# Evidence for the effectiveness of immunologic therapies in women with subfertility and/or undergoing assisted reproduction

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Implantation is a critical step in the establishment of a successful pregnancy, depending on a complex immune-endocrine dialogue between the developing embryo and maternal endometrium. Research suggests that altered immunity in the maternal decidua results in implantation impairment and failure. Immunomodulatory drugs have, thus, been widely used in assisted conception to aid embryo implantation, despite an absence of consensus on their effectiveness and safety. We conducted a systematic review and meta-analysis of interventional studies investigating the use of immunomodulators in women undergoing assisted reproduction. Evidence was uncertain of an effect for most of the included interventions, owing to heterogeneous findings and a paucity of high-quality studies. For certain patient subgroups, however, the use of specific immunomodulatory therapies may offer some benefit. There is a need for further large randomized controlled trials to corroborate these findings. (Fertil Steril® 2022;117:1144–59. ©2022 by American Society for Reproductive Medicine.)

**Key Words:** Immunomodulatory drugs, implantation, infertility



The number of patients undergoing assisted reproductive technology (ART) for fertility treatment continues to increase. Yet, despite advances over the past decades, most ART cycles do not result in a live birth. Even when chromosomally normal embryos are transferred, only approximately 50% will implant (1). Implantation failure remains the likely outcome of most in vitro fertilization (IVF) cycles, and approximately 10% of women undergoing IVF are thought to experience recurrent implantation failure (RIF), although there remains no universally agreed definition (2).

Critical to successful implantation is the adequate decidualization of the endometrium. Endometrial immune cells are key to the transformation of the decidua into a receptive mucosa that will permit embryo attachment and implantation. This highly regulated response involving an influx of innate immune cells, including macrophages, dendritic cells, and neutrophils, in addition to a large population of natural killer (NK) cells, results in an inflammatory environment at the time of conception and implantation (3). However, this response is dynamic; recent data indicate that by the early first trimester, maternal immune inflammatory responses are restrained and modulated by complex and diverse signaling between fetal trophoblast cells and decidual immune cells (4).

Given the complexity of the implantation process, several factors may contribute to the failure of an embryo to implant, not least embryo aneuploidy. However, there has been much focus both in the scientific community and from patients on how the maternal immune response influences implantation and whether modulating maternal immunity can improve the ART success rates. For some patients and clinicians, the concept of embryo rejection has been an attractive one, on the basis of the knowledge that a specialized type of NK cell is the predominant immune cell in the peri-implantation endometrium. This concept of embryo rejection has often been given unscientific credibility simply because of its name.

Immunomodulators may be offered empirically to patients with a history of

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implantation failure where a clinician believes that there may be an immune mechanism underlying this or because specific immune cell testing has been undertaken and found to be abnormal. Blood NK cell testing (with or without associated cytotoxicity assays) is commonly offered, despite the fact that circulating NK cells are phenotypically and functionally different from their specialized endometrial counterparts (5) and their numbers are not correlated with endometrial NK cells (6). Neither blood nor endometrial NK cells have been robustly demonstrated to be associated with subfertility or RIF (7). After some studies reported alterations in the expression of T helper (Th)1 and Th2 cytokines in circulating T cells, tests including measurement of Th1/Th2 cytokine ratios have also found their way into clinical practice (8–10). Others have reported an association between RIF and altered ratios of cytokine messenger ribonucleic acid within the endometrium, including interleukin (IL-)15, IL-18, and tumor necrosis factor (TNF)-like weak inducer of apoptosis, hypothesizing that immunomodulators may improve the implantation rates in such patients (11). Additionally, some clinics test for autoantibodies, such as antinuclear, antiphospholipid, and thyroid autoantibodies. Although there may be associations with autoantibodies and infertility, causal links remain to be established (12).

Immunologic treatments have been used for decades in ART. Recent data have shown that up to 1 in 4 women undergoing IVF treatment may use add-on therapies, such as aspirin, heparin, or corticosteroids (13–16). Although less commonly used, other drugs, such as intralipid, intravenous immunoglobulin (IVIG), granulocyte colony-stimulating factor (G-CSF) and TNF alpha (TNF-$\alpha$) inhibitors, are also administered to ART patients (15).

We have systematically reviewed the literature to evaluate the effectiveness and safety of immunomodulatory therapies used commonly in clinical practice and consider their potential mechanisms of action in the context of subfertility, ART, and implantation failure. We included randomized and nonrandomized interventional full-text studies where outcome data were reported per participant. Trials investigating participants with recurrent pregnancy loss were excluded. The primary effectiveness outcome considered in this review was the composite rate of ongoing pregnancy rate (OPR) or live birth rate (LBR) per participant. Ongoing pregnancy was defined as a viable intrauterine pregnancy at $\geq$12 weeks of gestation identified on ultrasound, and live birth was defined as the delivery of a live fetus after 22 weeks of pregnancy (17). Where possible, we performed meta-analysis of randomized controlled trials (RCTs) using a random-effects model and considered heterogeneity to be substantial where $I^2 > 50\%$. Subgroup analyses were also undertaken where data were available for women with previous implantation failure, known autoimmunity, and conditions hypothesized to be associated with an altered inflammatory response (e.g., elevated NK cell activity or numbers).

## ASPIRIN

Low-dose aspirin is one of the most widely used adjuvants in ART (15). Aspirin inhibits cyclooxygenase (COX) in platelets, preventing the conversion of arachidonic acid into prostaglandins and, thus, inhibiting thromboxane production (18). There are 2 types of COX: 1 and 2. By irreversibly inhibiting both COXs 1 and 2, aspirin may improve uterine and ovarian blood flow and reduce inflammation, all of which may enhance fertility or the success of ART (19, 20).

There have been numerous studies investigating aspirin for women with subfertility undergoing ART (21–23). We identified 12 studies that reported the OPR or LBR comparing the use of aspirin vs. a placebo or no intervention (21, 24–34) (Table 1). Most of the 6 nonrandomized studies reported uncertain findings (21, 24–27) except for that of Frattarelli et al. (28), where the use of aspirin was associated with a 20% increase in the LBR compared with that of placebo (relative risk [RR], 1.20; 95% confidence interval [CI], 1.04–1.38). The 6 RCTs that reported the OPR or LBR included 1,319 participants (29–34). Meta-analysis of these RCTs showed that aspirin probably makes little or no difference to the OPR or LBR (RR, 1.04; 95% CI, 0.81–1.33; 6 RCTs; $I^2 = 28\%$; moderate-certainty evidence) (Fig. 1 and Table 2). None of these studies reported significant adverse events although aspirin is known to be associated with gastrointestinal disturbances and bleeding. Albeit very commonly used by women undergoing ART, we did not find evidence that aspirin improved pregnancy outcomes. In addition, the subgroup analyses of good-prognosis patients, women with at least 1 previous implantation failure or a thin endometrium did not alter these findings, and therefore, recommending aspirin to patients undergoing ART to date has no evidence-based justification.

