Immunotherapy for recurrent pregnancy loss: a reappraisal

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1. Title Page:

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2. Abstract:

Recurrent pregnancy loss (RPL) is frequently encountered in the outpatient setting. Despite extensive investigation, up to 50% of patients will be diagnosed with idiopathic RPL, for which no effective treatment exists. While the immune system is intricately involved in the initiation and maintenance of pregnancy, there are no validated diagnostic tests to confirm immune mediated pregnancy loss. Therefore, drugs aiming to modulate or suppress the immune system are often used on speculation with limited scientific evidence. As the literature is heterogenous and difficult to assimilate, we wanted to provide the reader with an objective and comprehensive review of each type of treatment (progesterone, aspirin, low-molecular weight heparin, granulocyte colony stimulating factor, human chorionic gonadotropin, corticosteroids, intralipids and intravenous immunoglobulins), highlighting the possible mechanisms of action, potential efficacy or futility and risks associated. This review aims to summarize current knowledge on the topic, provide a clinical guide for decision making and identify knowledge gaps required to harmonize practices and develop guidelines for suspected immune-mediated RPL management.

3. Keywords: Immunomodulation, recurrent pregnancy loss, miscarriage, recurrent miscarriage, progesterone, aspirin, heparin, granulocyte colony stimulating factor, human chorionic gonadotropin, corticosteroids, intralipids, intravenous immunoglobulin

4. Essential Points:

- Recurrent pregnancy loss affects close to 3% of couples attempting to procreate, remains unexplained in 50% of cases and is associated with a decreased live birth rate with subsequent pregnancies. There are no proven effective treatments to enhance live birth rates in patients with unexplained recurrent pregnancy loss.
Immune-mediated reproductive failure is often suspected in patients with unexplained recurrent pregnancy loss. However, validated and widely accepted biomarkers to prove this diagnosis are not available.

Many studies have evaluated the use of immunomodulatory therapy in patients with unexplained recurrent pregnancy loss. However, the literature is heterogenous and studies are often underpowered to detect clinical effect.

Immune modulation for unexplained recurrent pregnancy loss remains controversial.

Immune modulation for recurrent pregnancy loss is probably most effective when individualized to the underlying immune defect and when started prior to conception.
5. Manuscript:

**Introduction**

Recurrent pregnancy loss (RPL) as defined by $\geq 3$ consecutive first trimester miscarriages is a devastating condition affecting up to 3% of couples attempting to conceive (1). Extensive investigation of both partners often fails to identify an explanatory cause, and the risk of a repeat miscarriage can be as high as 45% in a subsequent pregnancy. Apart from continuing attempts, there are no proven effective treatment to enhance the live birth rate (LBR) in patients with unexplained RPL (uRPL) (2).

An immune etiology underlying uRPL has long been suspected. Indeed, for a pregnancy to be successful, the maternal immune system must develop selective tolerance to the semi-allogeneic fetus while preserving competence required for anti-pathogen defense. This fine balance is achieved by a complex interplay of immune events occurring prior to and during implantation (3) (Figure 1). These events establish a dialogue between the embryo and the maternal decidua which dictate the appropriateness of the ensuing maternal immune adaptation and likely the fate of the pregnancy (4). Any deviations in this controlled and tightly regulated process can lead to abortive pathologies (5).

Despite advances in our understanding of reproductive immunology, there are no easily available, widely accepted biomarkers to diagnose patients with immune-mediated recurrent pregnancy loss. Many studies use peripheral blood immune markers to identify such patients. Yet, it is unclear if peripheral blood reflects endometrial-specific immunity (6) or predicts reproductive outcomes (7).

Since the 1980's, various immunomodulatory agents have been evaluated to improve pregnancy outcomes in patients with uRPL (8). However, due to the inherent difficulty in selecting appropriate
patients to treat or study, the heterogeneity in treatment protocols and the incomplete comprehension of the precise immune events leading to miscarriage, the use of immune modulation to treat patients with uRPL remains highly controversial. This article provides a comprehensive review of the various immunomodulatory treatments (progestins, aspirin, heparin, granulocyte-colony stimulating factor, human chorionic gonadotropin, intralipids and intravenous immunoglobulin) used in women with unexplained and suspected immune-mediated recurrent pregnancy loss (referred herein as RPL) as well as a critical appraisal of the available literature.

**Materials and methods:**

A PUBMED and EMBASE search with the keywords ‘recurrent pregnancy loss’, ‘recurrent miscarriage’, ‘recurrent abortion’ AND ‘immunomodulation’, ‘progesterone’, ‘aspirin’, ‘heparin’, ‘low molecular weight heparin’, ‘granulocyte colony stimulating factor’, ‘human chorionic gonadotropin’, ‘intrlipid’, ‘intravenous immunoglobulin’ (1950-May 2021) was performed to identify studies for this review. For each individual immunomodulatory therapy, English language meta-analysis or randomized controlled trials (RCT) recruiting patients with ≥3 consecutive unexplained first trimester RPL for which the live birth rate (LBR) was measured as the primary outcome were favored. In the absence of this, non-randomized studies or controlled cohort studies in patients with ≥ 2 RPL for which at least the clinical pregnancy rate (CPR) was measured were also included, but limitations were identified.

**Progesterone:**

In addition to its essential role in the establishment and maintenance of pregnancy, progesterone exerts a crucial immunomodulatory role during implantation and early pregnancy (9, 10) (Figure 2). This combined with an excellent safety and tolerability profile provides a sound rationale for
exogenous progesterone supplementation in patients with RPL. However, while luteal phase progesterone support is routinely incorporated in assisted reproductive cycles, its use in RPL women is still debated.

The largest RCT published to date including 826 women with ≥ 3 consecutive RPL, did not find that vaginal micronized progesterone supplementation in early pregnancy improved the LBR compared to placebo (11). However, in a later RCT, Coomarasamy et al reported that intravaginal micronized progesterone improved the LBR in patients with ≥ 3 RPL (n=285) presenting with first trimester bleeding compared to placebo (RR 1.28, 95% CI 1.08-1.51); no statistically significant difference in LBR was noted for patients with 1-2 previous miscarriages (n=1515) (RR 1.05, 95% CI 1.00-1.12) (12).

Two meta-analyses are worth mentioning. Saccone et al analyzed data from 10 RCTs (n=1586) and found that synthetic but not natural progesterone was associated with a lower risk of miscarriage compared to placebo in patients with ≥ 2 RPL (RR 0.69, 95% CI 0.35-0.88 for intramuscular progesterone (IM) and RR 0.47, 95% CI 0.30-0.73, for oral dydrogesterone). While the authors mentioned that progesterone was likely to prevent miscarriage in a subgroup of women with >3 RPL (RR 0.6, 95% CI 0.4-2.09)(11, 13-17), the details of this analysis are not presented in the article (18). Likewise, in a subgroup analysis of 1334 women with ≥3 miscarriages (progesterone n=670, placebo n=664) from 4 RCT (11, 13, 15, 16) Haas et al suggested that progesterone supplementation in early pregnancy trended to decrease the miscarriage rate in women with ≥ 3 RPL (RR 0.59, 95% CI 0.34-1.01); however, their results were not statistically significant. There was no evidence to suggest that a type or route of administration of progesterone was superior (19).

