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

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**Running title:**

Intralipid in unexplained recurrent miscarriage and implantation failure

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

28

## ABSTRACT

### **Introduction:**

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

### **Patients and methods:**

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

### **Results:**

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

## **Conclusion:**

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

## **INTRODUCTION**

Recurrent miscarriage (RM) is a frequent condition concerning about 1-3% of couples<sup>1</sup>. Recurrent implantation failure (RIF) is considered after at least 3 unsuccessful transfers of good quality embryos, and remain unexplained in 45% of infertile couples<sup>2</sup>. Various conditions can cause RM and RIF. A standard workup includes search for uterine malformations, genetic abnormalities, and endocrine, infectious or autoimmune diseases. Immune abnormalities have been reported in women with RM and RIF, such as increased blood natural killer (NK) cell levels, regulatory T cell deficiencies and increased proinflammatory cytokines<sup>3</sup>. Uterine NK cells (uNK) represent up to 70% of the cells in endometrium during the implantation phase and secrete several cytokines (IL-12, IL-15, Fn-14, IL-18, LIF, TWEAK) modulating the uterine environment. An excessive number of uNK cells and the imbalance between IL-12/Fn-14 and IL-18/TWEAK have been recently shown as markers of immune profile dysregulation in women with RIF<sup>4</sup>. The direct effect of intralipids on fertility is unclear but seems to rely on the inhibition of NK cell cytotoxicity, possibly mediated through short fatty acids stimulating PPAR $\gamma$  receptors. Intralipids were proposed as an immunomodulatory therapy in 1994<sup>5</sup>. A decrease of NK cell cytotoxicity has been shown several weeks after a single infusion of intralipids<sup>6,7</sup>. Intralipid therapy has been mostly reported in women with increased peripheral NK cells, whereas recent metanalysis did not demonstrate an association of NK cell rates in preconception with the fetal loss<sup>8</sup>. We analyzed the efficacy and safety of intralipid therapy in a retrospective

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

## **PATIENTS AND METHODS**

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

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

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

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

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

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

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

## **Literature Review and Meta-analysis**

### *Search Strategy*

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

### **Statistical analysis**

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

### **Literature review and meta-analysis**

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

## **RESULTS**

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



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

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

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

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

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

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

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

### **Meta-analysis**

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

### **DISCUSSION**

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

Our findings reinforce results of previous studies analyzing the potential benefit of intralipids in infertility (**Table 3**). In a randomized trial comparing intralipids and immunoglobulins in women with recurrent miscarriages with more than 20% of peripheral NK cell levels, the rate of successful pregnancies were 91% in intralipid group and 88% in immunoglobulin group<sup>9</sup>. A randomized trial using an intralipid infusion on the day of oocyte retrieval versus placebo in 296 women with unexplained infertility and peripheral NK cells >12% showed 54% of live births in intralipid group versus 34% under placebo (p=0.005), whereas the frequencies of clinical pregnancy and miscarriages were not different between 2 groups<sup>10</sup>. A cohort study of 127 women with unexplained miscarriages and infertile women having peripheral NK cells >19% showed no differences of live births in comparison to the historical cohort<sup>11</sup>. Based on endometrial immune profiling in 94 women with recurrent implantation failure, the live birth rate was 55% under intralipid therapy<sup>12</sup>. Our study analyzed intralipids in women with unexplained infertility, showing that intralipid therapy could be beneficial even in women without increased peripheral NK cell levels. We did not find any significant factor associated with live birth except intralipid therapies, even considering blood cytokine levels, peripheral NK cells and endometrial immune profiling. Various intralipid regimens have been previously used, from single infusion to weekly infusions, and the best regimen remains to be determined.

While the mechanism underlying improvement of live birth rate with intralipid therapy remains unclear, data previously showed that intralipids modulate several immune functions, in particular NK cell cytotoxicity. NK cell activity was significantly decreased under intralipid therapy<sup>6</sup>, and this effect lasted from 4 to 9 weeks<sup>7</sup>. A previous study also reported an in vitro effect on T lymphocytes (decreased activation) and on cytokine secretion (decreased TNF- $\alpha$ , IL-2 and IL-1 $\beta$  levels)<sup>12,13</sup>.

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

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

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

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

#### **Authors contributions:**

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

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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]    |
| TNFα, 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.**

| Characteristics                          | Live births<br>(N=12) | Fetal loss<br>(if ongoing pregnancy)<br>(N=7) | Fetal loss / no pregnancy<br>despite embryo transfer<br>(N=14) |
|--|-----------------------|---|--|
| Age                                      | 32 [31-42]            | 35 [31-43]                                    | 35 [30-43]   |
| <b>Medical history</b>                   |                       |   |  |
| 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)   |
| <b>Procreation history</b>               |                       |   |  |
| 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]  |
| <b>Laboratory data</b>                   |                       |   |  |
| 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)   |
| <b>Pregnancy under intralipids</b>       |                       |   |  |
| 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

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

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