## HEPARIN

In addition to its antithrombotic effects, there are several mechanisms by which heparin has been hypothesized to influence implantation. Both unfractionated heparin and low-molecular-weight heparin (LMWH) modulate insulin-like growth factors 1 and 2, which in turn may facilitate trophoblast invasion. Heparin may also increase the decidual expression and secretion of heparin-binding epidermal growth factor, which has been shown to promote an invasive trophoblast phenotype (35). In addition, heparin may promote trophoblast invasion by inducing matrix metalloproteinase activity with a concomitant suppression of tissue inhibitors of matrix metalloproteinases (36, 37).

Three cohort studies reported uncertain findings as to the effect of heparin on the LBR (21, 38, 39). Additionally, we identified 3 RCTs including 386 women that reported the LBR (40–42). Our meta-analysis did not demonstrate an increase in the LBR in patients receiving subcutaneous LMWH, although the quality of the evidence was assessed as being of very low certainty (RR, 1.55; 95% CI, 0.80–3.00; 3 RCTs; $I^2 = 51\%$) (Fig. 1 and Table 2).

Heparin is a drug with a good safety profile in pregnancy. Nevertheless, the evidence to date does not support its use routinely in women with subfertility. Importantly, heparin may cause bruising and discomfort around the injection site as well as bleeding, although in the studies included in this analysis, adverse events were reported in

## TABLE 1

**Characteristics of included studies reporting on the ongoing pregnancy or live birth rate.**

| Interventions | Study | Country | Design | Duration | Population | Inclusion criteria | Subgroup | Total analyzed | Outcome |
|---|---|---|---|---|---|---|---|---|---|
| Aspirin | Chen et al. (2017) (24) | People's Republic of China | Prospective cohort | January 2015 to December 2015 | IVF | Age of <40 y; serum autoantibodies; normal karyotype; no infectious diseases; normal basal level of hormones; normal uterine anatomy | Autoimmunity | 76 | LBR |
| | Dirckx et al. (2009) (29) | Belgium | RCT | Unstated | IVF | First IVF/ICSI cycle | Unselected | 201 | LBR |
| | Frattarelli et al. (2006) (28) | USA | Retrospective cohort | January 2000 to August 2003 | IVF | Egg recipient cycles | Low ovarian response | 460 | LBR |
| | Frattarelli et al. (2008) (25) | USA | Retrospective cohort | January 2000 to July 2006 | IVF | Low-responding women | Low ovarian response | 1,250 | LBR |
| | Gizzo et al. (2014) (26) | Italy | Prospective cohort | January 2010 to December 2012 | IVF | Age of 25–45 y; normal ovarian response; previous 1–2 failed IVF/ICSI cycles | Previous IF (≥1) | 206 | OPR |
| | Haapsamo et al. (2010) (30) | Finland | RCT | Unstated | IVF | Age of <40 y; <4 ovarian stimulations; no contraindications for aspirin | Good prognosis | 487 | LBR |
| | Hurst et al. (2005) (27) | USA | Retrospective cohort | 1995 to 2001 | IVF | Unstated—consecutive cycles | Unselected | 316 | LBR |
| | Lambers et al. (2009) (31) | The Netherlands | RCT | Unstated | IVF | Age of <39 y; FSH level of ≤10 IU/L; ≥1 previous failed IVF/ICSI treatment | Previous IF (≥1) | 169 | OPR |
| | Madani et al. (2019) (32) | Iran | RCT | May 2012 to February 2015 | IVF | Age of <40 y; FET; no history of uterine surgery; no uterine disorders, endometriosis, RPL or contraindications to aspirin | Good prognosis | 60 | LBR |
| | Pakkila et al. (2005) (33) | Finland | RCT | 2000 to 2003 | IVF | Age of <40 y; <4 previous ovarian stimulation cycles; no contraindication for aspirin | Good prognosis | 374 | LBR |
| | Weckstein et al. (1997) (34) | USA | RCT | September 1993 to January 1995 | IVF | Oocyte recipient cycles; thin endometrium (<8 mm); normal uterine cavity | Thin endometrium | 28 | LBR |
| LMWH (subcutaneous) | Berker et al. (2011) (38) | Turkey | Prospective cohort | June 2007 to October 2009 | IVF | 2 previous IFs; normal uterine; normal hormone profile; negative thrombophilia screening | Previous IF (≥1) | 207 | LBR |
| | Noci et al. (2011) (40) | Italy | RCT | May 2008 to December 2008 | IVF | Age of <40 y; no congenital or acquired thrombophilia; no recent treatment with LMWH; no endocrine/hematologic abnormalities, chronic diseases, or tubal or uterine pathology interfering with embryo implantation | Good prognosis | 153 | LBR |
| | Qublan et al. (2008) (41) | Jordan | RCT | October 2004 to March 2006 | IVF | Age of 19–35 y; ≥3 previous IVF failures; basal FSH level of ≤10 IU/L; BMI of 19–29 kg/m$^2$; presence of both ovaries; ≥3 previous IVF failures; good-quality embryos for transfer; endometrial thickness of 8–14 mm; GnRH agonist down-regulation protocol | Previous IF (≥1) | 83 | LBR |
| | Urman et al. (2009) (42) | Turkey | RCT | January 2006 to May 2008 | IVF | ≥2 failed previously fresh embryo transfer cycles; age of ≤38 y; fresh ejaculate sperm to be used for ICSI; no hormonal, coagulation, or immunologic disorders; normal uterine cavity as assessed by hysteroscopy or saline infusion sonography; normal female and male peripheral karyotype | Previous IF (≥1) | 150 | LBR |
| | Siristatidis et al. (2018) (39) | Greece | Retrospective cohort | February 2012 to June 2017 | IVF | Age of 25–40 y; BMI of 19–35 kg/m$^2$; ≥2 failed fresh IVF/ICSI cycles followed by embryo transfer of at least 2 very-good-quality embryos on day 3; basal FSH level of ≤12 mIU/mL; absence of coagulation and/or autoimmune disorders | Previous IF (≥1) | 230 | LBR |