These studies evaluated the administration of progesterone after pregnancy diagnosis. However, progesterone’s immunomodulatory effect begins prior to implantation and post-conception
supplementation may not provide full immunological benefit. In a prospective cohort study of 116 patients (163 pregnancies) with ≥ 2 consecutive unexplained RPL, Stephenson et al found that luteal phase start of intravaginal micronized progesterone trended to improve the odds of a successful pregnancy compared to no treatment (68% (86/126) versus 51% (19/37); OR 2.1, 95% CI 1.0–4.4; p=0.05) (20). Although these results are not statistically significant, they do provide a rationale for a RCT to evaluate the effectiveness of this approach in RPL patients.

Progesterone supplementation in early pregnancy probably improves pregnancy outcomes in women with RPL. However, patient selection, timing of administration, route and dosing remain to be optimized. While periconception administration may be more effective than the traditional post conception start, this remains to be assessed in a randomized-controlled setting. Awaiting these studies, we recommend that luteal phase progesterone supplementation be considered for all patients with ≥3 pregnancy losses (Table 3).

**Aspirin:**

Low dose aspirin’s (LDA) mechanism of action (21, 22) (Figure 2), ease of administration as well as safety and tolerability during pregnancy (23) makes it an attractive drug to improve pregnancy outcomes in patients with RPL. However, due to LDA’s widespread availability over the counter, RCTs are difficult to perform as patients in the control group may self-administer LDA. This was noted in a large percentage of patients during a previous placebo-controlled trial by Laskin et al.

Few RCTs have been performed evaluating LDA treatment in women with unexplained RPL. Most studies were small, started LDA after diagnosis of pregnancy or used LDA in combination with other drugs. A 2014 Cochrane systematic review found no benefit of LDA in patients with RPL with or without anti-phospholipid antibodies, however, their conclusions were limited by the heterogeneity of
available data (24). The same year, Schisterman et al performed a RCT evaluating preconception LDA treatment versus placebo in 1078 women with 1-2 previous miscarriages. While LDA did not improve the LBR compared to placebo in the intent to treat analysis (25), the per protocol analysis (n=664) showed an increased LBR in patients adherent to their LDA regimen (RR 1.33, 95% CI 1.08-1.64)(26). In a subgroup analysis of patients with baseline elevated C-reactive protein (CRP), a biomarker of systemic inflammation, a higher LBR occurred with LDA treatment (RR 1.35, 95% CI 1.08-1.67) (27). While this data is interesting, no subgroup analysis was performed for patients with ≥3 RPL. Blomqvist et al found that treatment with LDA did not improve LBR compared to placebo in 400 women with ≥3 RPL (28), but LDA was initiated after the detection of a fetal heartbeat, a stage where the outcome of pregnancy is favorable without any treatment. Neither study evaluated aspirin levels in the participants.

The available literature does not support routine post-conception use of LDA in women with RPL. However, there is some evidence that pre-conception start in a compliant patient may increase the probability of live birth in patients with 1-2 previous miscarriages; certain patient populations such as those with elevated baseline CRP may also benefit. While Aspirin has been associated with gastro-intestinal side effects and increased bleeding risk, available data from recent RCTs does not demonstrate any increased maternal of fetal side effects in the treatment group, even at doses up to 160 mg daily (25, 27-29). We recommend that pre-conception LDA be considered in women with ≥2 previous miscarriages as well as in patients with RPL and elevated CRP (Table 3).

**Heparin**

Low molecular weight heparin (LMWH) is widely used for both acute treatment and prophylaxis of thrombosis. The potential anti-inflammatory (30, 31) and pro-angiogenic properties (32, 33) of LMWH
(Figure 2), as well as safety and tolerability during pregnancy makes it an attractive drug to treat RPL (34). Prophylactic dose of LMWH has also been postulated to aid in trophoblast invasion in animal models by improving local blood flow and endometrial expression of adhesion receptors required for embryo implantation (35). Few RCTs have evaluated the use of LMWH only in women with RPL; most studies have used LMWH in combination with aspirin (reviewed below). Possible adverse reactions include bleeding (<0.2%), thrombocytopenia (0.4%), heparin induced thrombocytopenia (HIT) (0.2%), osteoporosis (with prolonged use) and hypersensitivity reactions (36).

**Enoxaparin:** Dolitzky et al randomized 104 women with ≥3 consecutive RPL to receive enoxaparin or aspirin starting at detection of the fetal heartbeat. Similarly, Badawy et al investigated the use of enoxaparin versus placebo in 340 women with ≥3 unexplained miscarriages. While neither study reported any beneficial effect of LMWH over control group, both studies initiated treatment after detection of a viable pregnancy, representing a good prognosis group irrespective of intervention (37, 38). Both studies reported similar rates of side effects amongst groups, however, six patients in the enoxaparin group developed thrombocytopenia between 32-34 weeks’ gestation, resolving after premature cessation of the LMWH (38).

While starting LMWH after the confirmation of a viable pregnancy may be too late to observe beneficial effects in RPL, studies starting enoxaparin earlier failed to demonstrate any treatment effect. Indeed, in the HABENOX trial, authors randomized 207 women with ≥ 2 first or second trimester pregnancy losses, with or without thrombophilia, to receive LDA alone (n=76), LDA and enoxaparin (n=62) or enoxaparin alone (n=68); patients were randomized prior to 7 weeks gestation. Compared to aspirin alone, Enoxaparin and combination treatment were not associated with a significant increase in LBR. Four patients in the enoxaparin groups required transfusions after delivery, but otherwise, bleeding complications were comparable across all treatment groups (39). Later, Pasquier et al randomized 258 patients, 186 of which had ≥3 RPL, to receive Enoxaparin...
(n=100) or placebo (n=86) started at diagnosis of pregnancy (<7 weeks). Live birth rates were similar in both groups (RR 0.86, 95% CI 0.7-1.05). In the enoxaparin group, two patients required blood transfusion after delivery despite enoxaparin being stopped 10 days prior, and 7 patients developed thrombocytopenia (none with a diagnosis of HIT) (40).

