort study N=26	≥4 unexplained miscarriages or infertility	36 [39-43]	5 [4-8] / 9.5 [2-19]	Day-8 of the cycle of embryo transfer then at 3, 5 and 9 weeks of amenorrhea	12 (63) vs 5/19 (26)(p=0.005) 7 (70) vs 3 (15)(p=0.005) for recurrent miscarriages groups; 5/9 (55) vs 2/6 (33)(p=0.5) for implantation failures groups