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## TABLE 1

**Continued.**

| Interventions | Study | Country | Design | Duration | Population | Inclusion criteria | Subgroup | Total analyzed | Outcome |
|---|---|---|---|---|---|---|---|---|---|
| Corticosteroids | Bider et al. (1996) (49) | Israel | RCT | February 1993 to December 1994 | IVF | FET; normal uterus; tubal occlusion; normal hormone profile; normal SFA | Good prognosis | 99 | LBR |
| | Bider et al. (1999) (48) | Israel | Retrospective cohort | Unstated | IVF | PCOS; irregular menstrual cycles; failure of clomiphene citrate or hMG/hCG treatment; LH/FSH ratio of >2; high DHEAS and testosterone levels | Good prognosis | 71 | LBR |
| | Litwicka et al. (2015) (51) | Italy | RCT | January 2011 to April 2012 | IVF | Age of <40 y; BMI of 18–29 kg/m$^2$; thyroid autoimmunity; regular (21–35 days) menstrual cycles; presence of both ovaries; normal ovarian reserve; normal ovaries on ultrasound | Autoimmunity | 60 | LBR |
| | Moffitt et al. (1995) (50) | USA | RCT | January to September 1993 | IVF | Unselected | Unselected | 206 | LBR |
| | Ozmen et al. (2018) (47) | Turkey | Retrospective cohort | January 2010 to June 2013 | IVF | Age of 18–40 y; first IVF cycle only; normal baseline hormone profile; tubal or unexplained infertility; ICSI treatment | Good prognosis | 964 | LBR |
| | Turi et al. (2010) (52) | Italy | RCT | January 2006 to August 2008 | IUI | Age of 20–38 y; positive antithyroid antibodies; ≤2 previous ART cycles; regular menstrual cycles of 24–35 days; BMI of 17–29 kg/m$^2$; no treatment with clomiphene citrate or gonadotropins within 1 month before the date of recruitment; normal uterine cavity; bilateral tubal patency | Autoimmunity | 48 | LBR |
| | van Kasteren et al. (1999) (53) | the Netherlands | RCT | Unstated | OI-TI | Age of 18–40 y; idiopathic premature ovarian failure; normal karyotype; no history of radiotherapy or chemotherapy. | Low ovarian response | 36 | LBR |
| Aspirin plus corticosteroid | Revelli et al. (2008) (56) | Italy | RCT | October 2002 to April 2006 | IVF | Age of ≤40 y; first IVF/ICSI cycle; only fresh embryo transfer cycles | Good prognosis | 395 | OPR |
| G-CSF (intrauterine) | Eftekhar et al. (2016) (67) | Iran | RCT | March to September 2015 | IVF | Age of 18–40 y; normal endometrial thickness | Good prognosis | 113 | OPR |
| | Huang et al. (2020) (68) | People's Republic of China | RCT | December 2015 to July 2017 | IVF | Age of ≤38 y; BMI of 18–24 kg/m$^2$; primary infertility; previous IF (≥2); normal endometrial thickness (8–16 mm); 2 or more frozen embryos available | Previous IF (≥1) | 104 | LBR |
| | Jain et al. (2018) (69) | India | RCT | Unstated | IVF | Age of 21–38 y; BMI of 18.5–29.9 kg/m$^2$; normal hormone profile | Good prognosis | 150 | OPR |
| | Kalem et al. (2020) (70) | Turkey | RCT | March 2016 to December 2017 | IVF | Age of <40 y; ≥3 previous IFs; FSH level of<15 mIU/mL | Previous IF (≥1) | 173 | LBR |
| | Kunicki et al. (2017) (65) | Poland | Prospective cohort | October 2011 to October 2014 | IVF | Thin endometrium; FET; previously cancelled IVF due to thin endometrium (<7 mm); previous treatment of unresponsive endometrium with oral/vaginal estradiol, sildenafil citrate, or aspirin; lack of contraindications for G-CSF treatment; own embryo FET | Thin endometrium | 62 | LBR |
| | Mao et al. (2020) (71) | People's Republic of China | RCT | March 2017 to May 2018 | IVF | Age of 20–42 y; BMI of 20–28 kg/m$^2$; FET; regular menstrual cycles; normal hormone profile; thin endometrium (<7 mm) or mild to moderate intrauterine adhesions; no contraindications for G-CSF treatment; no fibroids, polyps or PCOS; availability of at least 2 good-quality embryos | Thin endometrium | 304 | LBR |
| | Xu et al. (2015) (66) | People's Republic of China | Prospective cohort | July 2012 to July 2013 | IVF | Age of <40 y; FSH level of <10 IU/L; endometrial thickness of <7 mm; no uterine malformations; no contraindications for G-CSF treatment | Thin endometrium | 66 | LBR |

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## TABLE 1

Continued.

| Interventions | Study | Country | Design | Duration | Population | Inclusion criteria | Subgroup | Total analyzed | Outcome |
|---|---|---|---|---|---|---|---|---|---|
| G-CSF (subcutaneous) | Arefi et al. (2018) (73) | Iran | RCT | May 2010 to October 2015 | IVF | Age of 22–44 y, previous IF (>2) | Previous IF (≥1) | 52 | LBR |
| Intralipid | Al-Zebeidi et al. (2020) (79) | Saudi Arabia | RCT | January 2015 to December 2016 | IVF | Age of <42 y; BMI of <30 kg/m$^2$; 3 previous IFs; normal uterine cavity; normal hormone and lipid profile | Previous IF (≥1) | 142 | LBR |
| | Singh et al. (2019) (78) | India | RCT | January 2017 to January 2018 | IVF | Age of 20–40 y; BMI of 20–32 kg/m$^2$; nondonor oocyte IVF; ≥1 previous IF; normal baseline hormonal profile; morphologically normal oocytes and embryos | Previous IF (≥1) and thin endometrium | 102 | LBR |
| IVIG | Ahmadi et al. (2017) (84) | Iran | Prospective cohort | February 2015 to March 2016 | IVF | 3 IFs; preconception Th1/Th2 ratio and NK cell frequency and activity elevation | Previous IF (≥1) and high inflammation | 72 | LBR |
| | Chernyshov et al. (2016) (85) | Ukraine | Prospective cohort | Unstated | IVF | Age of 23–35 y; RIF (≥3); good-quality embryos and quantity | Previous IF (≥1) | 238 | LBR |
| | Ho et al. (2020) (86) | People's Republic of China | Prospective cohort | January 2007 to October 2011 | IVF | RIF (≥2 previous failures) of unknown etiology | Previous IF (≥1) | 283 | LBR |
| | Moraru et al. (2012) (82) | Spain | Prospective cohort | May 2005 to May 2011 | IVF | RIF (definition unstated); high NK or NK-like cell level | Previous IF (≥1) and high inflammation | 40 | LBR |
| | Sher et al. (1998) (87) | USA | Prospective cohort | January 1992 to 1996 | IVF | Age of <40 y; antithyroid antibodies; negative APL antibodies | Autoimmunity | 82 | LBR |
| | Stephenson and Fluker (2000) (88) | Canada | RCT | March 1995 to July 1998 | IVF | Age of 18–44 y; ≥2 previous failed fresh or frozen embryo transfers resulting in IF, biochemical pregnancy loss, or clinical miscarriage at ≤8 weeks of gestation | Previous IF (≥1) | 51 | LBR |
| r-LIF | Brinsden et al. (2009) (91) | UK | RCT | Unstated | IVF | Age of 21–37 y; 2 or more failed ART cycles; BMI of 20–30 kg/m$^2$; normal hormone profile; normal SFA | Previous IF (≥1) | 150 | LBR |
| PBMCs | Li et al. (2017) (95) | People's Republic of China | Unstated | July 2013 to March 2015 | IVF | Previous IF (≥1) | Previous IF (≥1) | 633 | LBR |
| | Okitsu et al. (2011) (93) | Japan | Prospective cohort | May 2007 to February 2010 | IVF | Previous IF (≥1) | Previous IF (≥1) | 253 | LBR |
| | Pourmoghadam et al. (2020) (96) | Iran | RCT | October 2017 to September 2018 | IVF | Age of <45 y; BMI of <30 kg/m$^2$; previous IF (≥3); primary infertility; regular menstrual cycles; normal SFA | Previous IF (≥1) | 100 | LBR |
| | Yoshioka et al. (2006) (94) | Japan | Unstated | Unstated | IVF | Previous IF (≥4); normal ovarian reserve (FSH level of <15 mIU/mL) | Previous IF (≥1) | 35 | LBR |
| | Yu et al. (2016) (97) | People's Republic of China | RCT | September 2013 to May 2014 | IVF | Age of <35 y; RIF (≥3); normal ovarian reserve (FSH level of <15 mIU/mL) | Previous IF (≥1) | 212 | LBR |
| Aspirin ± subcutaneous heparin | Akhtar et al. (2013) (21) | UK | Retrospective cohort | January 2005 to September 2010 | IVF | Age of 23–44 y; previous failed implantation (≥1) | Previous IF (≥1) | 206 | LBR |
| | Kutteh et al. (1997) (22) | USA | Prospective cohort | June 1995 to August 1996 | IVF | Age of <42 y; first IVF cycle; FSH level of <20 mIU/mL, estradiol level of <50 pg/mL; normal uterine cavity | Good prognosis | 191 | OPR |
| | Sher et al. (1994) (23) | USA | Cohort - unstated | January 1992 to June 1994 | IVF | Antiphospholipid antibody positivity; normal uterine cavity as observed by hysteroscopy | Autoimmunity | 194 | OPR |
| IVIG plus TNF-α inhibitor | Winger et al. (2009) (83) | UK | Retrospective cohort | May 2003 to December 2006 | IVF | Age of <38 y; elevated Th1/Th2 cytokine ratio before index fresh IVF cycle; negative tuberculin skin test; good embryo development (≥5 day 3 embryos with ≥5 cells) | High inflammation | 75 | LBR |