**Tinzaparin:** Shaaban et al randomized 300 women with ≥3 consecutive RPL to receive either Tinzaparin or placebo at the diagnosis of pregnancy. Women in the Tinzaparin group experienced less miscarriages compared to the control group (23.6% vs 48.9%, p=0.002) and a higher LBR (65.7% vs 36.2%, p=0.001). Two patients in the LMWH group experienced thrombocytopenia but none had maternal bleeding (41). Yuskel et al conducted an observational study of 150 women with ≥ 2 unexplained first trimester RPL. Three groups were compared; Tinzaparin (n=50), Enoxaparin (n=50) or placebo (n=50) were started once pregnancy viability was confirmed by ultrasound. A statistically significant increase in the LBR occurred in patients treated with LMWH; live births occurred in 84% of patients in the enoxaparin group, 86% in the tinzaparin group and 66% in the control group (LBR in LMWH group 85% vs control 66%, p=0.007). One patient in the Tinzaparin group experienced a cutaneous allergy, but no other adverse events were reported (42).

**Dalteparin:** Schleussner randomized 449 women with ≥2 consecutive first trimester miscarriages (≤ 12 weeks) or ≥1 miscarriage >12 weeks with or without thrombophilia to receive Dalteparin or no treatment. Unblinded medical intervention was started at diagnosis of pregnancy. Ongoing pregnancies >24 weeks gestation, were similar in both groups. Subgroup analysis showed no evidence that LMWH was superior in women with ≥3 RPL, primary or secondary miscarriages, or in women with second trimester miscarriages (43).

Finally, two recently published meta-analysis including the aforementioned RCT suggest LMWH may be a useful adjunct for women with RPL. Wang et al analyzed 5 RCT which encompassed 1452
women with ≥ 2 RPL (38, 40, 41, 43, 44). They concluded that LMWH reduced the risk of miscarriage for women with ≥ 3 RPL (RR 0.46; 95% CI 0.35-0.61, p=0.00) but not for women with < 3RPL (RR 0.70; 95% CI 0.57-0.86, p=0.26); however, LBR were similar between groups (RR 1.19; 95% CI 0.99-1.43) (45). Similarly, Jiang et al pooled data from 8 RCT (38, 40-44, 46) including 1854 patients with ≥ 2 RPL and concluded that LMWH improved LBR (RR 1.19; 95% CI 1.03-1.38, p=0.02) and decreased miscarriage rate (RR 0.62; 95% CI 0.43-0.91, p=0.01) compared to placebo (47).

Routine use of UFH or LMWH for patients with RPL has been heavily debated over the last few years (48). Yet, many of the RCTs initiated treatment after documentation of fetal viability. At this stage, the prognosis of pregnancy in women with RPL is excellent and approaches 80% LBR without any intervention (49). In keeping with the fact that endometrial immune and vascular remodeling begins prior to implantation, pre or peri-conception use of UFH/LMWH may be more beneficial in RPL patients. While data from the recurrent implantation failure (RIF) literature does not support peri-conception LMWH use to improve outcomes (50, 51), RIF and RPL may share different pathophysiology and extrapolation from the RIF literature does not necessarily apply to RPL. Additionally, heparin has anti-inflammatory properties through its ability to neutralize complement (33) and interfere with leukocyte chemotaxis and activation (52). Since LMWHs are fragments of the full-length heparin molecule produced by different manufacturing processes, it is likely that LMWHs differ in their anti-inflammatory properties; perhaps certain LMWH are best suited for the treatment of RPL. However, this does not seem to translate clinically as no LMWH formulation has been shown to have superior efficacy (42).

Based upon the two recently published meta-analysis, we recommend that LMWH be considered in women with ≥3 RPL and no preexisting thrombocytopenia. Patients should be regularly screened for thrombocytopenia during treatment and LMWH should be discontinued at 36 GW to mitigate any bleeding risks associated with delivery (Table 3).
**Heparin and Aspirin:**

While neither LDA nor LMWH alone improve outcomes in patients with RPL, it has been suggested that combination therapy may be more effective in improving live birth rates. This is based on the hypothesis that RPL is caused by thrombosis and inflammation of decidual vessels, leading to reduced endometrial/placental perfusion and enhanced trophoblast apoptosis. In-vitro studies have demonstrated that LDA reduces oxidative stress-induced trophoblast apoptosis (53), and that heparin acts similarly by increasing the production of anti-apoptotic proteins (54). In-vitro studies have suggested that LDA-heparin combination may be most effective in reversing trophoblast apoptosis and improving pregnancy outcomes in RPL patients; but this had not been substantiated in vivo (55) nor clinically (24, 39, 56). While the pre or peri-conception administration of LDA and LMWH would theoretically be of most immunological benefit, to our knowledge, no study has yet evaluated this dosing scheme.

**Granulocyte colony stimulating factor**

Granulocyte colony stimulating factor (G-CSF) and granulocyte macrophage colony stimulating factor (GM-CSF) production by the secretory endometrium act as a stimulus for leukocyte recruitment and differentiation and may thus indirectly promote decidualization, spiral artery remodeling (57) as well as trophoblast growth and proliferation (58). G-CSF has further immunomodulatory functions crucial for a successful pregnancy; it has been shown to downregulate uterine dendritic cell antigen presentation (59), enhance T regulatory cell differentiation and function (60) and significantly promote uterine NK cell phenotype and function (61) (Figure 2). G-CSF is generally safe and well tolerated, being associated mostly with dose-dependent musculoskeletal pain (Neupogen ® product monograph).
While colony stimulating factors seem to be an attractive treatment of RPL, the literature on the subject is scant. Eapen et al conducted a large, well designed multicenter trial, recruiting 150 patients (<38 years, BMI <35) from 21 centers with ≥ 3 consecutive or non-consecutive primary or secondary RPL. Patient were well matched and the study was adequately powered. Patients were given 130 mcg of recombinant G-CSF subcutaneously once daily (n=76) or equivalent placebo (n=74) from diagnosis of pregnancy until gestation week (GW) 12. The LBR was similar in both groups (RR 0.9; 95% CI: 0.7-1.2; p=0.48) as were adverse events and pregnancy outcomes (62). However, G-CSF was started after the diagnosis of pregnancy, which may be too late to observe any immunologic benefit. Of note, Zafardaoost et al did not find that intrauterine G-CSF administered prior to conception improved clinical pregnancy rates compared to no treatment their pilot study of 50 women with ≥ 2 miscarriages (63).

Although two studies have reported potential benefit of pre-conception subcutaneous G-CSF administration, conclusions must be interpreted with caution as they suffer from several methodological flaws. In a single center RCT, Scarpellini et al randomized 68 patients <39 years with ≥4 unexplained RPL to receive either daily subcutaneous Filgrastrim (1 ug/kg/day) from the 6th day after ovulation until the 9th week of pregnancy or a saline equivalent. The LBR was higher in the G-CSF group (OR= 5.1; 95% CI 1.5-18.4, p=0.0061), but the large confidence interval suggests that the study was not adequately powered (64). Similarly, Santjohanser et al reported that G-CSF (route of administration not specified) improved the LBR in a cohort of patients with RPL undergoing IVF compared to no treatment or treatment with LDA, LMWH, GC or doxycycline. However, treatment groups were not matched for important variables such as number of miscarriages and blastocyst transfers, limiting the validity of the study (65).