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**TABLE 1**

Continued.

| Interventions | Study | Country | Design | Duration | Population | Inclusion criteria | Subgroup | Total analyzed | Outcome |
|---|---|---|---|---|---|---|---|---|---|
| LMWH (subcutaneous) plus corticosteroid | Fawzy and El-Refaeey (2014) (43) | Egypt | Prospective cohort | January 2008 to October 2012 | IVF | Age of <39 y; failed previously 1 or 2 implantations; fresh ejaculate fertile sperm used for ICSI; no hormonal disorders; normal uterine cavity | Previous IF (≥ 1) | 295 | OPR |
| | Siristatidis et al. (2018) (44) | Greece and Egypt | Retrospective cohort | February 2012 to July 2016 | IVF | Age of <45 y; ≥ 2 failed IVF cycles; BMI of 19–35 kg/m$^2$; FSH level of ≤ 15 mIU/mL; absence of coagulation and/or autoimmune disorders | Previous IF (≥ 1) | 115 | LBR |
| TNF-α inhibitor | Onalan et al. (2018) (98) | Turkey | Retrospective cohort (case-control analysis) | January 2014 to January 2015 | IVF | Endometriomas | Good prognosis | 66 | LBR |

*Note:* APL = antiphospholipid; ART = assisted reproductive technology; BMI = body mass index; DHEAS = dehydroepiandrosterone; FET = frozen embryo transfer; FSH = follicle-stimulating hormone; G-CSF = granulocyte colony-stimulating factor; GnRH = gonadotropin-releasing hormone; hCG = human chorionic gonadotropin; hMG = human menopausal gonadotropin; ICSI = intracytoplasmic sperm injection; IF = implantation failure; IU = international units; IVF = in vitro fertilization; IVIG = intravenous immunoglobulin; LBR = live birth rate; LH = luteinizing hormone; LMWH = low-molecular-weight heparin; NK = natural killer; OI = ovulation induction; OPR = ongoing pregnancy rate; PBMC = peripheral blood mononuclear cell; PCOS = polycystic ovary syndrome; RCT, =randomized controlled trial; r-hLIF = recombinant human leukemia inhibitory factor; RIF = recurrent implantation failure; RPL = recurrent pregnancy loss; SFA = seminal fluid analysis; Th = T helper; TI = timed intercourse; TNF = tumor necrosis factor.

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similar numbers in the heparin and no treatment/placebo groups (40, 41, 43, 44). Further trials are needed to determine whether patients with previous implantation failure and evidence of an acquired or inherited thrombophilia may benefit from LMWH.

## CORTICOSTEROIDS

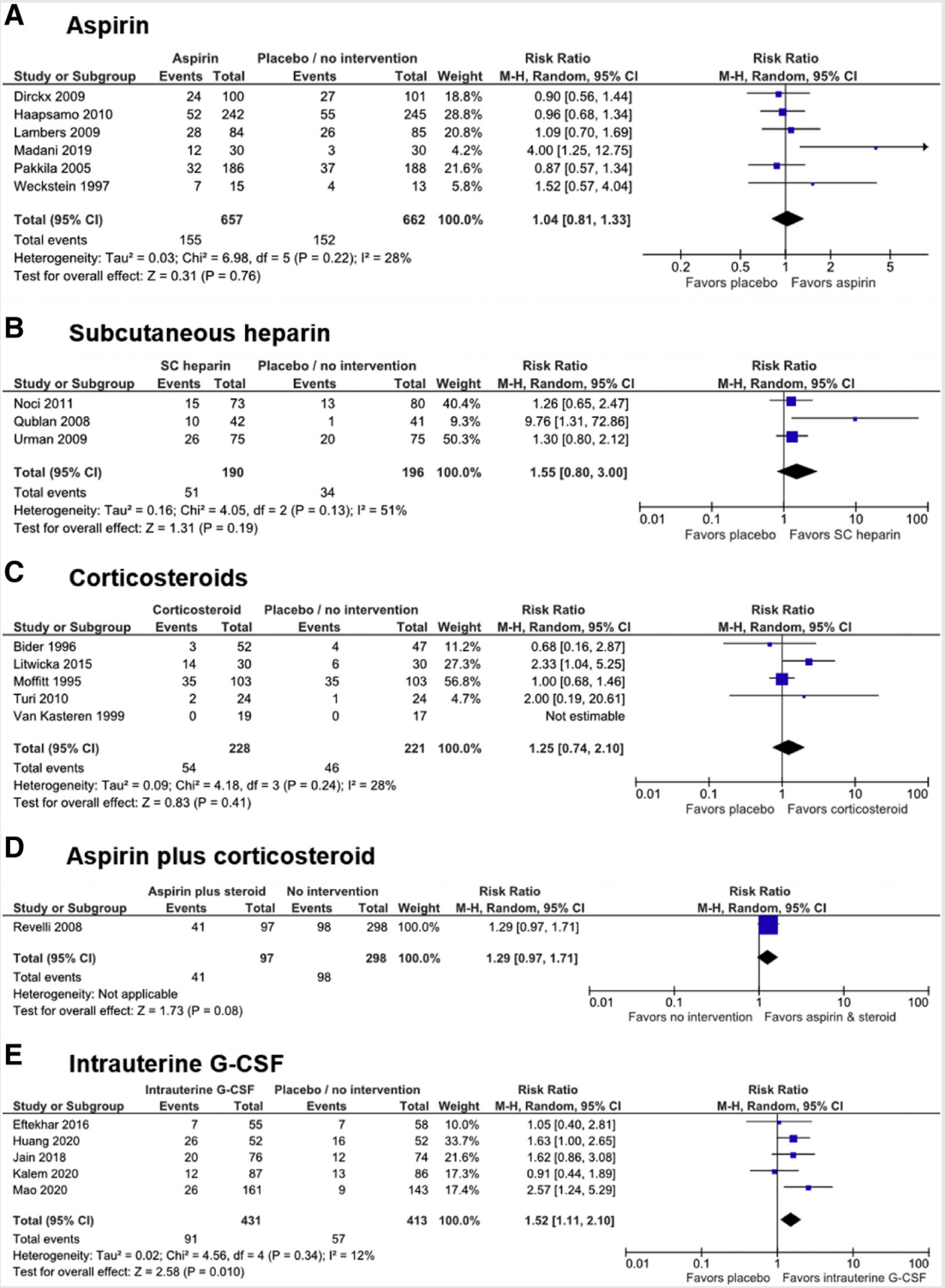
Corticosteroids have been widely used in the context of IVF treatment. It has been proposed that steroids may improve the uterine immune environment by either modulating the uterine NK cell count or activity or altering the endometrial cytokine environment (45, 46). We identified 2 nonrandomized studies that investigated the effect of corticosteroids vs. no intervention on the LBR; both reported uncertain findings for this outcome (47, 48) (Table 1). In addition, our meta-analysis of 5 RCTs including 449 patients investigating corticosteroids vs. placebo or no treatment showed no clear evidence of an increased number of ongoing pregnancies or live births (RR, 1.25; 95% CI, 0.74–2.10; 5 RCTs; $I^2 = 0$; low-certainty evidence) (49–53) (Fig. 1 and Table 2).