While current evidence does not support the routine use of adjuvant G-CSF for patients with RPL, one could wonder if peri-conceptual administration explains the success rates published by
Scarpellini et al. However, as demonstrated by the IVF literature, this approach has not been shown to improve live birth rates in patients with RIF (66). There is no data to suggest that G-CSF is a useful adjunct in preventing pregnancy loss in RPL patients (Table 3).

**Human chorionic gonadotropin**

After implantation, the syncytiotrophoblast secretes increasing amounts of human chorionic gonadotropin (hCG) (67). In addition to maintaining progesterone secretion from the corpus luteum during the first trimester of pregnancy, hCG is proposed to play a crucial role in mediating endometrial receptivity and modulating endometrial immune cell phenotypes during early pregnancy (68). In vitro assays have shown that hCG enhances local uterine NK cell proliferation and differentiation (57, 69), induces tolerogenic dendritic cells (70) and plays a role in the local recruitment, differentiation and suppressive function of uterine T regulatory cells (71, 72). HCG also acts on the trophoblast to promote trophoblast differentiation (73), survival (74), proliferation (75) and invasion (Figure 3).

Several studies have evaluated the efficacy of subcutaneous hCG in improving pregnancy outcomes in women with unexplained RPL. A Cochrane systematic review and meta-analysis of 5 RCT (n=596) (13, 76-79) was published in 2013. Each study compared hCG treatment against placebo or no treatment and started hCG soon after the diagnosis of pregnancy, varying widely in the dosing, length of treatment and intervals of administration of hCG. Despite high heterogeneity between RCTs, hCG appeared to decrease the rate of miscarriage compared to placebo (RR 0.51, 95% CI 0.32-0.81). However, when excluding the two oldest studies with ‘weaker methodological quality’ (76, 77), hCG benefit was no longer apparent (RR 0.74, 95% CI 0.44-1.23) (80). Of those three studies, only Harrison and El Zibdheh included patients with ≥ 3 consecutive RPL; neither study was able to demonstrate a beneficial effect of hCG (Table I). None of the included studies reported any adverse maternal or fetal side effects to hCG treatment (80).
Recently, a retrospective cohort study was published which included 98 women with ≥2 consecutive first trimester pregnancy losses, 53 of which received a single dose of subcutaneous hCG (5000 units) in the mid-luteal phase and 47 of which received no hCG. Luteal phase hCG injection was associated with an improved ongoing (>12 weeks) pregnancy rate (RR = 2.4; 95% CI 1.4–3.6; number need to treat (NNT) = 7; 95% CI 4.0-18.0) (81). However, these results must be interpreted with caution as the sample size did not reach the calculated 394 cycles required for adequate statistical power. Furthermore, the average body mass index was significantly higher in the control group than in the hCG group (31.2 vs 26.5, p=0.008). As obesity is an independent risk factor for miscarriage and an important cofounder (82), it is possible that the results reflect inherent metabolic differences between populations rather than hCG treatment effect itself. Regardless, this study introduces the important notion that peri-conceptual hCG administration may favorably impact pregnancy outcomes compared to a traditional post-conception start.

While available literature does not support the widespread use of supplemental hCG in improving pregnancy outcomes in patients with RPL, carefully selected groups may benefit from it. In fertile women with RPL undergoing a natural cycle, one dose of mid-luteal phase subcutaneous hCG can be considered (Table 3). The effectiveness of this approach remains to be demonstrated in a randomized controlled setting.

**Corticosteroids**

Because of their broad anti-inflammatory and immunosuppressive activities, synthetic glucocorticoids (GC) have been hypothesized to reverse ‘immune abnormalities’ underlying reproductive failure (83) (Figure 3). It must be noted that decidualization and implantation are
inflammatory, immune-driven processes. Leukocytes are recruited to the endometrium after ovulation and differentiate locally to take on pregnancy specific functions which include spiral artery remodeling, recognition of the implanting embryo and promoting trophoblast invasion (4). These leukocytes also influence downstream immune events which are required for the establishment of maternal tolerance to the semi-allogeneic trophoblast (3). Pre-implantation corticosteroid suppression of early immune events may thus impair endometrial receptivity, vascular adaptation and early induction of immune tolerance (84).

In terms of safety, exogenous GC administration has been associated with a wide range of side effects. In pregnancy, first trimester corticosteroids exposure is associated with an increased risk of oral cleft palate (85), gestational diabetes (86), gestational hypertension (87) and fetal adrenal suppression (88). While use of GC in pregnant women with autoimmune disease has been associated with an increased risk of pre-eclampsia, preterm delivery and low birth weight, high disease activity rather than GC use is felt to explain these adverse maternal outcomes (85, 89, 90).

Case reports have documented anecdotal success of GC administration in women with RPL (91, 92), however, larger trials have been mitigated in their outcomes. Indeed, in a prospective matched-paired study of women with ≥ 3 RPL, Tempfer et al administered preconceptual prednisone 20 mg/day until GW 12 along with progesterone and LDA (n=52) compared to 52 age-matched controls receiving no treatment. The LBR in the treatment group was higher than the control group (40/52 (77%) vs 18/52 (35%), p=0.04), however, the treatment group also received aspirin and progesterone which confounds the interpretation of the effect of prednisone. While no adverse events were recorded in the treatment group, the study was underpowered to comment on the safety of this prednisone dosing (93). Fawzy et al compared treatment with enoxaparin alone or combination of progesterone, LDA and prednisone 20 mg/d or placebo in 170 women with ≥3 RPL. Patients in the enoxaparin group (46/57; 80.7%) and patients in the combination group (45/53; 84.9%) had higher
LBR than the control group (24/50; 48%; p<0.05); the difference in the LBR in the enoxaparin and combination groups was not statistically significant. The adverse event rate was comparable across all three groups (44).

Gomaa et al compared the effectiveness of 20 mg of prednisone in combination with LDA and unfractionated heparin (UFH) in preventing miscarriage in 74 patients with ≥ 2 RPL and high peripheral blood NK cells compared to 76 matched controls receiving UFH, LDA and placebo. Patients were randomized once viable pregnancy was confirmed (<7 weeks). Successful outcomes were defined as ongoing pregnancy >20 weeks, which was achieved in 52/74 (70.3%) of patients treated with prednisone vs 7/76 (9.2%) in the placebo group (RR 7.63, 95%CI 3.71–15.7). While this study was well powered to detect differences between groups, there was no mention of the live birth rate in either group or the incidence of fetal or maternal complications. Furthermore, the miscarriage rate of 90.8% in the placebo group seems uncharacteristically high for a patient population with ≥2 miscarriages (94). Similarly, Tang et al randomized 40 women with high uterine NK cells and RPL to receive either prednisolone 20 mg at diagnosis of pregnancy or placebo. The LBR did not differ significantly between both groups (12/20 (60%) prednisolone versus 8/20 (40%) placebo, (RR 1.5; 95% CI 0.8-2.9). The study was underpowered to detect a difference in maternal or fetal side effects between both groups (95).