An additional rationale for the use of corticosteroids has been to improve outcomes for women with subfertility who have autoantibodies. However, studies investigating the association between subfertility and autoantibodies have shown varying results (54). Although a recent meta-analysis has failed to demonstrate an association between thyroid autoantibodies and poor outcomes in patients undergoing IVF or intracytoplasmic sperm injection (55), our subgroup analysis including solely women with positive antithyroid antibodies showed that treatment with corticosteroids may result in improved LBR (RR, 2.29; 95% CI, 1.07–4.94; 2 RCTs; $I^2 = 0$; low-certainty evidence). Notably, however, only 108 women participated in these studies, and in 1 publication, participants underwent intrauterine insemination, not IVF (52).

Corticosteroids are often prescribed in combination with other medications for women undergoing ART. We identified 1 RCT evaluating aspirin and corticosteroids vs. no intervention (56). The data were uncertain as to whether aspirin and corticosteroids in combination resulted in an increased OPR (RR, 1.29; 95% CI, 0.97–1.71; n = 395; low-certainty evidence) (Fig. 1 and Table 2).

Although generally considered to be safe in pregnancy, several studies have evaluated the possibility of teratogenicity with corticosteroid exposure. Initial evidence from the National Birth Defects Prevention Study in the United States suggested that corticosteroid exposure in the first trimester was associated with a significant, albeit small, increase in the risk of cleft lip and palate (57). However, more recent case-control data from the same registry including 1,577 children with cleft lip and palate no longer found this association (58). Adverse events reported from the trials included in this meta-analysis described typical effects of steroids, including insomnia and mild euphoria (53, 56). It is worth noting, however, that any use of corticosteroids beyond the first trimester of gestation should be restricted to women in whom the benefits are thought to outweigh the risks (e.g., asthma and autoimmune conditions). There is evidence suggesting that

## FIGURE 1




Meta-analysis of randomized controlled trials investigating different immunologic therapies in comparison with placebo or no intervention on the rate of ongoing pregnancy or live birth in women with subfertility and/or undergoing assisted conception. CI = confidence interval; df = degrees of freedom; G-CSF = granulocyte colony-stimulating factor; IVIG = intravenous immunoglobulin; M-H = Mantel-Haenszel test; PBMC = peripheral blood mononuclear cell; r-hLIF = recombinant human leukemia inhibitory factor; SC = subcutaneous.