Finally, Laskin et al evaluated the use of prednisone for patients with a perceived high risk of immune-mediated miscarriages. They randomized 202 pregnant women with ≥ 2 RPL and the serological presence of autoantibodies (anti-nuclear, anti-DNA, anti-lymphocyte and anticardiolipin antibodies as well as the lupus anticoagulant), to receive prednisone 0.5-0.8 mg /kg and LDA for the duration of pregnancy or placebo. Treatment was started with an appropriately rising hCG and continued throughout pregnancy. The LBR in the treatment group was similar to placebo (66/101 (65%) vs 57/101 (56%), p=0.19). However, there were more pre-term births in the treatment group.
and more infants in the treatment group were admitted to the neonatal intensive care unit. There were no cases of fetal growth restriction or fetal congenital anomalies. Maternal gestational hypertension and diabetes was more frequent in the treatment group and two women receiving prednisone developed cataracts (96).

Pre-conceptual GC administration may be useful for a subset of patients with unexplained reproductive failure. However, appropriate patient selection is difficult and there are no agreed-upon characteristics or biomarkers to identify whom may benefit most (97). Recently, Lédée et al have developed an endometrial immunophenotyping assay that may be useful to determine which patients are most likely to respond to adjunct GC (97), this remains to be validated on a large scale.

The administration of GC during pregnancy must also be weighed against the plethora of maternal and fetal side effects associated with GC use. Administering a low to moderate dose (equivalent ≤20 mg of prednisone/day) prior to conception in fertile RPL patients without metabolic risk factors (BMI >30, diabetes, high blood pressure) may mitigate some of the risks associated with GC therapy. Glucocorticoids should be used at the lowest effective dose during the first trimester and tapered once the patient reached her point of previous loss. Patients should be regularly evaluated for gestational diabetes and hypertension during GC treatment (Table 3). However, there is insufficient evidence thus far that this approach improves pregnancy outcomes.

**Intralipids:**

Intralipid is a fat emulsion composed of soybean oil, egg phospholipids and glycerin used as an integral component of total parenteral nutrition (TPN). Although conflicting research suggests that intralipids may have immunomodulatory properties (Figure 3) (98-102), the clinical relevance of this is unclear (103). Intralipids are considered safe for patients requiring an alternate source of nutrition. Contra-indications to their administration include hyperlipidemia, disordered fat metabolism, liver
insufficiency and allergy to egg, peanut or soy and should only be used during pregnancy if ‘absolutely necessary to the welfare of the patient’ (Intralipid® Monograph).

Interest in intralipids began in 1991, mainly by ‘mistake’. Johnson et al were assaying trophoblast membrane infusion (TMI) for patients with RPL, using intralipids as placebo; women treated with intralipids achieved a higher successful pregnancy rate than those treated with TMI (104). Of note, in a murine model of RPL, intralipid infusion was effective in preventing abortion but at 100 times the dose that would be used in a human (105).

Only a handful of published studies have since evaluated intralipids for patients with RPL. Meng et al conducted a prospective RCT where they randomized 192 patients with ≥3 RPL and elevated peripheral blood NK cells to receive pre-conceptual IVIg or intralipids. Patients achieving at least 12 GW were comparable in both groups (intralipid 98% (70/79) vs IVIg 88.2% (67/76) p=0.415), however, no placebo group was included (106). Dakhly et al performed a RCT evaluating the use of Intralipids in patients with ≥3 RPL, secondary infertility and elevated peripheral NK cells undergoing IVF; live births were more frequent in the intralipid group (37.5%, 54/144 vs 22.4%, 34/152; p= 0.005, OR 2.082 (1.25-3.46) (107). Of note, no sample size calculation was performed for this study.

In a prospective cohort study Martini et al described the outcomes of 127 patients with RIF or RPL and elevated peripheral NK cells who received intralipid. Forty-seven patients experienced live births (37%); but when compared to a historical cohort of untreated patients with similar obstetric histories, intralipids did not increase the rates of live births (108). Similarly, Plaçais et al described an unselected cohort of patients with RPL who received Intralipid and were matched with untreated patients having similar obstetric histories. There was an increase in LBR in the Intralipid treated RPL group (Intralipid 7/10 (70%) vs control 3/20 (15%) p=0.005). However, more patients in the Intralipid
group were receiving adjunctive therapies such as LDA, LMWH and prednisone and the study was underpowered to detect meaningful differences between groups (109).

Like most forms of immunotherapy for reproductive failure, the mechanism of action of Intralipids remains unclear. Some authors suggest that Intralipid administration is an inexpensive and effective adjunctive therapy for women with reproductive failure while others have not found any effect. Patient selection and pre-conceptual treatment may be key in the improved pregnancy outcomes of the positive studies, but this remains to be proven. Intralipid is safe and well tolerated in the general population, but there is a paucity of information with its use in gravid women. Most studies document that intralipid is well tolerated during pregnancy, however, one unpublished RCT reported increased incidence of congenital anomalies and maternal adverse events in the Intralipid treated pregnancies (110). Larger studies are required to evaluate the safety of Intralipids treatment during pregnancy and there is insufficient evidence to recommend intralipids for the treatment of RPL at this time (Table 3).

**Intravenous Immunoglobulin:**

Intravenous Immunoglobulin (IVIg) is extracted from the pooled sterilized plasma of thousands of healthy donors and contains mainly polyclonal immunoglobulin G (IgG). IVIg acts as a broad immunomodulator; mechanisms explaining its potential efficacy in patients with immune mediated reproductive failure are outlined in Figure 3 (111).

Intravenous immunoglobulin is well tolerated during pregnancy and has not been associated with an increased risk of pregnancy, fetal or maternal adverse events (112-116). However, risks of side effects mirror those of the general population and are dose related. The most common immediate adverse event is post-infusion headaches (117) followed by infusion reactions; both can be prevented
by administering the IVIg as a slow infusion, hydrating the patient and providing acetaminophen pre-
medication (118). Arrhythmia, anaphylaxis and hypotension are rare complications of IVIg infusions
(118), especially with current second generation iso-osmolar preparations and with subcutaneous
immunoglobulins (119).

Delayed adverse events occur rarely and are reported in less than 1% of patients receiving high
dose IVIg. IVIg related thrombotic events (0.01-1% of patients), aseptic meningitis (1% of patients),
acute hemolysis (1/10 000 infusions) most commonly affect patients with advanced age and
underlying medical comorbidities (120-122). The incidence of delayed reactions is reduced by several
orders of magnitude in patients receiving replacement doses of IVIg (0.4-0.8 g/kg) (119). Infectious
complications are very rare with modern IVIg preparations; the risk of bacteria, virus and prion
transmission only a theoretical possibility (118, 123, 124).

Unlike other immunomodulatory therapies, many RCTs have been performed to evaluate the
effectiveness of IVIg for RPL after several case reports and case series suggested a therapeutic
benefit. However, studies are very heterogenous, making available information difficult to interpret
and to compare. IVIg use remains highly controversial for the treatment of RPL.

Hutton et al performed a systematic review of seven RCTs consisting of 442 women with
unexplained RPL (125-131). Meta-analysis did not find that IVIg significantly improved LBR over
placebo (OR 1.28, 95% CI 0.78–2.10; p=0.33). However, subgroup analysis from 2 studies (n=102)
suggested benefit if started prior to conception (LBR: OR 2.39, 95% CI 1.08–5.33; p=0.03)(127, 129);
and in women with secondary RPL (4 RCT, n=195; LBR: OR 2.71; 95% CI 1.09–6.73, p=0.03) (126,
129-131). Side effects and obstetrical or neonatal complications were similar in both IVIg and placebo
treated pregnancies (132). Ata et al included 6 trials in their systematic review (125, 127-130, 133).
IVIg was not found to be beneficial for primary RPL (OR 0.67; 95% CI, 0.32-1.39) or for secondary
RPL (OR 1.15; 95% CI, 0.47–2.54). A dose response to IVIg was not observed and IVIg was not found to be effective if started prior to conception (3 studies; OR 1.21, 95% CI, 0.58–2.51) or after conception (3 studies; OR 0.71, 95% CI, 0.34–1.47)(134).

Egerup et al updated the above systematic reviews and meta-analysis and included 11 RCTs consisting of 531 women with RPL (125, 126, 128, 130, 131, 133, 135-137). While no difference in terms of 'no live birth' (RR: 0.92, 95% CI 0.75-1.12, p = 0.42) was found between IVIg and placebo treated groups, this study was underpowered to detect a difference between patient groups. Upon subgroup analysis, there was no benefit for IVIg at higher dose, in women with secondary RPL or in women with a high number of miscarriages. Adverse maternal, fetal and obstetrical outcomes were similar in both placebo and IVIg treated groups, although mild adverse events such as fever, headache, itching and rash were more frequent in women receiving IVIg (9 trials, 451 women; RR: 1.54, 95% CI 1.13–2.11, p=0.006) (138).

Finally, the most recent meta-analysis on the subject was conducted by Wang et al. Eleven RCTs and 582 women having experienced ≥ 2 consecutive RPL were included in the analysis (125-131, 133, 137, 139, 140). Random-effect analysis did show an overall marginally significant difference in terms of live birth with IVIg treatment (RR = 1.25, 95% CI 1.00 to 1.56; p=0.05). Upon subgroup analysis, 5 studies (n=213) started IVIg prior to conception; there was a significant difference in LBR in women treated with IVIg (RR = 1.67, 95% CI 1.30 to 2.14; P < 0.0001). This was not observed in 7 studies (369 women) who received IVIg after conception (RR = 1.10, 95% CI 0.93 to 1.29, p=0.27)(141).

IVIg has been used for over 50 years for the empiric and off-label treatment of women with RPL. Despite over a dozen of RCTs being published on the subject, studies have failed to demonstrate consistent benefit of IVIg over placebo. Unfortunately, due to the heterogeneity of the available
literature and the small numbers of patients included in RCTs, it is difficult to conduct a systematic review or meta-analysis and draw any firm conclusions. While starting IVIg after the diagnosis of pregnancy is ineffective, pre-conception administration may improve LBR in select patients with unexplained RPL. Indeed, some clinics routinely use IVIg and guidelines exist recommending IVIg for patients with RPL with immunologic anomalies (142). However, IVIg is a blood product and as such associated with potential shortages and high cost. Preconception start of IVIg can be considered in well selected patients with RPL who have failed euploid pregnancies and previous immunomodulation (Table 3).

**Other immunomodulatory treatments:**

Lymphocyte immunotherapy (LIT) involves isolating lymphocytes from an allogenic donor (usually the male partner) and injecting them into the potential mother to induce immunologic tolerance to paternal antigens (143). LIT was popular until a 2014 meta-analysis of 12 RCT (n=641) failed to demonstrate a beneficial effect on LBR in women with ≥ 3 unexplained RPL compared to placebo (144). These finding have recently been challenged by two other meta-analysis which included heterogenous data from RCT, controlled clinical trials, review articles and prospective cohort studies in women with ≥ 2 unexplained RPL (145, 146). LIT was historically associated with significant side effects in up to 8% of patients, including systemic reactions and viral infections such as primo infection with hepatitis and CMV (145, 146). Improved viral screening procedures have decreased infectious risks (143), however, patient selection, mode of administration, lymphocyte source and dose remain to be determined. LIT has largely been abandoned in North America and should only be offered to patients in a research setting and where rigorous infection control protocols can be respected.

Tumor necrosis factor inhibitors (TNFi) are monoclonal antibodies that target both soluble and membrane bound tumor necrosis factor α (TNFα). Their use in reproductive failure stems from the
theory that overexpression of TNF-α during early pregnancy enhances trophoblast death (147), antagonizes survival promoting growth factors (148) and inhibits trophoblast migration and invasion (149, 150). While TNFi use during pregnancy is safe and well tolerated when there is a legitimate medical indication for its use (151, 152), TNFi are associated with a plethora of side effects. Post-marketing surveillance of TNFi has identified rare instances of lymphoma (153) and an enhanced risk of serious infections, opportunistic infections and reactivation of latent infections (154). Other rare side effects include drug induced Lupus, infusion type reactions, anaphylactoid reactions, liver enzyme elevation (155) and ischemic heart disease (156). Evidence for TNFi use is scant and includes anecdotal success from case reports (157) and one small retrospective cohort study which failed to detect any benefit of combining IVIg with TNFi versus IVIg alone in 54 women with ≥ 3 RPL (158). TNFi should not be used as adjunctive treatment in women with unexplained RPL.

Other agents such as Tacrolimus and Hydroxychloroquine are also being used to treat RPL. Their effectiveness for improving pregnancy outcomes in patients with reproductive failure is anecdotal (159, 160) or hypothetical and mainly extrapolated from retrospective studies in which women with maternal auto-immune disease or organ transplantation required the continuation of these drugs during pregnancy (161, 162). The safety of Tacrolimus and Hydroxychloroquine has not been established in healthy women without a medical indication for them. However, a large randomized controlled trial is currently underway, aiming to determine the effectiveness of Hydroxychloroquine in preventing miscarriage in women with recurrent pregnancy loss (163). The authors are not aware of such planned studies for Tacrolimus.