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**FIGURE 1**

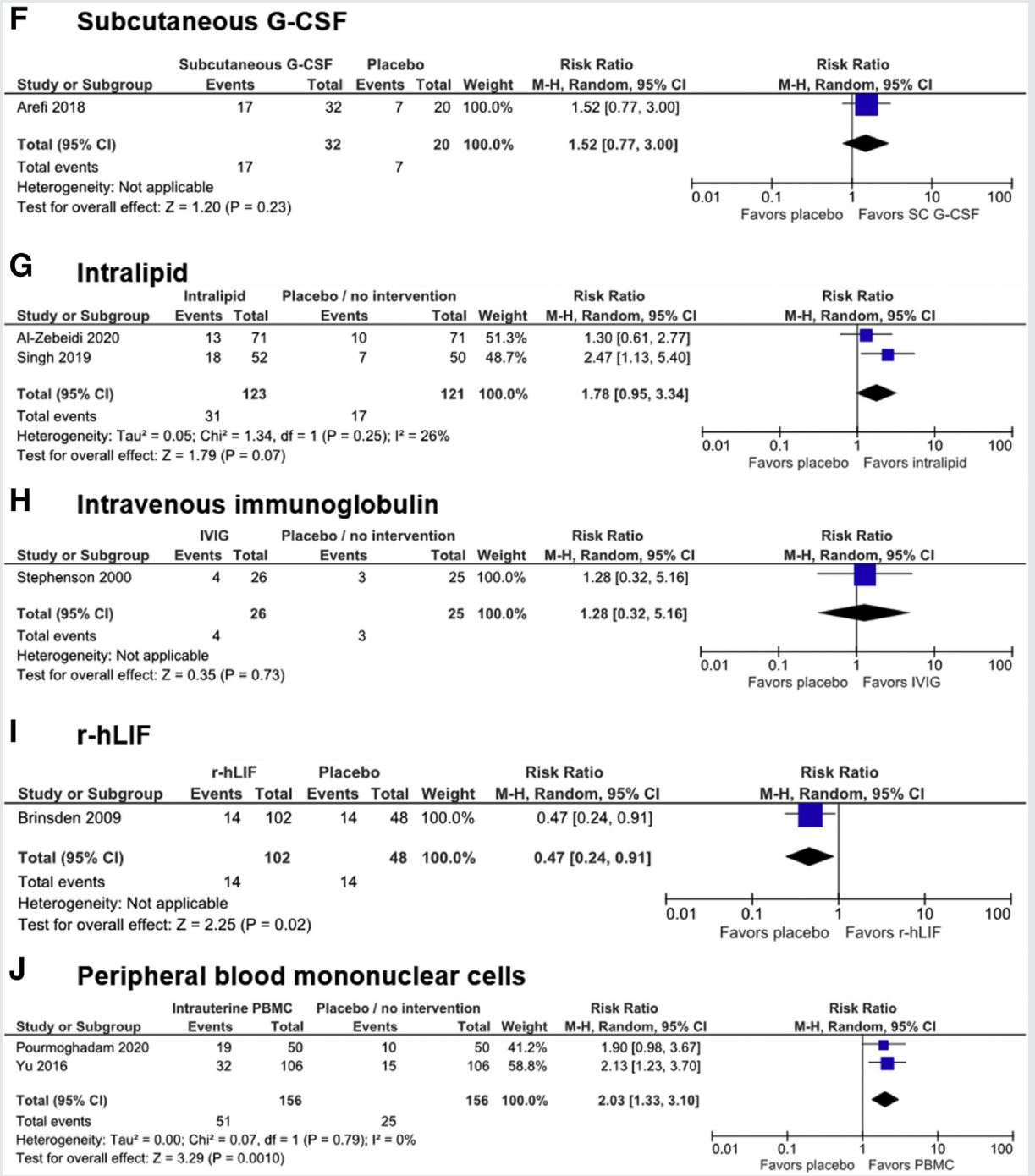


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**TABLE 2**

**Summary of findings of included randomized controlled trials for the outcome of ongoing pregnancy or live birth.**

| | Anticipated absolute effects (95% CI) | | | | |
|---|---|---|---|---|---|
| **Intervention** | **Risk with placebo or no intervention** | **Risk with intervention** | **Risk ratio (95% CI)** | **Number of participants (studies)** | **Certainty of the evidence (GRADE)** |
| Aspirin | 230/1,000 | 239/1,000 (186–305) | RR, 1.04 (0.81–1.33) | 1319 (6 RCTs) | ⨁⨁⨁◯ Moderate[a] |
| Subcutaneous heparin | 173/1,000 | 269/1,000 (139–520) | RR, 1.55 (0.80–3.00) | 386 (3 RCTs) | ⨁◯◯◯ Very low[a,b,c] |
| Corticosteroids | 208/1,000 | 260/1,000 (154–437) | RR, 1.25 (0.74–2.10) | 449 (5 RCTs) | ⨁⨁◯◯ Low[a,b] |
| Aspirin plus corticosteroids | 329/1,000 | 424/1,000 (319–562) | RR, 1.29 (0.97–1.71) | 395 (1 RCT) | ⨁⨁◯◯ Low[a,d] |
| Intrauterine G-CSF | 138/1,000 | 210/1,000 (153–290) | RR, 1.52 (1.11–2.10) | 844 (5 RCTs) | ⨁⨁◯◯ Low[a,b] |
| Subcutaneous G-CSF | 350/1,000 | 532/1,000 (269–1,000) | RR, 1.52 (0.77–3.00) | 52 (1 RCT) | ⨁◯◯◯ Very low[a,b,e] |
| Intralipid | 140/1,000 | 250/1,000 (133–469) | RR, 1.78 (0.95–3.34) | 244 (2 RCTs) | ⨁◯◯◯ Very low[a,b,e] |
| IVIG | 120/1,000 | 154/1,000 (38–619) | RR, 1.28 (0.32–5.16) | 51 (1 RCT) | ⨁⨁◯◯ Low[a,e] |
| r-hLIF | 292/1,000 | 137/1,000 (70–265) | RR, 0.47 (0.24–0.91) | 150 (1 RCT) | ⨁⨁◯◯ Low[a,e] |
| PBMCs | 160/1,000 | 325/1,000 (213–497) | RR, 2.03 (1.33–3.10) | 312 (2 RCTs) | ⨁◯◯◯ Very low[a,b,e] |

Note: Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.
CI = confidence interval; G-CSF = granulocyte colony-stimulating factor; IVIG = intravenous immunoglobulin; PBMCs = peripheral blood mononuclear cells; RCT = randomized controlled trial; r-hLIF = recombinant leukemia inhibitory factor; RR = risk ratio.
[a] Downgraded once for serious imprecision due to the low number of events and/or wide confidence intervals.
[b] Downgraded once for serious risk of bias in at least 1 of the included studies.
[c] Downgraded once for serious inconsistency due to high heterogeneity.
[d] Downgraded once for serious indirectness because the included study evaluated only participants with good prognosis, therefore limiting the applicability of its findings to subgroups.
[e] Downgraded once for serious indirectness because the included study or studies evaluated only participants with recurrent implantation failure, thus limiting the applicability of the findings to other subgroups.

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repeated antenatal exposure to corticosteroids is associated with obstetric complications (e.g., increased risk of infection) as well as mental and behavioral disorders in children (59–61).

Evidence from RCTs to date does not support the generalized use of steroids in improving the OPR or LBR in women undergoing assisted conception. However, some groups of patients, including those with autoantibodies or autoimmune disease, may benefit from steroid treatment (51). There is a need for large RCTs to better define the effectiveness of corticosteroids to improve outcomes in women with infertility.

## GRANULOCYTE COLONY-STIMULATING FACTOR

Granulocyte colony-stimulating factor is a cytokine produced by multiple cell types, including endothelium, epithelium, monocytes, macrophages, and bone marrow cells. Granulocyte colony-stimulating factor primarily stimulates the proliferation and survival of neutrophils (62). Recombinant G-CSF has been shown in an ex vivo model to alter endometrial gene expression, potentially influencing endometrial remodeling, cellular adhesion pathways, and local endometrial immune modulation (63). Intrauterine G-CSF treatment for patients with a thin endometrium was first reported in 2011 (64), and there have since then been a number of studies investigating its efficacy in the context of IVF.

Two cohort studies did not observe a difference in the LBR (65, 66) in patients treated with intrauterine G-CSF. In addition, we identified 5 RCTs including 844 participants treated with intrauterine G-CSF or a placebo/no intervention (67–71) (Table 1). Intrauterine G-CSF may result in a higher OPR or LBR than placebo or no intervention (RR, 1.52; 95% CI, 1.11–2.10; $I^2 = 12\%$), although the certainly of the evidence was found to be low (72) (Fig. 1 and Table 2). A subgroup analysis of women with a thin endometrium treated with intrauterine G-CSF suggested that this is the group in whom the increase in the LBR is most substantial (RR, 2.57; 95% CI, 1.24–5.29; 1 RCT; n = 304), although the evidence was judged to be of low certainty owing to the serious risk of bias and low number of events.

Although fatigue and bone and muscle pain are common side effects of G-CSF treatment, very few adverse events were reported in the included studies investigating the use of intrauterine G-CSF, presumably because the systemic dose of G-CSF is very low after intrauterine instillation (66, 74, 75).