**Conclusion and future perspectives:**

The immune adaptation to pregnancy is complex and involves a series of checks and balances to ensure vascular adaptation, adequate trophoblast invasion and tolerance to the antigenically dissimilar
fetus. While a dysfunctional immune response probably underlies reproductive failure in a subset of patients, the mechanisms by which this can occur are multiple and it is likely that immune treatment must be individualized to fit the specific pathology. Unfortunately, to date, immune modulation has led to disappointing clinical results. Immune-mediated RPL remains a diagnosis of exclusion, and no validated or readily available biomarkers currently exist to confirm it. As such, adequate patient selection for clinical trials is difficult, partly explaining why even well designed RCTs often fail to find significant differences between treatment and control groups. Most treatment recommendations are thus not evidence-based and mainly directed by expert opinion, physician gestalt and patient safety.

Emerging data suggests that immunomodulation may be more beneficial in women with RPL and evidence of autoantibodies (164), elevated NK cell numbers or cytotoxicity (165-167) and increased Th1/Th2 ratios (168, 169). However, it is unclear if peripheral blood immune parameters adequately reflect local endometrial immune events, and the validity of such testing has been questioned (170). A more recent approach involves mid-luteal phase endometrial immunophenotyping using markers of immune over-activation or under-activation to individualize immunomodulatory treatments (171, 172). While this approach remains to be standardized, reproducible and widely available, it could represent a useful adjunct to patient selection for future studies.

The field of reproductive immunology is gaining much attention and perhaps diagnostic testing and individualized medicine will be possible in the foreseeable future. This is relevant as patients with unexplained RPL represents a vulnerable population who will embark on experimental therapies if there is a chance for live birth. It is our obligation as physicians to manage their expectations and ensure their safety. While innovation is important, it should not be done at the expense of the patient without clear rationale for treatment efficiency and safety.


Abbreviations.

Arg1: Arginase 1
Arg 2: Arginase 2
DC: dendritic cell
dNK: decidual NK cells
E2: Estrogen
FGF2: fibroblast growth factor 2
GC: glucocorticoids
G-CSF: granulocyte colony stimulating factor
hCG: human chorionic gonadotropin
IFNγ: Interferon gamma
IL: interleukin
IP-10: Interferon gamma-induced protein 10
IVlg: Intravenous immunoglobulin
LDA: low dose aspirin
LMWH: low molecular weight heparin
MMP: matrix metalloproteases
NK cell: natural killer cell
P4: progesterone
PBMC: peripheral blood mononuclear cells
PIBF progesterone-induced blocking factor
PPAR: peroxisome proliferator activated receptors
TGFβ: Transforming growth factor beta
TNFα: Tumor necrosis factor alpha
TNFR: Tumor necrosis factor receptor
Treg: T regulatory cell
VEGF: vascular endothelial growth factor


Table 3: Summary of Recommendations

Figure 1: Implantation is a controlled inflammatory response. 1) After ovulation, the ovarian production of estrogen (E2) and progesterone (P4) acts on the endometrium to induce the differentiation of endometrial stromal cells into decidual stromal cells which produce interleukin-15 (IL-15). 2) This provides a stimulus for the recruitment and local differentiation of decidual NK cells (dNK cells) which possess receptors that mediate embryo recognition and secrete cytokines (IL-10, IP-10, TNFα, G-CSF) required to activate and control trophoblast invasion. 3) Decidual NK cells also participate in spiral artery remodeling through the production of pro-angiogenic factors (VEGF, Arg1, Arg2) and cytokines (IFNγ, TGFβ). 4) Phenotypically diverse macrophage populations are also recruited to the decidualizing endometrium. They assist trophoblast invasion through the secretion of matrix metalloproteases (MMP-7, MMP-9) which disrupt vascular smooth muscle and endothelial cells. Decidual macrophages are involved in tissue repair around the sites of implantation and are thought to scavenge apoptotic trophoblastic cells, thus limiting maternal exposure to alloantigen during implantation. 5) Both decidual macrophages and dNK cells promote maternal tolerance though their ability to regulate adaptive maternal immune responses and promote T regulatory cells (Treg).

Figure 2: Proposed mechanisms of action of immunomodulatory treatment for reproductive failure

Increasing progesterone (P4) levels triggers decidualization and influx of leucocytes to the decidua. Progesterone acts through leukocyte P4 receptors or through the action secreted progesterone-induced blocking factor (PIBF) on immune
Both P4 and PIBF induce immunomodulatory cytokine secretion by T-cells, favoring differentiation of NK cells into uterine NK cells, decrease uterine recruitment and activation of neutrophils and promote a tolerogenic M2 macrophage phenotype early in pregnancy.

Low dose aspirin (LDA) acts by inhibiting COX-1, inducing the production of leukotrienes, lipoxins and resolvins; and by modifying COX-2 to produce potent anti-inflammatory lipoxins. These metabolites inhibit pro-inflammatory cytokine production and cellular response to inflammation in leukocytes and lymphocytes. LDA may promote the upregulation of regulatory T cells.

Heparin is thought to bind and sequester pro-inflammatory chemokines and cytokines, prevent complement activation and inhibit leukocyte migration into inflamed tissue. Heparin fragments can bind to pro-angiogenic molecules (VEGF, FGF2) and may stimulate angiogenesis and promote tissue repair. LMWH also binds non-specifically to macrophages, endothelial cells, platelet factor 4 and may also exhibit anti-inflammatory properties and promote wound repair.

G-CSF stimulates leukocyte recruitment to the endometrium and plays a role in promoting decidualization, enhancing endometrial receptivity as well as vascular remodeling and angiogenesis. G-CSF also has an immunomodulatory role through downregulating antigen presentation, enhancing T regulatory responses and promoting uterine NK cell function.

Figure 3: Proposed mechanisms of action of immunomodulatory treatment for reproductive failure

HCG enhances endometrial receptivity, angiogenesis and maintains progesterone secretion from the corpus luteum during the first trimester of pregnancy. HCG acts on immune cell phenotypes to promote a tolerogenic response to the implanting embryo and promotes trophoblast survival.

Exogenous Glucocorticoids (GC) have been shown to influence up to 20% of genes expressed in leucocytes. They have potent anti-inflammatory actions, decreasing the production of pro-inflammatory cytokines, prostaglandins and leukotrienes. GC decrease the ability of leukocytes to migrate to inflamed tissue and can induce apoptosis of activated T cells.

Intralipids can bind PPAR receptors on macrophages and dendritic cells (DC), decreasing pro-inflammatory cytokine generation (IL-1, TNF-α) and CD1 restricted T cell activation respectively. Intralipids may also reduce NK cell cytotoxicity.