The effect of subcutaneous G-CSF during ART treatment cycles has also been investigated, although we identified no

## TABLE 3

**Summary of recommendations on the use of immunotherapies in assisted reproduction.**

| Intervention | ASRM | BFS | CFAS |
|---|---|---|---|
| Aspirin | "good evidence to recommend against the routine use of low-dose aspirin to improve the outcome of live birth in ART cycles in the general population" | "lack of proven efficacy for routine use of aspirin as an adjuvant in IVF cycles" | "aspirin should not be routinely offered in RIF"<br>"In patients with thin endometrium undergoing embryo transfer cycles, we suggest against the use of aspirin to improve pregnancy rates" |
| Heparin | — | "[the routine use of LMWH] in the wide population of women undergoing IVF treatment is not warranted"<br><br>"[LMWH] should be carefully considered in women with thrombophilia" | "empirical LMWH for RIF should be limited to research settings" |
| Corticosteroids | "good evidence to recommend against the routine use of corticosteroids during stimulation [and the implantation window] to improve the outcome of live birth in ART cycles in the general population"<br><br>Additional evidence required on the effectiveness of corticosteroids in subpopulations | "lack of robust evidence to support the routine use of corticosteroids empirically as an adjuvant in IVF cycles"<br><br>"limited evidence that corticosteroids may improve pregnancy rates in women undergoing conventional IVF and in the subgroup of women with autoimmunity or unexplained implantation failure | "the use of glucocorticoids in RIF patients should be limited to research settings" |
| G-CSF | "insufficient evidence to routinely recommend for or against G-CSF administered locally or systemically to improve IVF outcomes" | — | "the use of G-CSF in RIF patients should be limited to research settings"<br><br>"in patients with thin endometrium undergoing embryo transfer cycles, we suggest against the use of intrauterine infusion of G-CSF to improve pregnancy rates" |
| Intralipid | "insufficient evidence to routinely recommend intravenous fat emulsions for infertile women pursuing IVF"<br><br>Additional evidence required on the effectiveness of intralipid in subpopulations | "lack of evidence to recommend intralipid infusion therapy as an adjuvant in IVF cycles. The use of intravenous lipids in this setting cannot therefore be supported" | "the use of intralipid in RIF patients should be limited to research settings" |
| IVIG | "insufficient evidence to recommend IVIG administration to improve IVF outcomes"<br><br>Additional RCTs required to identify indications, risks, and benefits in subpopulations | "no convincing evidence for the use and safety of IVIg as adjuvants in women with recurrent implantation failure embarking on IVF. The use of IVIg in this setting cannot be supported" | "the use of immunotherapy in RIF patients should be limited to research settings" |
| r-hLIF | — | — | — |
| PBMCs | "insufficient evidence to recommend intrauterine infusion of autologous peripheral mononuclear cells before ET to improve IVF outcome" | — | — |
| TNF-$\alpha$ inhibitors | "insufficient evidence to recommend adalimumab treatment to improve IVF outcome" | "lack of evidence to indicate the effectiveness and safety of using anti-TNF-$\alpha$ agents as adjuvant in IVF cycles. The use of anti-TNF-$\alpha$ agents in this setting cannot therefore be supported" | — |

*Note:* ART = assisted reproductive technology; ASRM = American Society for Reproductive Medicine; BFS = British Fertility Society; CFAS = Canadian Fertility & Andrology Society; ET = embryo transfer; G-CSF = granulocyte colony-stimulating factor; IVF = in vitro fertilization; IVIG = intravenous immunoglobulin; LMWH = low-molecular-weight heparin; PBMCs = peripheral blood mononuclear cells; RCT = randomized controlled trial; r-hLIF = recombinant leukemia inhibitory factor; RIF = recurrent implantation failure; TNF-$\alpha$ = tumor necrosis factor alpha.

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cohort studies and only 1 RCT including 52 patients that reported no difference in the LBR (73). Given the limited therapeutic options for treating women who have a persistently thin endometrium, further good-quality studies are needed to assess the efficacy of G-CSF.

## INTRALIPID

Intralipid is an intravenous fat emulsion containing soybean oil, egg phospholipid, glycerin, and water and is licensed for parenteral nutrition. Its proposed mechanisms of action in the context of subfertility is the suppression of NK cell activity and proinflammatory cytokines (76). Interestingly, a recent study by Foyle et al. (77) investigated whether intralipids may modulate the adaptive immune response in women. The investigators identified no evidence of significant alterations to T cell populations (albeit in the blood rather than in the endometrium) after intralipid infusion. However, intralipid resulted in changes to circulating plasma cytokines, which the investigators suggested have the potential to enhance endometrial receptivity.

Despite the common use of intralipids in clinical practice, we identified only 2 RCTs including 244 patients in which the pooled effect of intralipid on the LBR was uncertain (RR, 1.78; 95% CI, 0.95–3.34; $I^2 = 26\%$) (Fig. 1 and Table 2). In both studies, women had experienced previous failed implantation after ART (78, 79). Clearly, further evidence for the efficacy of intralipid is required before using this treatment in patients outside of a research setting. No serious adverse events were described in these articles, yet at higher doses, intralipid has been associated with increased risks of infection, venous thromboembolism, fat embolism, acute kidney injury, and allergic reactions (80).

## INTRAVENOUS IMMUNOGLOBULIN

Intravenous immunoglobulin is a pooled blood product licensed for several inflammatory and autoimmune conditions, such as chronic inflammatory demyelinating polyneuropathy, immune thrombocytopenia, and Kawasaki disease (81). We found a number of cohort studies assessing the effect of IVIG vs. no intervention. Most treated women considered to have high preconception Th1/Th2 ratios or a peripheral blood NK cell abnormality (82–84); others investigated participants who had previous implantation failure after ART treatment (85, 86), and 1 assessed IVIG use in women with antithyroid autoantibodies (87). Four of these studies found that treatment with IVIG led to a higher LBR (82, 84, 86, 87). The largest of these studies was a prospective analysis by Ho et al. (86) of 283 women with previous implantation failure (RR, 1.43; 95% CI, 1.05–1.95). In contrast, Chernyshov et al. (85) did not show a benefit to IVIG treatment, whereas the data from a retrospective cohort by Winger et al. (83) are difficult to interpret given multiple group comparators with a very small number of patients receiving no treatment. Despite the apparently encouraging results in some of these cohort studies, it is notable that we only identified 1 RCT evaluating 51 patients that demonstrated no clear effect of IVIG on the LBR (RR, 1.28; 95% CI, 0.32–5.16; low-certainty evidence) (88) (Fig. 1 and Table 2).

Intravenous immunoglobulin is commonly used as an adjuvant to ART, particularly in women with RIF or apparent immune dysregulation, despite the lack of high-quality evidence of a benefit in the OPR or LBR. Those studies that reported adverse events did not describe significant side effects (86, 88). In view of the positive data presented in several cohort studies, further large trials of this intervention are warranted, but the current evidence does not support routine clinical use in any specific patient population.

## RECOMBINANT HUMAN LEUKEMIA INHIBITORY FACTOR

Leukemia inhibitory factor is a cytokine that was first identified as critical in mouse implantation (89). It has subsequently been investigated in humans, where it is expressed in the endometrium in the luteal phase of the menstrual cycle and thought to play a critical role in endometrial receptivity (90). Only 1 RCT has evaluated recombinant human leukemia inhibitory factor (r-hLIF) in a population of women with previous implantation failure undergoing ART (91). That study found that r-hLIF may result in a lower LBR (RR, 0.47; 95% CI, 0.24–0.91; n = 150; low-certainty evidence) (Fig. 1 and Table 2). This trial also reported more serious adverse events in the r-hLIF group, although the evidence was uncertain due to the relatively low numbers of patients in the study (RR, 4.24; 95% CI, 0.55–32.48; n = 150; low-certainty evidence). The apparent negative impact of r-hLIF on the LBR has undoubtedly discouraged others from further investigating this treatment.