Intravenous immunoglobulin (IVIg) can neutralize pro-inflammatory cytokines and complement proteins as well as their receptors, thus inhibiting their downstream inflammatory effects. IVIg also acts on various effector immune cells to increase their activation threshold and reduce their trafficking into target tissue. IVIg enhances immune tolerance by inducing immunomodulatory cytokine production from monocytes and increasing the polyclonal expansion and suppressive functions of Tregs.
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<tr>
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<th>Outcome</th>
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<td>≥ 3 RPL</td>
<td>Treatment n=404</td>
<td>Control n=432</td>
<td>Treatment: 400 mg BID intravaginal micronized progesterone at diagnosis of pregnancy until GW12</td>
<td>LBR similar in both groups: RR 1.04, 95% CI: 0.94-0.15)</td>
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<td>Subgroup analysis (5 RCT)</td>
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<td>Treatment n=670</td>
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<td>Reduced miscarriage rate in progestosterone group (RR 0.59, 95% CI 0.34-1.01)</td>
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<td>&lt;40 years of age</td>
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<td>Control: equivalent placebo</td>
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<td>Naimi 2021</td>
<td>RCT</td>
<td>1-2 pregnancy losses</td>
<td>Treatment: Aspirin 80 mg prior to conception until GW 36, adherent to per-protocol treatment</td>
<td>LBR higher in compliant ASA group: RR 1.33, 95% CI 1.08-1.64</td>
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<td>Treatment n=313</td>
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<td>LDA may improve LBR if started prior to conception in a compliant patient</td>
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<td>Treatment: Enoxaparin 40 mg s/c daily at detection of fetal heartbeat until GW 37</td>
<td>LBR similar in both groups: RR 0.92, 95% CI 0.58-1.46</td>
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<td>Badawy 2008</td>
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<td>No evidence that LMWH improves LBR or reduces miscarriage rate</td>
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<td>Treatment n=170</td>
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<td>Control: Aspirin 100 mg</td>
<td>Early miscarriage (OR 1.41, 95% CI 0.16-1.2) and late miscarriage (OR 1.21, 95% CI 0.06-3.18) similar between groups</td>
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<td>Treatment n=78</td>
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**Granulocyte colony stimulating factor**

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<td><strong>Human chorionic gonadotropin</strong></td>
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<td>Treatment: IM Pregnyl 10 000 IU at diagnosis of pregnancy, 5000 IU twice weekly until GW 12, 5000 U once weekly until GW 16</td>
<td>LBR similar between groups: hCG 30/36 (83%) Control 31/39 (79%) p=0.45</td>
<td>No evidence that hCG initiated after pregnancy diagnosis improves LBR</td>
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<td>RCT</td>
<td>Treatment: prednisone 20 mg/d + progesterone 20 mg/d from diagnosis of fetal pole until GW 12 + aspirin 75 mg/d until GW 32</td>
<td>LBR in both treatment groups was similar and higher than in the placebo group Treatment: 45/53 (84.9%) Control: 46/57 (80.7%) Placebo: 24/50 (48%) *p&lt;0.05</td>
<td>No evidence that prednisone is superior to LMWH</td>
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<td><strong>Intralipids</strong></td>
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<td>Meng 2016</td>
<td>RCT</td>
<td>Treatment: 20% intralipid (250 ml) started on day 3 of cycle, then q 2 weeks before pregnancy and weekly until GW12</td>
<td>Pregnancy rate after GW12 similar between groups Treatment: 70/79 (88%) Control: 67/81 (82%) p=0.415</td>
<td>Intralipid may be considered for patients with RPL in a research setting</td>
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<tr>
<td>Dakhly 2016</td>
<td>RCT</td>
<td>Treatment: 20 ml Intralipid 20% on the day of oocyte retrieval, then weekly until GW12</td>
<td>LBR higher in the treatment group: 54/144 (37.5%) Control: 34/152 (22.4%) p= 0.005; OR 2.08 (1.25-3.46)</td>
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<tr>
<td>Study</td>
<td>Year</td>
<td>Type</td>
<td>No. of RCTs</td>
<td>No. of RPLs</td>
<td>Treatment</td>
<td>Control</td>
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<tr>
<td>Hutton</td>
<td>2007</td>
<td>Meta-analysis</td>
<td>7</td>
<td>≥ 2</td>
<td>Treatment: heterogenous IVIg protocols</td>
<td>Control: equivalent placebo (saline or albumin)</td>
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<td>Ata</td>
<td>2011</td>
<td>Meta-Analysis</td>
<td>6</td>
<td>≥ 2</td>
<td>Treatment: heterogenous IVIg protocols</td>
<td>Control: equivalent placebo (saline or albumin)</td>
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<td>Egerup</td>
<td>2015</td>
<td>Meta-Analysis</td>
<td>11</td>
<td>≥ 2</td>
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<tr>
<td>Intervention</td>
<td>Recommendations</td>
<td>Treatment considerations</td>
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<tr>
<td>Progesterone</td>
<td>Consider for all patients with $\geq 2$ RPL</td>
<td>Luteal phase start may be more beneficial than post-conception administration</td>
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<td>Low dose Aspirin (LDA)</td>
<td>Consider starting LDA prior to conception for all patients with $\geq 2$ RPL and in patients with $\geq 1$ miscarriage with elevated baseline CRP</td>
<td>Ensure adequate patient compliance to LDA during treatment</td>
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<td>Low molecular weight heparin (LMWH)</td>
<td>Consider in women with $\geq 3$ RPL and no pre-existing thrombocytopenia</td>
<td>Start LMWH at diagnosis of pregnancy, preconception start can be considered for patients with biochemical losses</td>
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<td>Regularly screen for thrombocytopenia during treatment</td>
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<td>Stop LMWH at GW 36 or earlier if risk of pre-term delivery</td>
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<td>Granulocyte colony stimulating factor (G-CSF)</td>
<td>There is no evidence for adjunct G-CSF for RPL women</td>
<td>Post conception administration is not effective in improving LBR</td>
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<td>Luteal phase administration may be effective but remains to be assessed in a randomized controlled setting.</td>
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<td>Human chorionic gonadotropin (hCG)</td>
<td>Mid-luteal phase dose can be considered in fertile patients with $\geq 3$ RPL attempting a natural conception</td>
<td>Use lowest effective dose ($\leq 20$ mg prednisone/day), gradually taper once patient reaches her point of previous loss</td>
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<td>Regular evaluation for gestational diabetes and hypertension</td>
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<td>Glucocorticoids (GC)</td>
<td>Can be considered patients with $\geq 3$ RPL and no metabolic risk factors (BMI $&gt;$ 30, diabetes, hypertension)</td>
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<td>Intralipids</td>
<td>There is no evidence for adjunct Intralipids for RPL women</td>
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<td>Intravenous Immunoglobulin (IVlg)</td>
<td>Can be considered patients with $\geq 3$ RPL who have failed proven euploid pregnancies and previous immunomodulatory treatment</td>
<td>IVlg should be initiated prior to conception</td>
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<td>First trimester serologies (hepatitis B and Rubella) should be obtained prior to IVlg treatment</td>
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</tbody>
</table>
Progestosterone

Decidualization

Angiogenesis

G-CSF

Heparin

Leukotrienes

Cox-1

Cox-2

Aspirin

Proinflammatory cytokines

Leukoreceptor recruitment and differentiation

Immunomodulatory Cytokines

Tissue repair

Inflammation