## PERIPHERAL BLOOD MONONUCLEAR CELLS

Peripheral blood mononuclear cells (PBMCs) include T and B lymphocytes, NK cells, as well as monocytes and dendritic cells. It has been hypothesized that intrauterine infusion of autologous PBMCs may enhance endometrial receptivity and improve the implantation rates. In most studies, PBMCs are cultured with human chorionic gonadotropin or corticotropin-releasing hormone before transfer (92). Some cohort studies have identified no difference in the LBR using intrauterine PBMCs (93), whereas others suggest an increase in the LBR (94). Most studies have investigated this treatment in patients with RIF, and 1 large cohort study demonstrated an increase in the LBR in participants with higher-order ($\geq 4$) implantation failure (95).

We identified 2 RCTs including 312 participants comparing intrauterine PBMC treatment with a placebo or no intervention that reported on the LBR (96, 97). In both studies, PBMCs were cocultured with human chorionic gonadotropin before transfer. Meta-analysis of these studies demonstrated a pooled RR of 2.03 (CI, 1.33–3.10; $I^2 = 0$) (Fig. 1), with anticipated absolute effects of achieving an LBR of 325 ongoing pregnancies or live births per 1,000 treated women compared with 160 patients receiving no treatment or placebo (Table 2). However, it must be noted that the certainty of the evidence was very low in these studies. Further, both trials investigated participants with previous implantation failure and, therefore, may not be generalizable to other subgroups of women with subfertility.

The putative mechanism of action of intrauterine PBMC therapy remains unclear. It is unlikely that the cells will breach the uterine mucosa, but in vitro culture of PBMCs activate cells and may stimulate the production of cytokines or factors beneficial to implantation (92). Endeavoring to identify which specific factors produced by cocultured PBMC may be ultimately more beneficial is the quest for studies investigating therapies for women with RIF.

## TNF-α INHIBITORS

Tumor necrosis factor alpha is an inflammatory cytokine produced mainly by activated macrophages, T lymphocytes, and NK cells as well as nonimmune cells. Tumor necrosis factor alpha is synthesized within minutes of proinflammatory stress or injury, and chronic elevation of TNF-α levels is associated with several inflammatory conditions. Tumor necrosis factor alpha inhibitors are monoclonal antibody drugs licensed for the treatment of several of these conditions, including severe rheumatoid arthritis and other arthropathies, as well as inflammatory bowel disease. Some studies have described the ratios of Th1 and Th2 cytokines as being discordant or abnormal in the context of subfertility and RIF (8–10). This has led to the hypothesis that these medications may be beneficial, particularly in ART patients with RIF. Our systematic review identified no RCTs evaluating anti-TNF-α therapies on the OPR or LBR and found only 2 cohort studies where the data were expressed per participant (83, 98) (Table 1). In the study by Winger et al. (83), patients undergoing ART who were identified by the investigators as having an abnormal TNF-α/IL-10 ratio were administered adalimumab alone, IVIG alone, a combination of adalimumab and IVIG, or no treatment. The treatment was based on patient choice, and only 5 patients received no treatment. Although the investigators identified a higher LBR using the combination therapy than that in no treatment, the study design precludes drawing meaningful conclusions from these data. In another small retrospective study, Onalan et al. (98) evaluated the effectiveness of etanercept in women with endometrioma undergoing ART and found no difference in the LBR. Tumor necrosis factor alpha inhibitors should not be recommended to patients outside the context of a well-designed RCT. Most patients using this medication experience only mild side effects; however, biologic medications can result in more serious adverse events, such as an increased risk of severe infections (99).

## CONCLUSION

Despite the widespread use of immunomodulatory drugs in clinical practice, this systematic review of the literature once again demonstrates a real lack of good-quality evidence for the use of immunologic treatments in women with subfertility or who are undergoing ART. In both research and clinical practice, patient selection remains controversial. Some clinicians administer immunologic therapies exclusively to women with known risk factors for implantation failure, for example, RIF or the existence of concomitant autoimmune conditions, such as antiphospholipid syndrome (100). Others apply less stringent criteria and use these drugs in the absence of known pathology that may impair implantation. Table 3 summarizes existing recommendations from different international societies on the use of immunotherapies in ART, highlighting that for most interventions, the evidence is scarce (101–104).

The use of immunologic treatments often accrues significant financial burden to patients and their partners (14, 105). Commonly prescribed drugs, such as aspirin and LMWH, are relatively inexpensive, yet the added cost of other immunotherapies can be substantial. For example, 1 injection of recombinant G-CSF solution (300 mcg) costs upward of US$360, with some centers administering more than 1 injection per treatment cycle (106, 107). Treatment with IVIG (approximately 1 g/kg) is even more expensive and can add up to US$6,000 to the cost of 1 ART cycle (108). It is also worth noting that IVIG is a blood product derived from the plasma of healthy donors and, thus, constitutes a finite resource (109). Clinicians have a duty to thoroughly counsel patients on the absence of conclusive evidence demonstrating a benefit of these therapies in women undergoing assisted conception.

Crucially, embryo aneuploidy represents the leading cause of implantation failure, abnormal implantation, and miscarriage, especially with advancing female age. In cases of embryo aneuploidy, the use of immunotherapy drugs remains futile (110). However, none of the included studies in this review restricted their samples to euploid embryos. There is a need for additional trials investigating immunomodulatory treatments in women having ART with embryos known to be chromosomally normal.

Recent studies have begun to elucidate the very complex cellular composition of the human endometrium and early decidua, including multiple subtypes of NK cells with distinctive immunomodulatory profiles (4, 111). In light of these data, current testing for immune dysfunction is likely to be far too simplistic. For example, the population of CD3+CD56+ endometrial cells identified and quantified by several clinical tests will in fact encompass a diverse range of cells, including subtypes of innate lymphoid cells and not just NK cells (112). Further, there is emerging evidence on various other etiologic pathways in RIF, including the role of killer immunoglobulin-like receptors/human leukocyte antigen incompatibility. However, our searches found no interventional studies evaluating the effectiveness and safety of immunotherapy drugs in such cases (113).

Despite the lack of certainty in the existing evidence, it would be premature to dismiss a future for immunologic treatments to improve outcomes for patients undergoing ART. Perhaps before embarking on major RCTs, clinicians and researchers need to agree on what pathology is being treated. The first challenge for the scientific community is to define tests that identify a true population of patients with an immune-mediated pathology and then undertake well-designed RCTs in suitably phenotyped patients who have the potential to benefit from immune treatments. In an era of personalized

medicine, there remain the scope and opportunity for reproductive immunology to improve outcomes for patients.

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